TECHNICAL STUDIES UNDER RESOLUTION WHA63.1

Final document

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EXECUTIVE SUMMARY

This document is a response to a request from the World Health Assembly in the context of the Open-Ended Working Group on Pandemic Influenza Preparedness. It provides Member States with technical information to assist them in reaching final agreement on the Framework for the sharing of influenza viruses and access to vaccines and other benefits. The study covers three technical areas of importance for increasing global preparedness for pandemic influenza: (i) laboratory and surveillance capacities of countries, (ii) global influenza vaccine production capacity and (iii) access to vaccines and other necessary pandemic supplies by countries without such access. With a common approach, the current state of global capacity is reviewed for each technical area, gaps in those capacities are identified, and targets to reduce the gaps are proposed. Options and associated costs for achieving the targets are then presented. The final section of the study addresses sustainable financing mechanisms to meet the estimated costs. By identifying gaps and assessing the costs for reducing those gaps, concrete funding needs emerge, allowing a realistic assessment of financing requirements over time.

Parts of the study, covering laboratory and surveillance capacity, vaccine production and access to vaccines, were presented to Member States in December 2010 as Preliminary Findings. The entire study has now been edited, resulting in certain editorial and typographical changes in the text and footnotes; however, no substantive changes have been made to the Preliminary Findings that were available in December 2010 or to the supporting evidence.

As indicated in the Preliminary Findings, two new sections have now been added: a discussion of antiviral medicines and diagnostic tests. Likewise the section on financing mechanisms was updated with data on antiviral medicines. Annexes for each section are presented in the last section of this document.

Summary of findings

1. Laboratory and surveillance capacity-building

Globally, influenza-specific laboratory and surveillance capacity in many developing countries needs to be strengthened. Low capacity is most frequently found in three WHO regions: the African, Eastern Mediterranean and South-East Asia regions. Over the next five years, increasing surveillance and laboratory capacity in several countries in these regions will require specific, targeted activities. Depending on the number of countries in which work is carried out, the total estimated one-time start-up cost will range from US$ 10.4 million to US$ 44.9 million, and the annual cost thereafter will be US$ 32.2–101 million per year.

2. Expanding global influenza vaccine production capacity

The global production capacity of pandemic influenza vaccine is currently approximately 876 million doses per year. It is based on demand and on the capacity to produce seasonal influenza vaccine. If there are no interventions, production is anticipated to increase to approximately 1.8 billion doses per year in 2015, due mainly to investments by multinational companies and the governments of high-income countries.

Many complementary strategies may be used to increase global production capacity and global access to pandemic vaccines. A coordinated approach could result in increased pandemic vaccine production, which would significantly increase access to such vaccines by countries that currently do not have

access. The strategies that could be considered include increasing the uptake of seasonal vaccine (estimated at US$ 280 million to US$ 3700 million); shifting to higher yield technologies, such as the production of live attenuated vaccine (estimated at US$ 450 million) and use of adjuvants (estimated at US$ 230 million to US$ 420 million); and maintaining or building new vaccine production capacity (estimated at US$ 125 million to US$ 490 million).

3. Increasing access, affordability and effective deployment of vaccines, antiviral agents, diagnostics and other materials for pandemic preparedness and response

Vaccines

One constraint to real-time access to pandemic influenza vaccines by countries without access is a lack of supply, because of pre-purchase agreements held by other countries. The main mechanism to address this constraint is to establish pre-purchase agreements on behalf of countries that do not have access, either by expanding existing country agreements or through new agreements. The estimated costs of this option generally include a reservation fee (estimated at US$ 0.5/dose), to be paid annually to the manufacturer, and purchase and deployment of vaccine at the time of a pandemic (estimated at US$ 4.2/dose). Both costs will vary according to the number of doses reserved. On the basis of the target groups identified by the WHO Strategic Advisory Group of Experts on immunization, three potential groups of people were identified who should be targeted for vaccination (ranging from 8 million to 334 million people); the costs were forecasted from current information on prices. The costs of pre-purchase agreements range from US$ 10 million to US$ 335 million for reserve fees and an estimated US$ 70 million to US$ 2795 million at the time of purchase.

Antiviral medicines

In contrast to vaccines, antiviral drugs for pandemic influenza could be made available at the start of a pandemic. Seasonal demand for influenza antiviral drugs, is, however, usually low, especially in lower income countries; therefore, stocks of antiviral medicines may not be immediately available. Both price and availability are determined by market conditions in higher-income countries. WHO has highlighted two options:

- procurement and maintenance of an antiviral agent stockpile to meet immediate needs at the time of the emergence of a pandemic and

- establishment of agreements with manufacturers and concomitant financing to purchase antiviral medicines to sustain the public health response throughout a pandemic.

As for vaccines, the cost of these options will vary with the number of countries, populations and treatment courses (estimated range of US$ 82 million to US$ 763 million).

Diagnostic reagents and test kits

In a pandemic, diagnostic tests are used mainly to identify and confirm outbreaks of pandemic influenza and to guide clinical decisions on treatment. The network of National Influenza Centre laboratories and Collaborating Centres in the WHO Global Influenza Surveillance Network represents the main mechanism by which countries identify outbreaks and monitor influenza activity in their countries and regions. Some laboratories in the Network provide critical reagents and set standards under their WHO terms of reference. The costs associated with this activity are included in the regular recurrent costs of WHO Collaborating Centres.

In the clinical setting, some tests are conducted with so-called "rapid point of care diagnostic kits" for influenza. These tests have the advantage that they can be performed without a laboratory; however, they must be purchased commercially, their price varies, they generally have low sensitivity, and they provide less specific information than laboratory tests.

Sustainable financing, solidarity mechanisms and other approaches

To the extent possible, the estimated costs were broken down into "units" to allow development of implementable "packages" and estimated yearly financial requirements. With this approach, "packages" of activities and their estimated costs were formulated, comprising elements from each of the three technical areas (laboratory and surveillance capacity, vaccine production capacity, and access). Costs were estimated for 5- and 10-year periods. Existing financing mechanisms and tools are described, and some are applied to show their potential use in financing these activities. Various types of financing will be needed to suit various implementation and funding needs. A separate document provides further details of potential financing mechanisms for concrete packages of benefits.

I. BACKGROUND

In finalizing the "Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and Other Benefits",[1] the Sixty-third World Health Assembly, in resolution WHA63.1, requested the Director-General, inter alia, to continue to work with Member States and relevant regional economic integration organizations and to undertake technical consultations and studies as necessary in order to support the work of the Open-Ended Working Group in reaching a final agreement.

The Working Group listed the following areas for further technical consideration and study, drawing on lessons learnt from the pandemic (H1N1) 2009 and on-going outbreaks of influenza H5N1[2]:

> current activity, financing and unmet financial and other needs in relation to:
>
> (a) laboratory and surveillance capacity-building, including that required under the International Health Regulations (2005);
>
> (b) expanding global influenza vaccine production capacity, including under the Global Action Plan to Increase Supply of Pandemic Influenza Vaccines (GAP); and
>
> (c) increasing access, affordability and effective deployment of vaccines, antiviral agents, diagnostics and other materials for pandemic preparedness and response;
>
> possible sustainable financing and solidarity mechanisms and other approaches to address the needs identified in subparagraph (a) above.

Process

Work to establish the terms of reference for studies, based on the report of the Open-Ended Working Group (document A63/48), began immediately after the Sixty-third World Health Assembly, in May 2010. The terms of reference were finalized and sent to Member States on 22 July 2010. Given the breadth of the areas under study and the limited human and financial resources of the Organization to carry out the full studies, the Secretariat sought external support. The Bill & Melinda Gates Foundation provided support through a contract with McKinsey & Company, which was selected on the basis of its broad expertise in public health, financing, health economics and influenza vaccines; its ability to start work on the project quickly; and its global team.

On the basis of the report of the Working Group and the terms of reference, the WHO Secretariat and the McKinsey team began to develop the outline of the study in mid-August 2010. First, the parameters of the study and the timetable for delivery were addressed, and, in view of the broad scope of the studies, a phased approach was agreed, so that preliminary findings could be shared at the meeting of the Working Group in December 2010 and the full study would be completed before the Sixty-fourth World Health Assembly.

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[1] As contained in document A62/5 Add.1.

[2] See document A63/48, Annex, paragraph 7.

