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Epidemic and Pandemic Alert and Response

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Contents

Acronyms and abbreviations

The acronyms and abbreviations listed below have been used in this report.

CpGs	immunostimulatory oligonucleotide containing cytosine-guanosine sequence
DNA	deoxyribonucleic acid
ECBS	WHO Expert Committee on Biological Standardization
GIVS	Global Immunization Vision and Strategies
HA	haemagglutinin
H5N1	highly pathogenic avian influenza virus, type H5N1
LAIV	live attenuated influenza vaccine
NA	neuraminidase
NIP	national immunization programme
PAHO	Pan American Health Organization
SPF	specific pathogen-free
UNICEF	United Nation Children's Fund
VLP	virus-like particles
WHA	World Health Assembly
WHO	World Health Organization

Executive summary

The objective of the Global Vaccine Action Plan is to increase the supply of a pandemic vaccine and thereby reduce the gap between the potential vaccine demand and supply anticipated during an influenza pandemic.

To mitigate the potential impact of an influenza pandemic, control interventions include two strategies – one, a non-pharmaceutical approach such as social distancing and infection control and the other, a pharmaceutical approach such as the use of influenza vaccines and antivirals for treatment and prophylaxis. In an influenza pandemic most of the world's population will be highly susceptible to the virus infection and it is conceivable that the virus will spread rapidly. The availability of a pandemic vaccine will be delayed by several months because of the requirements for vaccine formulation and production lead-time. Furthermore, it is probable that insufficient production capacity will restrict global access to the vaccine, at least during the first phase of the pandemic.

Immunization against influenza is considered to be an essential public-health intervention to control both seasonal epidemics and pandemic influenza. Influenza vaccine development and deployment are critical elements of pandemic influenza preparedness. There are marked differences between countries in terms of their respective capacities, priorities and resources to establish a seasonal influenza vaccination policy and programme. The major influenza vaccine producers operate and supply almost exclusively in Australia, Europe, North America and some countries in Asia and Latin America. Most resource-constrained countries do not have the means to access seasonal influenza vaccines and could face this challenge during an influenza pandemic. Planning for appropriate availability of vaccines to manage a pandemic response requires a global perspective and concerted effort, not only in developing a vaccine but also in producing and distributing it.

At the present time, if an influenza pandemic were to occur, the potential vaccine supply would fall several billion doses short of the amount needed to provide protection to the global population.

Countries can assist by: a) developing seasonal influenza vaccination programmes if they can afford to, and b) increasing influenza vaccine coverage in existing programmes. This will provide industry with the clear forecast of demand that is integral to ensuring an incremental increase in seasonal vaccine production-capacity. This approach, although highly valuable, would be unlikely to raise production capacity to sufficient levels to serve the global population in the foreseeable future. One important option for the global health community to consider, therefore, is countries' willingness to pay vaccine manufacturers for unused excess capacity of vaccines.

Together with the current production challenges, it must be stressed that there are several scientific and technological issues that need to be addressed to facilitate development of effective pandemic vaccine. New influenza candidate vaccines are in the pipeline and clinical trials to evaluate the safety and immunogenicity of candidate H5N1 vaccines are under way. Recently published preliminary results with split-virus inactivated vaccines show suboptimal immunogenicity. However, more encouraging results have been obtained with whole-virus adjuvanted, inactivated vaccines.

In response to these challenges and in order to develop a Global Vaccine Action Plan for Pandemic Influenza Vaccines, WHO organized a consultation in Geneva on 2–3 May 2006 and invited key stakeholders – from national immunization programmes, national regulatory authorities, vaccine manufacturers and the research community – to participate. The objective of the consultation was to identify and prioritize practical solutions for reducing the anticipated gaps in vaccine supply. The participants drew up an Action Plan with strategies for the short, mid and long term, aiming to increase influenza vaccine production and surge capacity before and during an influenza pandemic. They identified three main approaches: a) an increase in seasonal vaccine use; b) an increase in production capacity; and c) further research and development. The implementation of this plan will require the concerted efforts of countries, industry and the global health community.