A working outline of the study was provided to Member States on 20 October 2010 in the six official languages of WHO.[1] On 10 December 2010, the preliminary findings of the study were presented, including the current state of each technical area, several possible targets, options and costs and possible funding scenarios.[2] As stated in the working outline, the preliminary findings focused on vaccines in the section on access, affordability and effective deployment. The study of other commodities was deferred to this final document, which contains the full study, as requested by Member States.

Data and sources

Given the short time available for the study, existing data were used when possible to determine potential targets and options. New data were generated in order to project pandemic vaccine capacity and identify barriers to access. Lessons learnt from the pandemic (H1N1) 2009 and on-going outbreaks of influenza H5N1 were considered when appropriate. All the costs are estimates, from a range of sources, including publicly available information and interviews with manufacturers and other experts.

II. METHOD OF WORK, APPROACH TO THE TECHNICAL STUDIES AND ASSUMPTIONS

Method of Work

The starting point for the studies was guidance and information contained in WHO documents A62/5 Add.1, A63/48 and A/PIP/IGM/13 Annex 4.[3] A fact-based approach was used, based on data in WHO reports and other publicly available documents. All country-specific data were aggregated. Consistent with the request of the Health Assembly in resolution WHA63.1 and other relevant resolutions, the Director-General consulted stakeholders to ensure the appropriateness and feasibility of the proposed targets and options.

As announced in the preliminary findings, this document contains annexes for each section. All data and sources are identified in either the main sections of the report or the relevant annex.

Approach to the technical studies

Studies in each technical area systematically addressed the following areas:

current state: description of current capacity and capacity gaps at country level;

targets: potential targets for improving pandemic preparedness in the next five years, all of which are scientifically sound, technically feasible, quantified and measurable;

strategic options for reaching the targets: activities for achieving each potential target; and

[1] See http://apps.who.int/gb/pip/e/E_Pip_oewg2.html.

[2] See http://apps.who.int/gb/pip/pdf_files/OEWG2/PIP_OEWG_Preliminary-findings-en.pdf.

[3] All documents are available at http://apps.who.int/gb/pip/e/E_Pip_oewg2.html.

costing: an estimate of costs for each option identified.

The "financing section" addresses the current state of influenza funding, scenarios for future funding needs and potential funding sources and mechanisms to meet those needs.

Assumptions

No two influenza pandemics are alike. The appropriate assumptions were used to determine a potential target, option or model. All the assumptions are clearly described.

III. LABORATORY AND SURVEILLANCE CAPACITY-BUILDING

Goal

To enable Member States and the global community to detect, isolate and characterize influenza viruses appropriately, in order to prevent and respond to a pandemic event, including production of vaccine.[1]

This goal is consistent with and supports the notification, reporting and verification requirements under the International Health Regulations (2005) (IHR).

Approach, assumptions, data sources and limitations

Approach

The current laboratory and surveillance capacities of Member States were assessed from three influenza-specific elements in the "Core capacity requirements for surveillance and response", set out in Annex 1 of the International Health Regulations (2005) (Figure 1):

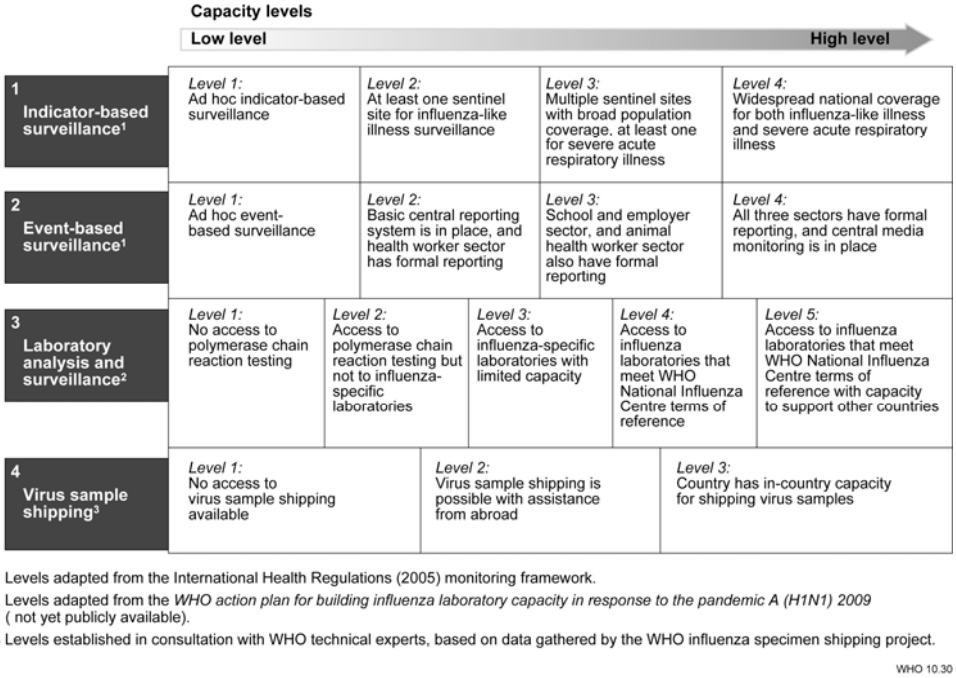
indicator-based surveillance: routine surveillance for influenza-related disease conducted through the health-care system;

event-based surveillance: early detection of notable events (like outbreaks) through various channels, particularly health-care workers, animal health professionals, schools, employers and the media; and

laboratory analysis and surveillance: analysis of clinical specimens to characterize virus subtype, genetic sequence and antigenic and other viral properties, including shipping virus samples from national to regional and global facilities (e.g. to WHO H5 Reference Laboratories and WHO Collaborating Centres).

[1] Document A62/5 Add.1, section 6.6, Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits.

Figure 1. Laboratory and surveillance capacity elements and levels



1 Levels adapted from the International Health Regulations (2005) monitoring framework.

2 Levels adapted from the *WHO action plan for building influenza laboratory capacity in response to the pandemic A (H1N1) 2009* (not yet publicly available).

3 Levels established in consultation with WHO technical experts, based on data gathered by the WHO influenza specimen shipping project.

WHO 10.30

Assumptions

The estimated costs in indicator- and event-based surveillance are the incremental costs over and above current surveillance spending. The estimates do not include the cost of strengthening non-influenza-specific capacity as required under the International Health Regulations (2005).

In the event of a pandemic, the annual operating costs for laboratories and surveillance sites will be substantially higher because of increased activity.[1] The estimated costs reflect this increase.

Data sources and limitations

Indicator-based surveillance and event-based surveillance:

- Self-reported, non-influenza-specific Member State data reported to WHO pursuant to Annex 1 of the International Health Regulations (2005) (data not publicly available).

- Capacity analyses based on the 116 Member State responses (regionally representative) to a survey on core capacities sent by WHO to all Member States received as at October 2010.[2]

[1] For example, during the pandemic (H1N1) 2009, laboratories in many countries processed more than five times the usual volume of virus samples. In addition, laboratory and surveillance systems reported hiring additional staff and reassigning staff working in other disease areas, thus increasing the costs for influenza.

[2] The number of countries that responded from each WHO region were: Africa (23), The Americas (17), Eastern Mediterranean (17), Europe (29), South-East Asia (10), and the Western Pacific (20).

Laboratory analysis and surveillance and virus sample shipping:

- Data collected by WHO for development of the "WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009" (draft document not yet publicly available).

- 2009 analyses conducted by the WHO influenza specimen shipping project, based on a survey of courier companies and expert interviews. Findings include capacity linked to the WHO influenza specimen shipping project only.

Data sources for estimated costs

- All sources listed above.

- Benchmark costs established through the WHO-CHOICE project[1] and other global costing projects.[2]

- Experience in capacity building gained through the Global Polio Eradication Initiative.

- Consultation with WHO experts in laboratory costs at global, regional and national levels.

- Costs for summary calculations based on averages for low- and middle- income countries.

Detailed methodologies for each cost component can be found in Annex X.

Indicator-based surveillance

Capacity is at a low level (i.e. capacity level 1 or 2; see Figure 1)[3] in 48% of countries. Surveillance systems at these levels do not meet minimal draft WHO definitions[4] for surveillance of influenza-like illness or severe acute respiratory illness, those contained in influenza surveillance guidance documents produced by the regional offices for the Americas, Europe or the Western Pacific[5] or the guidelines issued by WHO during the pandemic (H1N1) 2009.[6]

Low capacity is found primarily in middle-income and smaller countries (with a population of less than 1 million).

[1] See http://www.who.int/choice/en/ (accessed on 19 November 2010).