Increase in seasonal vaccine use

The first approach relies on countries establishing clear immunization policies to increase the use of seasonal influenza vaccine. This will provide the vaccine industry with a solid demand forecast and stimulate it to increase production capacity. For purposes of the discussion, the participants divided countries into three categories based on their probable demand for seasonal influenza vaccine.

Group 1: Countries that already use seasonal influenza vaccine and that could reach the goal of immunizing 75% of their target population either in the near future or by 2010, as recommended by WHA Resolution 58, 2005.

Group 2: High-income or middle-income countries that currently do not use seasonal influenza vaccine.

Group 3: Low-income countries.

Increased consumption of seasonal influenza vaccine in Group 1 countries could raise demand by 60% above the current annual level of distribution – that is, 350 million annual doses – bringing the annual total demand to 560 million doses.

Group 2 countries need to decide on a policy and conditions required to introduce influenza vaccines into their national immunization schedules in the near future. As an example, the 2006 demand for countries in the Region of the Americas is for approximately 40 million doses, of which 11 million doses of seasonal influenza vaccine will be purchased through the Pan American Health Organization (PAHO) Revolving Fund. This demonstrates that at least a proportion of Group 2 countries will generate demand and thereby promote expansion of the production capacity for influenza vaccines.

In Group 3 countries, competing health priorities and the price of trivalent inactive influenza vaccine (currently in the range of US $3–7.00 per dose) is a barrier to the introduction of seasonal influenza vaccination.

Participants identified priority strategies to increase demand for seasonal influenza vaccine, including:

- development of regional and national plans, and
- resource mobilization to assist countries to purchase both seasonal and pandemic influenza vaccines.

Increase in vaccine production-capacity

The second approach concentrates on increasing production capacity for pandemic vaccines, without taking into account the expected demand for seasonal vaccine. Should there be a pandemic that appears to cause high mortality, there will probably be calls to vaccinate the global population – currently estimated to be 6.7 billion. A pragmatic approach in the short term will be to provide surge-capacity by using antigen-sparing methods; this could result in the availability of more doses.

The participants evaluated various strategies to increase production capacity for pandemic vaccines and considered the following to be the most promising:

- improving production yields and immunogenicity for vaccines based on H5N1 influenza strains;
- building new production plants in both developing and industrialized countries;
- focusing on further development of adjuvanted vaccines with adjuvants widely used in licensed vaccines;
- expanding the production of live attenuated influenza vaccines (LAIV);
- evaluating the immunogenicity of inactivated whole-virus vaccines;
- evaluating the potential for delivering vaccines by alternative routes – for example, the intradermal route using needle-free delivery devices such as jet injectors.

Further research and development

The third approach builds on research and development efforts being undertaken by the research community – including 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 develop a highly immunogenic and safe vaccine with broader and longer efficacy, together with more sophisticated tools for vaccine evaluation, the plan focuses on:

- optimization of the protective efficacy and immunogenicity of existing vaccine types, using novel adjuvants and delivery strategies;
- development of novel vaccine concepts (based on conserved influenza proteins) that induce broad-spectrum and long-lasting immune responses;
- improvement of the current methods to evaluate the performance of vaccine candidates.

In conclusion, the participants identified a number of strategies to bridge the anticipated gap between vaccine demand and supply in the event of a pandemic. Importantly, none of the strategies will be able to fill the gap in the immediate short term but, if action is taken now, should bear fruit within a future time frame of three to five years. Implementation of the Global Vaccine Action Plan will require substantial funding – preliminary estimates indicate from 3–10 billion US dollars. All stakeholders have important but different and complementary roles to play. Countries that decide to increase coverage with seasonal influenza vaccines will contribute to a sustained augmentation of manufacturing capacity. The international community will be required to shoulder some of the financial burden of: a) improving seasonal influenza vaccine coverage in resource-constrained countries, and b) establishing vaccine production-capacity. This can be done by means of direct investment or technology transfer in developing or middle-income countries. The private sector will also be required to invest in expanding its manufacturing capacities and developing new production technologies.

International organizations, including the World Health Organization, need to take an active role in coordinating and streamlining many of the planned activities. An effective partnership and a commitment to sustaining the effort over 5–10 years are indispensable. Action must start now – this fact cannot be emphasized strongly enough – *action must start now* if the world is to prepare itself in the shortest possible time for a potential influenza pandemic.

1. Introduction

Although the global burden of seasonal influenza is unknown, it is currently acknowledged to be a burden that spreads across both rich and resource-constrained countries. Pandemic influenza becomes possible when there is an antigenic shift in the haemagglutinin (HA) of an influenza virus to a new type – a type to which virtually the entire human population lacks immunity. Three criteria are needed for a global influenza pandemic to occur:

1) a new virus emerges with a new HA to which there is almost universal susceptibility;
2) this virus is capable of causing significant disease in humans;
3) this virus is efficiently transmitted from human to human.

While reassortment appears to have been the mechanism that accounted for the 1957–1958 and 1968–1969 pandemics, direct mutation of an avian strain and adaptation to humans appears to have been the cause of the 1918–1919 pandemic.

In the last decade a highly pathogenic epizootic H5N1 avian influenza virus has crossed the species barrier, without major antigenic changes, and has affected some humans that have been in close contact with animals infected with the virus. This viral strain has been associated with a high case–fatality rate and is considered to pose an imminent pandemic threat.

Previous influenza pandemics have arrived with no forewarning. The widespread circulation of H5N1 viruses since 1997 is, however, giving the world an opportunity to prepare for the next pandemic. It is impossible to predict the exact timing or nature of a future pandemic, but modelling studies suggest that an influenza pandemic would create an enormous burden – not only on public health and health-care systems, but also on providers of other essential services around the globe.

It is broadly accepted that vaccines can play a key role in limiting the impact of such a pandemic. There are, however, many challenges to advancing the development of a vaccine for a pandemic.

1) A vaccine cannot be developed with certainty until after the pandemic virus emerges.
2) Current global capacity to manufacture influenza vaccines is limited.
3) Two doses may be needed for a pandemic vaccine because of the absence of pre-existing immunity. This could further delay time to achieve protection and add operational challenges to delivery.

4) High antigen content may be required; this would limit the total number of doses that can be made available with the current egg-based technology for inactivated vaccines.

5) The target population for vaccination could potentially be the entire global population of over six billion; this would require comprehensive resources to support operational and logistic demands in many countries.

Within the above scenario, many industrialized countries are in the process of securing a supply of vaccines, based on current circulating H5N1 avian influenza strains, to protect their populations. For the poorest and most vulnerable populations, pandemic vaccine availability and use will be the most challenging.

2. Overall objectives

In order to strengthen pandemic-influenza preparedness and response, the Fifty-eighth World Health Assembly (WHA 58.5, agenda item 13.9, 23 May 2005) requested the World Health Organization (WHO) secretariat to seek solutions with international and national partners, including the private sector, to: a) reduce the present global shortage of influenza vaccines for both epidemics and pandemics, b) establish vaccination strategies that economize on the use of antigens, and c) develop and license antigen-sparing vaccine formulations. Following this request, the WHO Global Influenza Programme and the WHO Department of Immunization, Vaccines and Biologicals held a consultation to develop a Global Vaccine Action Plan to identify the most promising approaches to increasing availability of vaccines for an influenza pandemic.

The consultation brought together over 120 scientific experts – representatives from national immunization programmes, national regulatory authorities and vaccine manufacturers – from both industrialized and developing countries. Their two main objectives were to:

1) prepare a Global Vaccine Action Plan with specific activities – for the short, medium and long term – designed to increase influenza vaccine production and surge- capacity, to identify key obstacles and driving forces, and to estimate funding needs; and

2) strengthen the engagement and collaboration of key partners and stakeholders.

For the purpose of the consultation, short-term activities were defined as those for which returns would be expected in less than 5 years, medium-term activities would reach fruition in 5–10 years, and long-term activities would take more than 10 years to yield tangible results.