[2] See http://www.who.int/bulletin/volumes/86/1/07-045096.pdf (accessed on 19 November 2010).

[3] See Figure 1 for definitions of capacity levels.

[4] Forthcoming from the WHO technical working group on influenza surveillance.

[5] e.g. *WHO Regional Office for Europe guidance for influenza surveillance in humans*. Copenhagen, WHO Regional Office for Europe, 2009. Available at: http://www.euro.who.int/__data/assets/pdf_file/0020/90443/E92738.pdf, (accessed 7 November 2010).

[6] See http://www.who.int/csr/resources/publications/swineflu/surveillance/en/index.html (accessed 19 November 2010).

Event-based surveillance

Capacity is at a low level (i.e. capacity level 1 or 2) in 84% of countries.

Laboratory analysis and surveillance[1]

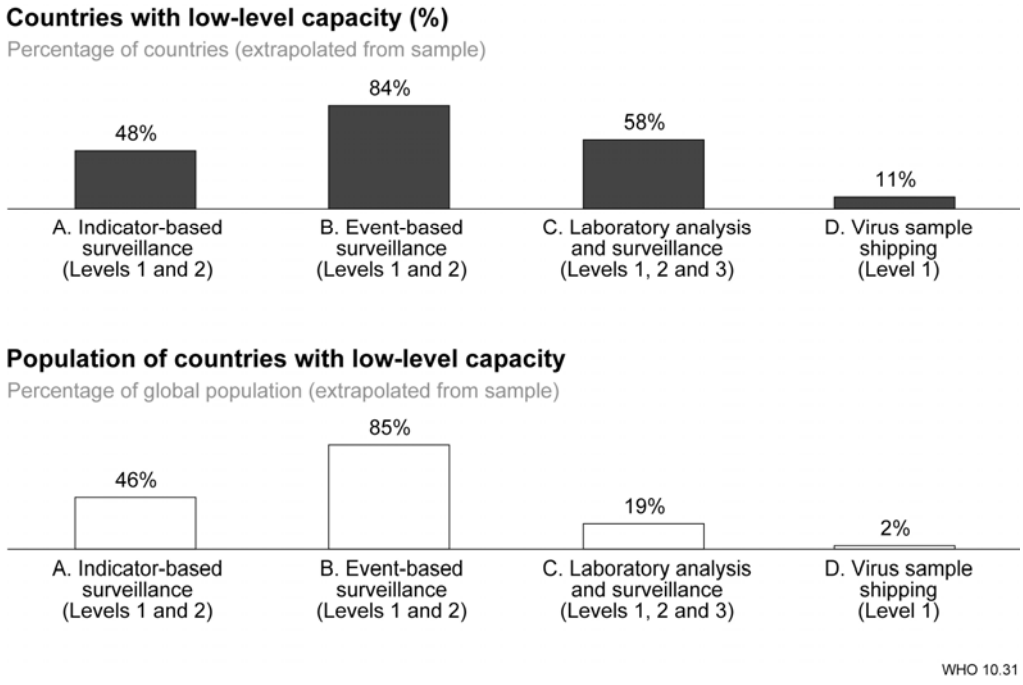
Capacity is low in 114 countries. These countries do not have access to a laboratory with the capacity to type or subtype or isolate influenza viruses or to integrate laboratory data into influenza surveillance.

Lower laboratory capacity is common among smaller countries (with a population of less than 1 million), in low- and lower–middle-income countries and in the African and Eastern Mediterranean regions.

Virus sample shipping

Twenty-one countries, representing 2% of the global population, currently cannot ship virus samples through the WHO influenza specimen shipping project or other means. Low shipping capacity is most common in the Western Pacific Region, in small-island countries and in countries with a population of less than 1 million, and in the Eastern Mediterranean Region.

Figure 2. Current capacity levels for laboratory analysis and surveillance



[1] A detailed discussion of laboratory methods and reagents is provided in section V.

Potential targets and strategic options

Proposed potential targets aim to ensure that all Member States strengthen their influenza-specific capacity for epidemiological indicator- and event-based surveillance, laboratory analysis and surveillance and virus sample shipping and their capacity for information-sharing in each of these areas. Two options are proposed for achieving the potential targets:

- build capacity at the national level in all countries;
- build capacity at the regional and/or sub-regional levels.

(Detailed costs for each strategic option are shown in Annex 1)

Indicator-based surveillance

Target 1: 100% of countries at capacity level 1 or 2 reach capacity level 3 (develop surveillance, including multiple sentinel sites for influenza-like illness and at least one sentinel site for severe acute respiratory illness or an equivalent reporting system)

Target 2:

- 100% of countries at capacity level 1 or 2 reach capacity level 3 (develop surveillance, including multiple sentinel sites for influenza-like illness and at least one sentinel site for severe acute respiratory illness or an equivalent reporting system), and
- at least 20% of countries in each region reach capacity level 4 (develop a widespread national surveillance system for influenza-like illness and severe acute respiratory illness)

Target 3:

- 100% of countries at capacity level 1 or 2 reach capacity level 3 (develop surveillance, including multiple sentinel sites for influenza-like illness and at least one sentinel site for severe acute respiratory illness or an equivalent reporting system), and
- at least 40% of countries in each region reach capacity level 4 (develop a widespread national surveillance systems for influenza-like illness and severe acute respiratory illness)

Strategic option 1: Support capacity-building in all countries.

- Build or expand the sentinel surveillance system for influenza-like illness by training health workers and providing equipment and salaries. The average indicative costs per sentinel site would be:
  - US$ 6000–6500 for a one-time set-up and
  - US$ 6400–6900 annual recurring costs.

- Build or expand the sentinel surveillance system for severe acute respiratory illness by training health workers and providing equipment and salaries. Existing sites for influenza-like illness could be upgraded to sites for severe acute respiratory illness. The average indicative costs per site would be:

  - US$ 1700–2000 for a one-time set-up (in addition to the costs of setting up a site for influenza-like illness) and

  - US$ 300–500 annual recurring costs (in addition to the annual costs of a site for influenza-like illness).

- Build central data analysis capacity, including equipment, training and salaries for epidemiologists. The indicative cost of building central data analysis capacity would be:

  - US$ 10 000–14 000 per country for a one-time set-up and

  - US$ 35 000–45 000 per country annual recurring costs.

  The costs for technical assistance would be US$ 6000–40 000, depending on local costs and the duration of assistance.

Strategic option 2: Support capacity-building in larger countries (i.e. with a population of more than 1 million) and support access of smaller countries to external capacity (e.g. neighbouring countries or regional networks).

- In all countries, build or expand sentinel surveillance networks for influenza-like illness and severe acute respiratory illness, as described in strategic option 1.

- In larger countries lacking such capacity, build central data analysis capacity, as described above.

- For smaller countries, facilitate connections to regional networks by building reporting infrastructure at sentinel sites. The indicative costs for these countries would include those for influenza-like illness sites, severe acute respiratory illness sites and technical assistance, as detailed above.

Costs

The costs of achieving targets 1, 2 and 3 (Table 1) are based on average costs in low- and middle-income countries. They are additional to current spending on surveillance and include one-time costs associated with initial capacity-building and annual recurrent costs estimated for both a non-pandemic and a pandemic year. The estimates do not include the costs of building non-influenza-specific capacity under the International Health Regulations (2005).

The estimated costs for setting-up a full, stand-alone influenza surveillance system (with both indicator-based and event-based surveillance) would be US$ 8000–30 000 per 1 million population, with annual recurring costs for running and maintenance of US$ 5000–20 000 per 1 million population.

Table 1. Costs for indicator-based surveillance

Target	Strategic option	Set-up costs (US$ million)	Annual recurring costs (US$ million)	
			Non-pandemic year	Pandemic year
1. All countries reach capacity level 3.	1	4.4–6.6	9.8–14.7	30–74
	2	4.4–6.5	9.8–14.6	30–74
2. All countries reach capacity level 3, and at least 20% reach capacity level 4.	1	4.6–6.8	9.9–14.9	30–74
	2	4.5–6.8	9.9–14.8	30–74
3. All countries reach capacity level 3, and at least 40% reach capacity level 4.	1	6.8–10.3	12–17.9	30–74
	2	6.8–10.2	11.9–17.9	30–74

Event-based surveillance

Target 1:

- 100% of countries currently at capacity level 1 reach capacity level 2 (basic central infrastructure and regular reporting of influenza-related unusual events in humans by health workers) and

- 50% of countries in each region reach capacity level 3 (ensure regular reporting from all three main sectors: animal health, human health, and schools and employers).