3. The present situation and current challenges

Short-term potential availability of influenza vaccine (per year)	
Estimate of production capacity for current influenza vaccine:	350 million doses (inactivated trivalent vaccine containing 15 µg of HA per dose).
Estimate of production capacity for potential influenza vaccine, if manufacturers optimize current output (e.g. by working 3 shifts/24 hours):	500 million doses (inactivated trivalent vaccine containing 15 µg of HA per dose).
Planned expansion for extra vaccine production-capacity in the next 2–3 years (280 million):	780 million doses (inactivated trivalent vaccine containing 15 µg of HA per dose).
Estimate if production should switch to monovalent pandemic influenza vaccine, assuming only 15 µg of HA per dose (2009 projection):	2340 million doses of pandemic vaccine (inactivated monovalent vaccine containing 15 µg of HA per dose).

The above table summarizes the expected short-term global vaccine production-capacity in a scenario based on an inactivated influenza vaccine containing 15µg HA. Of note, current inactivated split-virus pandemic vaccine candidates require a higher antigen content to show acceptable immunogenicity. Current global vaccine production-capacity is concentrated mostly in nine industrialized countries: Australia, Canada, France, Germany, Italy, Japan, the Netherlands, the United Kingdom and the United States of America. It should be acknowledged that, at this point in time, the ratio of supply to demand for seasonal vaccine is close to 1:1. The planned expansion outlined in the table above is based on market-driven business investments keeping up with the growing demand for seasonal influenza vaccines in industrialized, and some emerging, economies. By 2008 or 2009 the full production capacity for monovalent pandemic influenza vaccine – based on the assumption of 15µg of HA per dose, as for seasonal vaccine – would not exceed 2340 million doses per year. This would be several billion doses short of the expected demand if there were to be a pandemic.

In addition, current egg-based production yields of H5N1 influenza virus are significantly inferior to yields of classical seasonal influenza strains. The yield of monovalent pandemic vaccine per year would be a maximum of 500 million doses – that is, approximately one third of the yield of seasonal vaccine strains. Moreover, if two doses of vaccine were to be needed to induce protective immunity, as currently believed, only 250 million people would receive a full vaccination course in one year.

4. Major approaches to increasing supplies of pandemic influenza vaccine

4.1 Develop an immunization policy to increase demand for seasonal vaccines.

Objective:

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

4.1.1 Strategy 1: Develop regional and national plans for seasonal influenza vaccination programmes.

The objective is to have each WHO region prepare a regional influenza vaccination plan that will become incorporated into its overall Influenza Pandemic Preparedness Plans. The figure below outlines a navigational tool on the policy and programmatic issues that need to be considered – either when increasing current seasonal influenza vaccination coverage or when considering the establishment of a seasonal influenza vaccination programme. The tool may also be useful to countries that decide not to introduce seasonal influenza vaccination into the national immunization programme, but still plan to use a pandemic influenza vaccine should an influenza pandemic occur.

First activity: Map the landscape

In order to assist in policy-making and to provide WHO regions, countries, donors and the vaccine industry with relevant information, WHO has undertaken a survey to "map the landscape" to assess current vaccine use, future planned increases in seasonal influenza uptake, and possible pandemic vaccine requests from countries.