Target 2: 100% of countries currently at capacity level 1 or 2 reach capacity level 3 (regular reporting from all of three main sectors: animal health, human health, and schools and employers).

Target 3:

- 100% of countries currently at capacity level 1 or 2 reach capacity level 3 (regular reporting from all three main sectors: animal health, human health, and schools and employers).

- At least 20% of countries in each region meet the requirements of capacity level 4 (regular reporting from all three main sectors and central media monitoring in place).

Strategic option 1: Support capacity-building in all countries.

- Build or support basic infrastructure for central reporting of unusual events by, for example, establishing a central telephone reporting "hotline". The estimated set-up and annual recurring costs are US$ 500–700 each.

- Increase awareness of unusual reportable influenza events by distributing educational materials to networks of health workers, schools, employers and animal health workers.

  - Estimated set-up costs, US$ 800–1200 per network per country

  - Annual recurring costs for distributing influenza-specific material:
    - US$ 0.5–1.0 per health worker per year,
    - US$ 800–1200 per 1 million population for schools and employers and
    - US$ 300–700 per 1 million population for animal health workers.
- Build central media monitoring infrastructure: salary and equipment for one media monitor.
  - Estimated set-up costs, US$ 6000–9000 per country and
  - Annual costs, US$ 10 000–50 000 per country.
- Technical assistance: US$ 2000–5000, depending on local costs and duration of technical assistance. The technical assistance would be additional to that for indicator-based surveillance.

Strategic option 2: Support capacity-building in larger countries (i.e. with a population of more than 1 million) and support access of smaller countries to external capacity (e.g. neighbouring countries or regional networks).

- For all countries, support increased awareness of reportable unusual influenza events (see strategic option 1).
- For large countries, support basic central infrastructure and media monitoring (see above).
- For small countries: set-up costs, US$ 2500–3500; annual recurring costs, US$ 7500–25 000 per country. These costs are additional to the costs of building and maintaining reporting networks (see strategic option 1).
- Technical assistance, US$ 2000–5000, depending on local costs and duration of assistance. The technical assistance would be additional to that for indicator-based surveillance.

Costs

The costs (Table 2) are additional to current spending on surveillance. The estimates do not include the costs of building non-influenza-specific capacity under the International Health Regulations (2005).

Table 2. Costs for events-based surveillance

Target	Strategic option	Set-up costs (US$ million)	Annual recurring costs (US$ million)	
			Non-pandemic year	Pandemic year
1. All countries reach capacity level 2, and at least 50% reach capacity level 3.	1	0.7–1.0	13.2–19.8	74–221
	2	0.6–1.0	13.2–19.8	74–221
2. All countries reach capacity level 3.	1	1.4–2.1	29.0–43.5	74–221
	2	1.4–2.1	29.0–43.5	74–221
3. All countries reach capacity level 3, and at least 20% reach capacity level 4.	1	2.0–3.0	29.4–44.1	74–221
	2	1.9–2.8	29.2–43.9	74–221

Laboratory analysis and surveillance

Target 1: 100% of countries currently at capacity level 1 or 2 reach capacity level 3 (access to an influenza laboratory with limited capacity for influenza virus subtype analysis and virus culture).

Target 2: 100% of countries currently at capacity level 1, 2 or 3 reach capacity level 4 (access to an influenza laboratory that meets the full terms of reference for a National Influenza Centre).

Target 3:

- 100% of countries currently at capacity level 1, 2 or 3 reach capacity level 4 (access to an influenza laboratory that meets the full terms of reference for a National Influenza Centre).
- At least 20% of countries in each region have a National Influenza Centre with capacity to support other States (i.e. meet capacity level 5).
- At least one WHO Collaborating Centre for Influenza exists per Region.

Strategic option 1: Build and/or support appropriate laboratory capacity to achieve recognition as a National Influenza Centre and ensure global-level support from WHO Collaborating Centres.

- Support for salaries and training for technical and administrative staff: indicative set-up cost, US$ 27 000–76 000 per country
- Annual recurrent costs, US$ 21 000–57 000
    - Support for equipment and maintenance:
        - Set-up costs: US$ 110 000–134 000
        - Annual recurrent costs, US$ 33 000–40 000

- Support for operating expenses, including utilities, telephone, Internet and transport: annual recurrent costs, US$ 24 000–36 000

- Reagents and other material required for sample collection and analysis supplied by WHO collaborating centres: estimated annual cost, US$ 81 000–99 000

- Global coordination of virological surveillance and timely analysis of surveillance information (WHO Network): estimated annual global cost, US$ 6–8 million.

Strategic option 2:

- Build or support appropriate laboratory capacity and global-level support for larger countries (e.g. with a population of more than 1 million), and support of access of smaller countries to external capacity (e.g. neighbouring countries or regional networks).

- For larger countries, build and support appropriate laboratory capacity, as in strategic option 1.

- For smaller countries (i.e. with a population of less than 1 million), support access to regional laboratory capacity, including:

  - Set-up costs, US$ 19 000–34 000

  - Annual recurrent costs, US$ 17 000–25 000

- Global coordination of virological surveillance activities and timely analysis of surveillance information (WHO Network): estimated annual global cost, US$ 6–8 million.

The costs for laboratory analysis and surveillance are shown in Table 3.

Table 3. Costs of laboratory analysis and surveillance

Target	Strategic option	Set-up costs (US$ million)	Annual recurring costs (US$ million)	
			Non-pandemic year	Pandemic year
1. All countries reach capacity level 3.	1	7.0–10.5	10.4–15.6	56–169
	2	4.6–6.9	8.7–13.1	56–169
2. All countries reach capacity level 4.	1	9.5–14.3	17.0–25.5	56–169
	2	6.2–9.3	13.2–19.8	56–169
3. All countries reach capacity level 4, at least 20% reach capacity level 5, and at least one Collaborating Centre per region	1	20.4–30.5	25.3–38.0	56–169
	2	17.1–25.6	21.6–32.3	56–169

Virus sample shipping

Target 1: 100% of countries at capacity level 1 or 2 reach capacity level 3 (in-country access to trained shipping personnel, triple packaging, dry ice and courier routes).

Target 2: 100% of countries currently at capacity level 1 reach capacity level 2 (access to trained shipping personnel, triple packaging, dry ice and courier routes to Collaborating Centres, possibly with assistance from abroad).

Strategic option 1: Support in-country capacity-building for all countries; provide dry-ice equipment, shipping material and training for personnel in all countries without these elements (capacity level 2).

- Estimated set-up costs, US$ 6400–9600 per country
- Annual running costs, US$ 2600–3900 per country

International coordination of shipper training, materials and contracts with couriers for sample shipments, including global mobile shipping capacity (e.g. contract for access to helicopter, chartering capacity, United Nations peace-keeping facilities): annual cost, US$ 500 000.

Strategic option 2: Extend the WHO influenza specimen shipping project to all countries lacking adequate in-country shipping capacity.

- Estimated annual cost, US$ 6000–9000 per country per year (based on WHO influenza specimen shipping project costs)
- Internationally coordinated training, materials, courier routes: annual cost, US$ 400 000–600 000.

The costs for virus sample shipping are shown in Table 4.

Table 4. Costs for virus sample shipping

Target	Strategic option	Set-up costs (US$ million)	Annual recurring costs (US$ million)	
			Non-pandemic year	Pandemic year
1. All countries reach capacity level 2.	2	Not applicable	0.5–0.8	1.1–3.2
2. All countries reach capacity level 3.	1	0.8–1.1	0.7–1.0	1.1–3.2

IV. EXPANDING GLOBAL INFLUENZA VACCINE PRODUCTION CAPACITY

Goal

The goal is to increase global capacity to produce pandemic influenza vaccine to meet global needs during a pandemic.[1]

Definitions

Adjuvant: Substance that, when mixed with an antigen and injected with it, enhances the immunogenicity of that antigen.[2] When an adjuvant is added to a vaccine, it reduces the amount of antigen required for the vaccine to elicit an immune response. Use of adjuvants can therefore increase the number of doses of vaccine that can be derived from a specific quantity of antigen.

Antigen: A substance that binds to a specific antibody.[3] In a vaccine, a substance that induces an immune response.

Antiviral agent: An agent (e.g. chemical preparation, drug) that acts directly against a virus, destroying it or impeding its ability to replicate.[3] An antiviral agent does not use the human immune system and therefore does not confer any immunity against a disease.