Second activity: Estimate disease burden

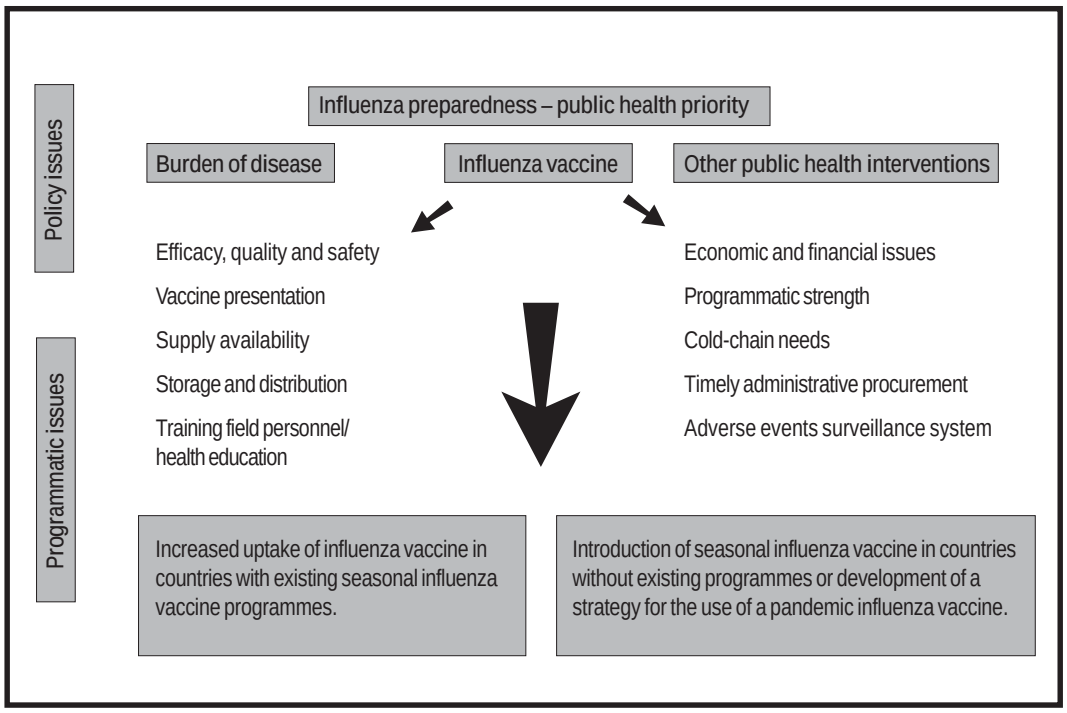
The lack of disease-burden data in many countries is a barrier to making evidence-based decisions on the introduction of seasonal influenza vaccine. Effective tools need to be developed to assist countries to estimate current influenza disease burden and evaluate the cost–effectiveness of seasonal influenza immunization.

Third activity: Develop regional plans of action

In consultation with its national governments, each WHO region should prepare a plan for influenza vaccination. National immunization programmes (NIPs) should subsequently incorporate this plan, in all its aspects, to design, implement and monitor

their seasonal influenza vaccine programmes. This process will help address the impediments currently faced by most countries: limited vaccine supply, shortage of financial and human resources, weak policies and infrastructure, and absence of disease-burden data to inform decision-making. In resource-poor countries the development of a plan will allow management to assess the required inputs and to analyse the cost–effectiveness. WHO will provide technical assistance to countries for the analysis of the appropriate influenza vaccination components of their national immunization programmes.

Overview of policy and programmatic issues for influenza vaccines



Endorsement of the regional plans by countries and regional advisory bodies will provide the policy basis for implementation. As stated in the *WHO–UNICEF Global Immunization Vision and Strategy* (GIVS)*, NIPs will provide the framework for implementing strong seasonal influenza vaccine programmes.

The strategic information on vaccine demand derived from NIPs will be important for vaccine manufacturers. It will provide a basis on which the industry can evaluate the investments required, including technology transfer, to be in position to meet the demand for seasonal vaccines. This approach will, furthermore, permit the creation of a larger infrastructure to increase vaccine supply.

* *WHO–UNICEF Global Immunization Vision and Strategy.* Geneva, World Health Organization, 2005 (WHO/IVB/05.05).

4.1.2 Strategy 2: Mobilize resources for the implementation of seasonal influenza vaccination programmes.

Activity: Mobilize resources for resource-constrained countries.

A number of countries may regard the introduction of seasonal vaccination into their NIPs as sound public health policy but be unable to afford the products because of competing public health priorities and limited management capacity. These are the major obstacles to successful implementation of yearly influenza vaccination programmes in developing countries. Nevertheless, even if the global community were to provide resources to purchase influenza vaccines in these countries, the resulting increase in demand might only be moderate – an estimated 100 million doses of seasonal vaccine. The development of regional plans will provide budget estimates for use in seeking support and discussions with donor agencies, foundations and governments. These countries will require additional resources to proceed with the introduction of seasonal influenza vaccination.