Candidate vaccine virus: Any high-growth reassortant virus or any influenza reference virus or WHO-recommended influenza virus that is provided to influenza vaccine manufacturers for the purposes of developing a prototype pandemic, pre-pandemic, pandemic or seasonal vaccine.

Dosage or antigen dose: In the context of this document, the amount of antigen, expressed in micrograms, present in a vaccine.

Monovalent or trivalent vaccine: A vaccine specific for a single antigen (mono) or three (tri) antigens or organisms.[3] In the case of influenza, the seasonal trivalent vaccine confers protection against three different strains or types of influenza virus, while the monovalent pandemic vaccine confers protection only against the influenza virus strain that causes the pandemic.

Production yield: The amount of virus or antigen that can be obtained per unit of production (egg or millilitres of cell culture). In this document, yield is expressed as a percentage to indicate the yield of pandemic vaccine production relative to the yield of seasonal vaccine produced on the same technological platform.

Rationalization of production: Matching production capacity to expected demand; may result in reduced production capacity or halting of plans for expansion.

Time to first dose: The time between the availability to manufacturers of a candidate vaccine virus and release of the first vaccine dose to market.

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[1] *Global pandemic influenza action plan to increase vaccine supply*. Geneva, World Health Organization, 2006 (WHO/IVB 06.13).

[2] Goldsby RA, Kindt TJ, Osborne BA. *Kuby immunology*, 4th Ed. New York, W.H. Freeman & Co., 2000.

[3] Dorland's medical dictionary. 31st Ed., Amsterdam, Elsevier, 2007.

Vaccine: A suspension of attenuated (non-pathogenic), killed microorganisms or recombinant product administered for prevention, mitigation or treatment of infectious diseases.[1] Vaccines act by increasing the ability of the immune system to react to the disease agent.

Approach, assumptions, data sources and limitations

Approach

The expansion of manufacturing capacity to produce enough pandemic vaccine to meet global needs was quantified in a five-step process:

1. *Technology review*: All influenza vaccine manufacturing technologies were reviewed, both those currently used and those in development.

2. *Current seasonal capacity*: Data on production capacity in all known facilities for manufacturing seasonal influenza vaccine by any technology were collected and aggregated to obtain the total global level.

3. *Conversion of seasonal to pandemic capacity*: Seasonal capacity was converted to potential pandemic capacity, as the same physical infrastructure is used for producing the two vaccine types. A range of conversion scenarios was developed on the basis of a review of actual production and experience with H5N1, H1N1 and seasonal vaccines, with three conversion factors:

    - Time to first dose: The time between release to manufacturers of the candidate vaccine virus for pandemic vaccine development and production of the first dose of vaccine. A shorter time to first dose will increase the number of doses produced over a fixed production time.

    - Pandemic dosage: The dosage required for pandemic vaccination relative to that for seasonal vaccination. Lower dosages will increase the number of doses available.

    - Relative production yield: The production yield of pandemic vaccine relative to that of seasonal vaccine. A higher relative yield will increase the number of doses produced.

4. *Forecasted pandemic capacity*: Future seasonal capacity was estimated for the period 2010–2015 on the basis of the expansion plans of all manufacturers (in high-, middle- and low-income countries). Future capacity was converted to potential pandemic capacity with the conversion factors described in step 3.

5. *Targets and gap*: A range of capacity expansion targets was developed in two dimensions: the production capacity required and the time allowed to produce all doses after the candidate vaccine virus has been made available to manufacturers. These targets were then compared with expected capacity.

[1] Dorland's medical dictionary. 31st Ed., Amsterdam, Elsevier, 2007.

Assumptions

Seasonal influenza vaccines are trivalent, i.e. they contain components of three different strains of influenza virus.

Pandemic vaccines are monovalent, i.e. they contain components of a single strain of influenza virus, the pandemic strain.

Complete immunization against pandemic influenza is obtained after two doses of pandemic vaccine. Experience with H1N1 and H5N1 suggests that the number of doses required can vary: two doses of H5N1 vaccines appear to confer protection against infection,[1] while one dose of H1N1 vaccine was sufficient.[2] Given the unknown nature of pandemic viruses and the vaccines derived from them, two doses are the safest assumption for planning. All reported estimates of coverage would have to be doubled if only one dose is required (a population coverage of 15% with two doses would be 30% with one dose).

In the event of a pandemic, manufacturers can increase their production capacity by approximately 10%.[3]

Influenza vaccine being produced by new technologies that are at development stages earlier than phase II clinical trials will not reach the market by 2015.

New methods for testing potency and sterility will become available by 2014, which will reduce the time to first dose by approximately 2 weeks.

All seasonal capacity levels are based on a theoretical full year of production, comprising 8 weeks of regular maintenance and 44 weeks of production.

Pandemic vaccine capacity levels are based on a theoretical full year of production, comprising the time to first dose, when no vaccine is produced, followed by a number of weeks of production up to week 52 after the release of the candidate vaccine virus.

Data sources

Current and forecasted seasonal capacity estimates were based on:

- a survey of 28 manufacturers that currently produce or will start producing seasonal vaccine by 2015, with 14 in high-income countries and 14 in middle-income countries;

[1] Use of licensed H5N1 influenza vaccines in the interpandemic period: Report of the H5N1 SAGE Working Group to the April 2009 meeting of the Strategic Advisory Group of Experts http://www.who.int/immunization/sage/SAGE_H5N1_26Mayb.pdf.

[2] Girard M. et al. Report of the 6th meeting on the evaluation of pandemic influenza vaccines in clinical trials. World Health Organization, Geneva, Switzerland, 17–18 February 2010. *Vaccine*, 2010; 28:6811–6820.

[3] Wyman O, International Federation of Pharmaceutical Manufacturers Association (IFPMA), WHO. Influenza vaccine supply and demand – summary of findings. March 2009.

- interviews with 17 manufacturers (10 in high-income countries and 7 in low- and middle-income countries), representing approximately 90% of current capacity (26 manufacturers were contacted);
- interviews with health officials in high-income countries that provide funding for expansion of influenza vaccine production capacity;
- a survey of the status and plans of 11 vaccine manufacturers in middle-income countries that received capacity grants under the GAP; and
- consultations with experts in influenza vaccine manufacture.

Scenarios for conversion of seasonal to pandemic capacity were based on:

- a full review of the literature on influenza vaccine production[1,2,3,4,5,6]
- telephone interviews with 17 manufacturers (10 in high-income countries and 7 in middle-income countries); and
- consultations with experts in influenza vaccine manufacture.

Illustrative targets for pandemic capacity were defined on the basis of:

- the GAP,[7]
- results of pandemic outbreak modelling,[8,9,10]

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[1] Hickling J. & D'Hondt E. *A review of production technologies for influenza virus vaccines, and their suitability for deployment in developing countries for influenza pandemic preparedness.* WHO December 2006. http://www.who.int/vaccine_research/diseases/influenza/Flu_vacc_manuf_tech_report.pdf, (accessed 1 Feb 2011).

[2] President's Council of Advisors on Science and Technology (PCAST). *Report to the president on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza.* August 2010. http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST-Influenza-Vaccinology-Report.pdf.

[3] Collin N. & de Radigues X. Vaccine production capacity for seasonal and pandemic (H1N1) 2009 influenza. *Vaccine*, 2009; 27:5184–5186.

[4] Partridge J. & Kieny MP. Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009–2010 and comparison with previous estimates and global action plan targets. *Vaccine*, 2010; 28:4709–4712.

[5] Bernat J, International Federation of Pharmaceutical Manufacturers Association (IFPMA). H1N1 vaccine production: the industry perspective. Geneva Health Forum 19 April 2010. http://www.ifpma.org/fileadmin/webnews/2010/pdfs/20100419_IVS223-2_Geneva_Health_Forum_19_April_2010_v2.pdf.

[6] Uppsala Monitoring Centre. *A/H1N1 pandemic influenza vaccines*. www.who-umc.org. (accessed 24 February 2010).

[7] *Global pandemic influenza action plan to increase vaccine supply*. Geneva, World Health Organization (WHO/IVB 06.13).

[8] Goldstein E. et al. Reproductive numbers, epidemic spread and control in a community of households. *Mathematical Biosciences*, 2009; 221:11–25. http://www.ncbi.nlm.nih.gov/pubmed/19559715.

[9] Yang Y. et al. The transmissibility and control of pandemic influenza A (H1N1) virus. *Science*, 2009; 326:729–733.