The possible costs associated with the activities described under point 4.1 – to develop an immunization policy to increase demand for seasonal vaccines – will require a minimum investment of US$ 300 million.

4.2 Increase influenza vaccine production-capacity

Objective

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

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

4.2.1 Strategy 1: Increase capacity for inactivated influenza vaccines.

First activity: Improve production yield of H5N1 viruses and immunogenicity of prototype H5N1 inactivated vaccine.

The most direct mechanism to make more doses available is to raise the production yield and immunogenicity of H5N1-based vaccines to levels similar to those regularly obtained for seasonal influenza vaccines. Resolving the current issue of low yield could, if successful, have a significant impact on the total number of vaccine doses manufactured. The current yield of 500 million doses per year could become 1.5 billion doses so, if two doses of vaccine were needed, 750 million persons could be vaccinated instead of 250 million.

Companies, researchers and institutes currently work independently of each other in attempting to increase production yields, without coordinated guidelines or a strategy to share their respective experiences. WHO plans to accelerate this search for practical solutions by creating a collaborative consortium of laboratories with the objective of developing better candidate prototype vaccine strains.

Second activity: Build new production facilities in developing and/or industrialized countries.

Establishing new production facilities will require a financial investment that is commensurate with the desired increase in vaccine supply. The major vaccine producers in industrialized countries already have plans to increase their production capacity by 280 million doses by 2009. These manufacturers may also consider further plant expansions as a result of market commitments from countries that introduce seasonal influenza programmes. Other options are to carefully assess the feasibility of transferring technology for egg-based or cell-culture production to potential new manufacturers, and to evaluate possible new vaccine suppliers in emerging industrial countries. Capital investment for the establishment of new production facilities for inactivated influenza vaccines has been estimated to be in the order of US$ 1.00 per dose.

Cost–effectiveness analysis should also be conducted on the feasibility of partial conversion of veterinary vaccine production facilities to produce human influenza vaccines.

In a pandemic a vaccine shortfall could lead to a public health crisis. Achieving the required production capacity to prevent a vaccine shortfall during a pandemic is critical. Countries may be required to pay for under-used capacity to assure that sufficient pandemic vaccines doses are produced within the required time frame.

4.2.2 Strategy 2: Explore formulations of influenza vaccine other than those commonly used for seasonal vaccination.

First activity: Conduct clinical trials with alum and MF-59 adjuvanted vaccine.

Clinical trials to evaluate H5N1 influenza vaccines – formulated with adjuvants that have a proven safety record in humans and are already used for other licensed vaccines – may allow for the selection of vaccines with reduced antigen content. Within the next two years, several vaccine candidates formulated with MF-59 or alum adjuvants will be assessed in clinical trials. The outcome of these trials will provide data to evaluate the impact that using these adjuvants could have on future capacity. As an example, if one of these adjuvants were to allow for a decrease of, for example 2 to 5 parts less antigen content, this would allow for the production of 1000 to 2500 million doses – as compared to 500 million doses currently. Not taking into account any potential yield improvement, 500 to 1250 million people could then be fully vaccinated with two doses of vaccine. Coordinated funding for clinical trials will be required to accelerate the systematic and comparative evaluation of the different formulations currently under development.

Second activity: Explore the opportunity to scale-up production of live attenuated influenza vaccines.

There is preliminary evidence that live attenuated influenza vaccines (LAIVs) might be more effective than inactivated vaccines. A full review of the available data should be undertaken to evaluate: a) the safety – especially in patients with asthma, the immunocompromised, the very young and the elderly; b) protection against homologous virus and minor variants; and c) evidence of herd immunity through vaccination of children.