[10] Germann T. et al. Mitigation strategies for pandemic influenza in the United States. *Proceedings of the National Academy of Sciences*, 2006; 103:5935–5940.

- actual coverage achieved for H1N1,[1] and
- a literature review on herd immunity.[2,3]

Limitations

The main limitation of this study is that capacity is forecast through 2015 on the basis of a survey of manufacturers about their expansion plans. Changes in seasonal demand and in pandemic preparedness by governments and international organizations could lead to a reduction of existing capacity or modification of expansion plans. Seasonal demand was not modelled in detail, nor was its impact on manufacturer expansion plans assessed.

Current state

Technology

Current technologies

Currently, three market-approved technologies are used for commercial production of influenza vaccines.

Egg-derived inactivated influenza vaccine (egg-IIV) was introduced in the 1940s. The vaccine is produced by growing influenza virus in hens" eggs, then purifying and inactivating it with a chemical agent. Three types of inactivated vaccine are manufactured: whole virus vaccines, split vaccines and subunit vaccines. Currently, at least 20 manufacturers produce egg-IIV vaccine, 12 in high-income countries and 8 in middle-income countries. At least 7 manufacturers are developing such vaccines, and all are in advanced stages of development (phase II or III) in middle-income countries (see Figure 3).

Cell-based inactivated influenza vaccine (cell-IIV, also referred to as "tissue culture-derived inactivated influenza vaccine") is produced in cell culture rather than in hens" eggs.[4] Three manufacturers in high-income countries and one in a middle-income country currently market cell-IIV vaccines. One manufacturer has a vaccine in early stages of development (preclinical or phase I clinical stage) (see Figure 3).

Egg-derived live attenuated influenza vaccine (egg-LAIV, also referred to as "cold-adapted influenza vaccine") contains live virus that is weakened so as not to cause influenza but still induce an immune response.[5] This technology has been used since 1954.[6] Egg-LAIV vaccines are produced by three

[1] [Anonymous]. Avec 60% de sa population vaccinée, la Suède figure loin devant la plupart des pays. *Le Monde*, 6 January 2010.

[2] Glezen WP Herd protection against influenza. *Journal of Clinical Virology*, 2006; 37:237–243.

[3] Asllani, I. & Ettkin A. (2010). A generic simulation model to manage a vaccination program. *Journal of Medical Systems*, Online First™, 2010; doi: 10.1007/s10916-009-9423-1.

[4] Novartis Vaccines press release, 5 November 2009. http://www.novartis.com/newsroom/media-releases/en/2009/1352736.shtml.

[5] MedImmune press release, 1 June 2009. http://pressroom.medimmune.com/press-releases/2009/06/01/hhs-awards-medimmune-contract-to-manufacture-live-attenuated-nasal-spray-vaccine-for-novel-influenza-a-h1n1/.

[6] http://www.who.int/vaccine_research/diseases/influenza/Roudenko.pdf.

manufacturers, one in a high-income and two in middle-income countries. One manufacturer has products in phase 2/3 stage (see Figure 3).

Inactivated influenza vaccines sometimes contain adjuvants, which vary from traditional adjuvants (alum) to newer, more potent ones (e.g. oil-in-water emulsions). Adjuvants can strongly affect the dosages required for pandemic production and confer potential cross-protection among strains.

Future technologies

Manufacturers and biotechnology companies are developing a number of new technologies[1] with the aim of making various improvements, including increased protection and more efficient production. Most of these products are in preclinical or phase I stages of development (Figure 3).

Cell-based live attenuated influenza vaccine (cell-LAIV) contains live virus grown in mammalian cells. The virus is weakened so that it does not cause influenza but produces an immune response. One known product is in phase 2/3 and 3 of development.

Recombinant haemagglutinin and viral-like particle influenza vaccines contain viral proteins, mainly haemagglutinin antigen, synthesized under the direction of molecularly cloned viral genes and expressed in various types of cell-based systems. While recombinant protein vaccines consist only of the purified antigen, viral-like particle vaccines include the antigen in a particle that resembles an actual influenza virus. Thirteen companies have products in development, including two in phase 2/3. One of these products is expected by the manufacturer to be licensed next year and the other by 2015. Several types of product in this category are under development.

- *Mammalian cell:* recombinant protein expressed in purified mammalian cells; two products are in early development phases.

- *Insect cells:* recombinant proteins expressed or viral-like particles generated in purified insect cells; four products are in development, with two in early development phases, one in phase 2 and one in phase 3 and undergoing regulatory approval.

- *Plant-based:* recombinant proteins expressed or viral-like particles generated in plants;[2] two products are in the preclinical or phase 1 development stage.

- *Other platforms:* recombinant proteins expressed or viral-like particles generated in other protein expression systems, such as bacterial, fungal or yeast cells; five products are in the preclinical or phase 1 stage of development.

"Universal" influenza vaccine consists of recombinant vaccine that protects against present and future strains of influenza virus by targeting the parts of the virus that do not mutate (e.g. stable elements of the haemagglutinin protein). Seven products are in early stages of development.

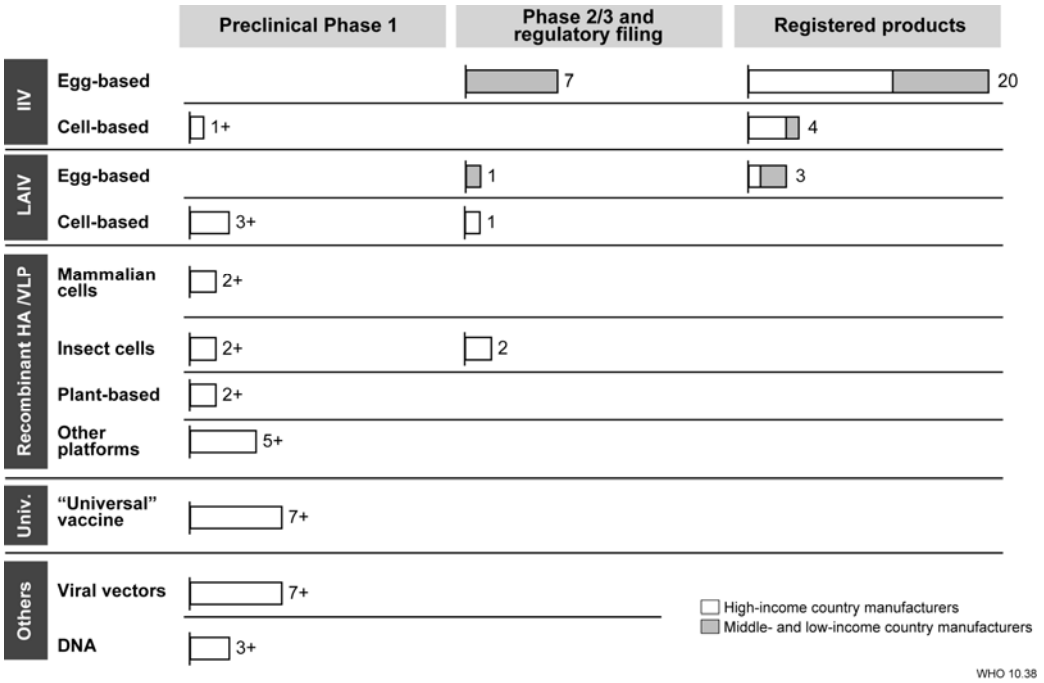
[1] The number of products under development listed here does not include those undertaken by academic institutions.

[2] PCAST US President's Council of Advisers on Science and Technology. *Report to the President on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza*, August 2010.

- *Viral-vectored influenza vaccine* was developed by genetically engineering various non-pathogenic viruses, e.g. adenovirus and poxviruses, to contain antigens from influenza viruses. Seven known products are in early development stages.

- *DNA influenza vaccines* use portions of the genetic code of a pathogen to cause the host to produce proteins of the pathogen that may induce an immune response. DNA vaccines may include components that provide cross-strain protection.[1,2] Three known products are in the preclinical or phase 1 development stage.

Figure 3. Numbers of manufacturers using each technology and stage of development



Overview of IP issues

There are no significant patent barriers to the manufacture of any of the marketed types of influenza vaccines. Some patents protect specific processes or products, but for each of the types of marketed vaccines, there is sufficient freedom to operate to permit manufacturers in developing and emerging economies to make the vaccine of their choice.

For future vaccines based on new technologies, there are potential intellectual property barriers; however it is not known which, if any, of those technologies could make marketable vaccines that could be sustainably produced.

The following is a summary of the known intellectual property related to the production of influenza vaccine, notably the vaccines that were produced for the 2009–2010 H1N1 pandemic.

[1] Web site of Vical biotechnology company (http://www.vical.com). (Accessed 1 February 2011).

[2] Id.

For the 2009–2010 H1N1 influenza pandemic the following vaccines were made:

- Egg-derived inactivated split vaccine
- Tissue-culture derived inactivated split vaccine
- Egg derived whole inactivated virus vaccine with aluminium adjuvant
- Split vaccine with oil-in-water emulsion adjuvant
- Live attenuated virus (for intranasal administration)

As described in detail in the 2007 WHO document on intellectual property[1] there are no intellectual property barriers which would prevent any of these types of vaccine from being made by developing- or emerging-economy vaccine manufacturers. The conclusions from that document are summarized below for each of the vaccine types above:

Egg-derived inactivated split vaccine

This type of vaccine accounts for the vast majority of all influenza vaccines produced. There is no intellectual property on the well-known processes of manufacture. Some new methods of obtaining higher yields have been patented but the actual benefit of those methods in terms of doses produced is not known.

Tissue-culture derived inactivated split vaccine

This is a more recent method of production which offers some advantages, such as independence from egg supply, but requires significantly greater capital investment. This type of vaccine accounts for a small percentage of influenza vaccines produced (very few manufacturers have adopted this technology to date). There are several patents on the use of specific cell lines or processes, however these patents do not present significant barriers to the manufacture of tissue-culture derived vaccines in developing countries since other cell-lines that can be used are available. Vaccines are currently produced by this method in India.

Egg derived whole inactivated virus vaccine with aluminium adjuvant

This type of vaccine has potential advantages for pandemic response over the split vaccine as described in the WHO document on production technologies.[2] This type of vaccine accounts for the minority of seasonal influenza vaccines produced. There are no patents on the vaccines made by current manufacturers of these vaccines.

[1] http://www.who.int/vaccine_research/diseases/influenza/Mapping_Intellectual_Property_Pandemic_Influenza Vaccines.pdf (accessed 1 February 2011).

[2] http://www.who.int/vaccine_research/diseases/influenza/Flu_vacc_manuf_tech_report.pdf (accessed 1 February 2011).

Split vaccine (as in paragraphs 1 and 2) with oil-in-water emulsion adjuvant

Oil-in-water emulsion adjuvants (o/w) have been shown to enable dose reduction of pandemic influenza vaccines and permit vaccination of a larger population with a limited supply of vaccine. Two o/w adjuvants were used extensively in the 2009–2010 pandemic influenza vaccines. For one of these adjuvants, MF59^{TM}, there is no patent protection outside of a few industrialized countries, hence there is freedom for developing- and emerging-economy vaccine manufacturers to produce an adjuvant of identical composition and to make pandemic influenza vaccines containing the adjuvant. Technology transfer of such adjuvants is currently taking place to selected developing countries.

Live attenuated virus

Live attenuated influenza vaccines (LAIV) are administered into the nose as a spray or drops. This technology has significant advantages over the inactivated vaccines: the yield when produced in eggs is much higher than for the inactivated vaccines, production is quicker, and administration does not require needles and syringes, facilitating immunization. Originally developed over 30 years ago, these vaccines are gaining increasing acceptance in the United States of America, have recently been recommended for use in the European Union, and are now also being manufactured in India.

There are no patents on the processes of generating and manufacturing live attenuated influenza vaccines. There is some intellectual property on specific sequences in specific strains but such patents do not prevent the development of new strains. However, in order to accelerate the approval of a vaccine based on one of the marketed strains, access to the regulatory dossiers is required. This requires a licence from the owners. WHO has negotiated a royalty-free license to one such strain for developing countries, which has so far enabled two manufacturers in developing countries to undertake development of the product and one of these already to have the product approved and marketed.

Know-how as a critical part of intellectual property

As identified above for influenza, patents are not a significant barrier to manufacture of vaccines. However know-how is. For many of the manufacturing processes the knowledge on how to perform these is in the hands of a few skilled people. It may be more efficient for a developing-country manufacturer lacking these skills to negotiate with a manufacturer who has these skills to undertake technology transfer, than to try and develop these skills independently.

Other intellectual property relating to preparation of pandemic influenza vaccines manufactured by the methods described above

Reverse genetics

Candidate vaccine virus strains which are provided by WHO Collaborating Centres to vaccine manufacturers to enable vaccine production are normally made by a classical reassortment process in eggs, a process that is not patented. However, for highly pathogenic strains of influenza virus (e.g. H5N1) this classical process does not work. In such cases the process of reverse genetics has to be used to make the candidate vaccine viruses. This process is patented and vaccine manufacturers who wish to make vaccines from the candidate vaccine viruses generated using this process need to

negotiate a license from the holder of the intellectual property (Medimmune).[1] For the H1N1 pandemic, both the classical and reverse genetics processes were used. However, the candidate vaccine viruses developed using the classical process were better in yield than those from reverse genetics, thus there was no need for manufacturers to negotiate licenses.

H5N1 sequences

An analysis of the intellectual property relating to H5N1 sequences did not identify any intellectual property which would prevent any H5N1 sequences from being included in vaccines made using any of the above manufacturing methods.[2]

Intellectual property relating to future technologies

There are numerous technologies under development that may one day simplify the production of influenza vaccines. These include processes for manufacturing the relevant influenza antigens in bacteria, insect cells or in tobacco plants or expressing influenza antigens on viral vectors or by nucleic acid (DNA). With regard to many of these technologies patent applications are pending in specific countries. It is however not known if these concepts will ever be approved for pandemic influenza prophylaxis nor if their production will be sustainable. Current predictions suggest that the cost of these new vaccines will not be significantly cheaper than that of existing vaccines[3] and any decision to invest in and adopt these technologies is a mix of business and public health.

If a promising new production technology is developed and comes under patent protection, other potential vaccine manufacturers wishing to use this new technology would have first to consider whether the technology is patented in their country. In this case the manufacturer would normally try to obtain a license and the relevant know-how from the patent holder. If such license negotiations are not successful, Member States may consider using relevant flexibilities of the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) as implemented in their respective national legislation such as government use or compulsory licenses to access the technology. As identified above, in the absence of know-how for these technologies, freedom from patent-barriers may not be enough to enable developing country manufacturers to use the technology.

Impact of current and future technologies on pandemic vaccine production for 2015

Conversion of seasonal to pandemic production varies by technology, in respect of seasonal dosage, time to first dose, pandemic dosage and pandemic production yield (Table 5).

Overview of seasonal to pandemic conversion factors by technology: The seasonal dosage, timeline to first dose, pandemic dosage, and pandemic production yields vary across the technologies.

> *Egg-IIV* requires 12–14 weeks from availability of candidate vaccine virus by manufacturers to production of the first dose. The trivalent seasonal vaccine requires 45 micrograms of antigen

[1] WHO is currently undertaking a detailed analysis of the scope and impact of the Medimmune patent portfolio and reviewing alternative methods of performing reverse genetics.

[2] http://www.who.int/csr/disease/influenza/avian_flu_landscape.pdf (accessed 1 February 2011).

[3] http://www.who.int/immunization/sage/Influenza_Vaccine_Access_Strategies_OCT2007.pdf (accessed 1 February 2011).

(15 micrograms per by strain). Yields for influenza strains of pandemic potential have ranged from 30–100% of seasonal production and dosages from 3.8 to 90 micrograms. For the purpose of this study, a most common range of dosages between 4 and 15 micrograms was assumed, noting that in case of poorly immunogenic viruses higher dosages may be required if no adjuvant is to be used (see below).

Cell-IIV has similar timeline and conversion factors to egg-IIV.

Egg-LAIV has a shorter time-to-first dose than IIV vaccines, requiring 10 weeks. LAIV has significantly lower dosage requirements (measured in number of live viruses), meaning that each egg can produce 10 to 20 times more doses than inactivated production. Egg-LAIV seasonal vaccines dosages vary between $10^{6.5}$ and $10^{7.5}$ PFU. Pandemic vaccines also vary with dosages of $10^{7.5}$ and up to 10^{8} for poorly immunogenic viruses like H5N1. For the purpose of this study, dosage of pandemic and seasonal vaccine was assumed to be $10^{7.5}$ PFU. Yields for influenza strains of pandemic potential vary but based on recent experience with H1N1 and H5N1, for the purpose of this study, 100% was considered.