LAIVs may require less complex downstream processing so would be more appropriate for technology transfer. In addition, cell-culture derived production technology for LAIV is under development. LAIVs have a lower unit cost and higher production yield, estimated to be 10 times higher than for inactivated vaccines. Furthermore, the capital investment for LAIVs is lower than for inactivated vaccines – estimated to be approximately US$ 0.1 per dose. This may be attractive for some manufacturers. Veterinary vaccine plants, which use specific pathogen-free (SPF) eggs to produce influenza vaccines for poultry, could potentially undertake production. The vaccine industry should explore the possibility of establishing agreements between companies (including veterinary vaccine companies) to increase production or to transfer the LAIV technology.

Third activity: Further evaluate whole-virus based inactivated vaccines.

To further assess the advantages of this option, comparative clinical trials using split- and whole-virus vaccine formulations, together with data on comparative production yields, are needed. It is generally accepted that whole-virus vaccines are more immunogenic and may provide higher protection with less antigen content. However, the safety of these vaccines needs to be carefully documented. It is estimated that conversion to whole-virus vaccine production could increase vaccine availability by 10–50%. This would bring current production from 500 million doses to a maximum of 750 million. In addition, superior immunogenicity of whole-virus vaccines as compared to split-virus vaccines may allow for substantial antigen sparing and increase the number of doses available. While some of the aforementioned activities will be undertaken by the vaccine industry and the research community, funds may still be needed to support additional research efforts.

4.2.3 Strategy 3: Assessment of alternative delivery routes.

Activity: Test the intradermal route of administration.

Studies with other vaccines (e.g. rabies vaccine) show that lower doses are needed when a vaccine is administered intradermally. Investment is needed to further develop and license new delivery devices, such as jet injectors or single disposable devices. Clinical trials will be needed to assess the suitability of the intradermal route to deliver influenza vaccine. Using the intradermal route could have a significant impact on vaccine use: possibly 2–5 times more vaccine could become available – that is, 1000 million doses as compared to the current estimate of 500 million doses per year. WHO is working with partners to evaluate this approach.

The possible costs associated with the activities described under point 4.2 – to increase influenza vaccine production-capacity – require an investment of a minimum of US$ 2–9 billion.

4.3 Promote research and development for new influenza vaccines

Objective

Develop more effective influenza vaccines using new technologies.

Vaccine that requires only one dose to provide protection to naive unprimed individuals would be more effective in controlling an influenza pandemic. The ideal product profile is a vaccine which:

- is safe and highly protective, preferably in all target groups, including infants, the elderly, pregnant women and immunosuppressed individuals;
- is easily and inexpensively produced on a large scale;
- is effective – preferably with a low dose of antigen;
- is delivered, ideally, as a single dose,
- is thermostable; and
- offers protection for a minimum duration of one year, including protection against antigenically drifted viruses.

4.3.1 Strategy 1: Enhance protective efficacy and immunogenicity of existing vaccine types.

First activity: Evaluate novel adjuvants.

Currently, only two adjuvants are included in vaccines licensed for human use. Newer adjuvant molecules such as CpGs should nevertheless be explored with influenza vaccines because they may provide higher immunogenicity and thereby allow antigen to be spared. In addition, they may assist in broadening the immune response and provide protection against drifted variants of influenza virus with vaccine designed to be cross protective.

Second activity: Assess the molecular basis of immunogenicity to design more potent vaccines.

Modern approaches, including reverse genetics, should be used to study the molecular basis of the immunogenicity of HA in order to discover approaches to develop more potent vaccines. This is a technically challenging research activity and may require extensive investment in the long term.

Third activity: Predict viral evolution.

To predict future viral evolution and enhance vaccine-strain selection, modelling is considered to be a promising long-term approach in developing vaccines based on the most appropriate virus strains.

4.3.2 Strategy 2: Develop novel vaccines that induce broad-spectrum and long-lasting immune responses.

First activity: Develop new generation vaccines.

Vaccines that induce broad immunity would protect against viruses with antigenically distinct HA molecules. This should allow for the preparation of vaccine lots in advance and would simplify the logistics of vaccine production. The development of broadly protective vaccines may also result in improved efficacy in certain high-risk groups, such as the elderly. There are several approaches that could be used for the development of such vaccines. Production of viral immunogens (HA, NA, M2, M1, NP, etc.) could be improved using baculovirus or other expression systems. Novel concepts like recombinant sub-unit, viral vectored, DNA vaccines, and virus-like particles (VLP) may offer advantages in production capacity and/or immunogenicity. These options would lead to greater availability of vaccine at lower cost.

Second activity: Determine potential benefits of immune priming.

Administration of a single dose of a pre-pandemic vaccine, such as an H5N1, to prime for an anamnestic response may allow more rapid induction of immunity with a single dose of a pandemic vaccine. Research specifically designed to address this issue needs to be conducted.

4.3.3 Strategy 3: Improve evaluation of vaccine performance.

First activity: Define correlates of protection.

Valid animal models that reliably predict the performance of candidate influenza vaccines in humans are crucial for future vaccine development. Immunological correlates of protection in humans need to be developed; this will provide information to guide vaccine development and enable registration of vaccines based on comparative immunological data. To accomplish this, public funding and collaborative work among regulatory agencies and vaccine producers is required.

Second activity: Standardize immunogenicity assays.

Basic requirements for the evaluation of new vaccine candidates are to: a) develop standardized protocols, b) establish reference laboratories, and c) ensure the expression of antibody results in international units. Standardization will facilitate comparison of product performance. WHO, the Expert Committee on Biological Standardization (ECBS), national control laboratories, and national regulatory agencies will provide guidance and standards.

The possible costs associated with the activities described under point 4.3 – research and development for new influenza vaccines – will require an investment of several hundred million US dollars over an extended period of time.

5. Conclusion

The goal of the Global Vaccine Action Plan is to increase capacity for the production of influenza pandemic vaccine in order to reduce the anticipated gap between potential vaccine demand and supply during a pandemic.

The success of this Action Plan depends on collaborative effort and the engagement of countries, the vaccine industry, the research community and donors to sustain their commitment over a period of 5–10 years.

Action must start immediately if the world is to be prepared in the shortest possible time for an influenza pandemic. Implementation of this Action Plan will require decisive leadership – combined with active and effective partnership and funding for the activities outlined. The Plan requires governments to commit to a large investment – in the range of perhaps 3–10 billion US dollars.

Finally, an international task force should be constituted to oversee the implementation of the Plan and to provide countries with timely information on accomplishments and/or impediments to increasing production capacity for a pandemic vaccine. The task force should meet as often as necessary and include representatives from countries, industry and the research community.

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The World Health Organization has managed cooperation with its Member States and provided technical support in the field of vaccine-preventable diseases since 1975. In 2003, the office carrying out this function was renamed the WHO Department of Immunization, Vaccines and Biologicals.

The Department's goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. Work towards this goal can be visualized as occurring along a continuum. The range of activities spans from research, development and evaluation of vaccines to implementation and evaluation of immunization programmes in countries.

WHO facilitates and coordinates research and development on new vaccines and immunization-related technologies for viral, bacterial and parasitic diseases. Existing life-saving vaccines are further improved and new vaccines targeted at public health crises, such as HIV/AIDS and SARS, are discovered and tested (Initiative for Vaccine Research).

The quality and safety of vaccines and other biological medicines is ensured through the development and establishment of global norms and standards (Quality Assurance and Safety of Biologicals).

The evaluation of the impact of vaccine-preventable diseases informs decisions to introduce new vaccines. Optimal strategies and activities for reducing morbidity and mortality through the use of vaccines are implemented (Vaccine Assessment and Monitoring).

Efforts are directed towards reducing financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies (Access to Technologies).

Under the guidance of its Member States, WHO, in conjunction with outside world experts, develops and promotes policies and strategies to maximize the use and delivery of vaccines of public health importance. Countries are supported so that they acquire the technical and managerial skills, competence and infrastructure needed to achieve disease control and/or elimination and eradication objectives (Expanded Programme on Immunization).

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