Recombinant technology could reduce time-to-first dose to 7 weeks. The trivalent seasonal vaccine closest to licensure utilizes 135 micrograms of antigen in total for the three strains, or 45 micrograms per strain.[1] Pandemic vaccine clinical trials are still ongoing with various dosages being tested. For the purpose of this study, 45 micrograms was considered. However, in case of poorly immunogenic viruses like H5N1, 90 micrograms may be required.

Table 5. Variables that affect the conversion factors for each technology

	Time to 1st dose	Seasonal dosage per strain[1]	Pandemic dosage	Production yield
Egg-IIV	12–14 weeks	15 mcg	3.8–90 mcg	30%–100%
Cell-IIV	12–14 weeks	15 mcg	3.8–90 mcg	30%–100%
Egg-LAIV	10 weeks	~$10^{6.5–7.5}$ PFU[2]	~$10^{7.5–8}$ PFU[2]	~100%
Insect cell-based recombinant	7 weeks	45 mcg	45–90 mcg	~100%

1 As most seasonal vaccines are trivalent, the total seasonal dosage is 3 times the dosage per strain.
2 Plaque Forming Units, a measure of the number of viruses.

WHO 10.39

[1] Protein Sciences FluBlok BLA review, Food And Drug Administration, Center For Biologics Evaluation And Research, Vaccines And Related Biological Products Advisory Committee, November 19, 2009. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM197912.pdf.

Seasonal to pandemic conversion scenarios for IIV

As IIV accounts for most of the seasonal capacity today (approximately 94% in 2009 and 82% expected in 2015), the uncertainty around pandemic dosage and production yield for this technology will have a high impact on potential pandemic capacity. Experiences from H1N1 and H5N1 provide evidence that can be used to forecast potential pandemic capacity.

For H1N1, the production yield ranged from approximately 30% to 60% of seasonal production.[1,2] The dosage level varied with the adjuvant used: the majority of unadjuvanted vaccines required 15 micrograms of antigen and vaccines using potent adjuvant technologies (oil in water emulsions) required 3.8 to 7.5 micrograms.[3]

The H5N1 case on the other hand, showed better production yields, reaching 100% for some of the vaccine viruses. Much larger amounts of antigen were required, however, to elicit an appropriate immune response, with up to 90 micrograms for vaccines without adjuvants. Adjuvanted H5N1 vaccines required 15–30 micrograms and 3.8–7.5 micrograms for aluminium and with oil-in-water adjuvants respectively. Nearly all H5N1 adjuvanted vaccines using whole instead of split virus formulations used 6–15 micrograms.[4] Nearly all H5N1 vaccines required use of two doses for appropriate immune response.

Since conversion factors for future pandemics cannot be predicted with certainty, three conversion scenarios were developed: (1) *Low case*, (2) *Base case*, and (3) *High case* with different assumptions for production yields and dosage requirements in each scenario:

- The *low case* conversion scenario assumes that the quantity of antigen required for a pandemic vaccine to confer full protection would be 15 micrograms. This is consistent with seasonal vaccine dosage and H1N1 vaccine dosage without the use of adjuvants. It is worth noting that if unadjuvanted H5N1 vaccines were required, an even lower conversion scenario would be expected. This scenario assumes a production yield similar to the lowest range obtained during H1N1 vaccine production (30%).[5] Of note is the fact that non-adjuvanted H5N1 vaccines contain up to 90 ug antigen.

- The *base case* conversion scenario assumes that the quantity of antigen required for a pandemic vaccine to confer full protection would be produced using the lowest amount of

[1] Partridge J. & Kieny MP (Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009–2010 and comparison with previous estimates and global action plan targets. *Vaccine*, 2010; 28:4709–4712.

[2] Bernat J, International Federation of Pharmaceutical Manufacturers Associations (IFPMA) *H1N1 vaccine production: the industry perspective*. Geneva Health Forum 19 April 2010. http://www.google.co.uk/search?sourceid=navclient&ie=UTF-8&rlz=1T4SKPT_enCH404CH404&q=H1N1+Vaccine+Production%3a+The+Industry+Perspective%22%2cvaccine+production%3a+the+industry+perspective.+Geneva+Health+Forum+19+April+2010.

[3] Uppsala Monitoring Centre. *A/H1N1 pandemic influenza vaccines*. 24 February 2010 (www.who-umc.org). 1 February 2011.

[4] Use of licensed H5N1 influenza vaccines in the inter-pandemic period: Report of the H5N1 SAGE Working Group to the April 2009 meeting of the Strategic Advisory Group of Experts; http://www.who.int/immunization/sage/SAGE_H5N1_26Mayb.pdf.

[5] Partridge & Kieny (2010) "Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009–2010 and comparison with previous estimates and global action plan targets", Vaccine 28(30):4709-12.

antigen currently licensed for each manufacturer, accounting for current licensing restrictions on the use of adjuvants in certain countries. This ranges from 3.8 micrograms for vaccines with potent adjuvants (oil in water) to 15 micrograms for vaccines using alum adjuvants (or with no adjuvants in the case of H1N1). The weighted average across manufacturers is approximately 10 micrograms and is consistent with previous estimates.[1] Production yields in the *base case* scenario are in line with the higher end of H1N1 production (60%).

- The *high case* conversion scenario assumes broad availability of potent adjuvant technology, resulting in lower antigen requirements (assumed to be 4 micrograms). It is worth noting that even higher conversion scenarios are possible if lower amounts of antigen are used. Currently there are vaccines being tested with as low as 1.9 micrograms of antigen. The *high* scenario assumes pandemic yields are the same as seasonal yields (100%).

Technologies other than the predominant IIV were assumed to have the same conversion factor across all three scenarios. For all conversion scenarios, the current average time to first dose was assumed to be 14 weeks, which is anticipated to decrease to 12 weeks by 2015 due to expected improvements in vaccine testing methods.

Current and forecasted pandemic capacity

Estimated current pandemic vaccine production capacity

Current seasonal influenza capacity (based on 2009 estimates) exists to produce 876 million doses in 44 weeks (one production year). The capacity comprises the following technologies: 94% IIV and 6% other technologies.

The estimated levels of pandemic capacity 38 weeks after the release of the candidate vaccine virus for manufacturing, will vary based on the conversion scenario:[2]

- *Low case* conversion scenario: 850 million doses,
- *Base case* conversion scenario: 2260 million doses, and
- *High case* conversion scenario: 8980 million doses.

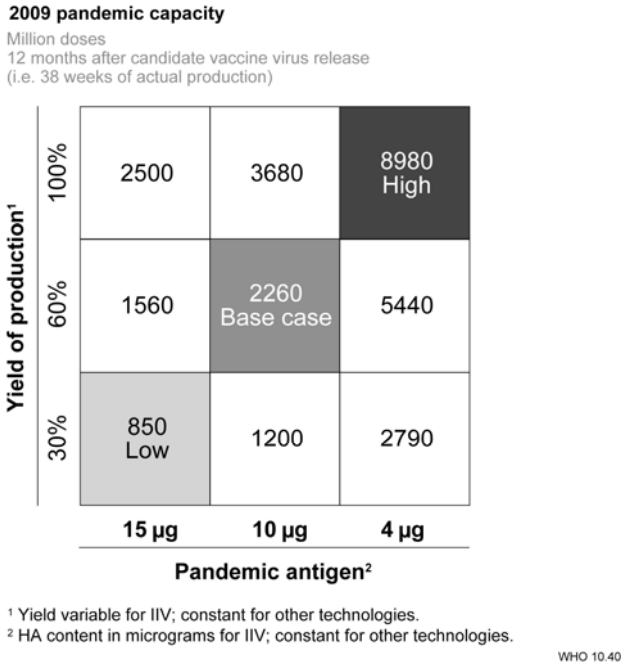
These estimates of pandemic vaccine production capacity include the potential output of all manufacture.[3] Figure 4 illustrates the full impact of the assumptions on pandemic vaccine dosage and production yields. The scenarios differ substantially. As the production yields are unknown, technology (e.g. potent adjuvants that can reduce pandemic dosage) may affect capacity the most.

[1] Oliver Wyman-IFPMA-WHO "Influenza vaccine supply and demand – Summary of findings", March 2009.

[2] The conversion factors for seasonal to pandemic capacity in the *low*, *base case,* and *high* scenarios are 1.1, 2.9, and 11.1 respectively (see Annex 2); the production time is 38 weeks for the first pandemic year.

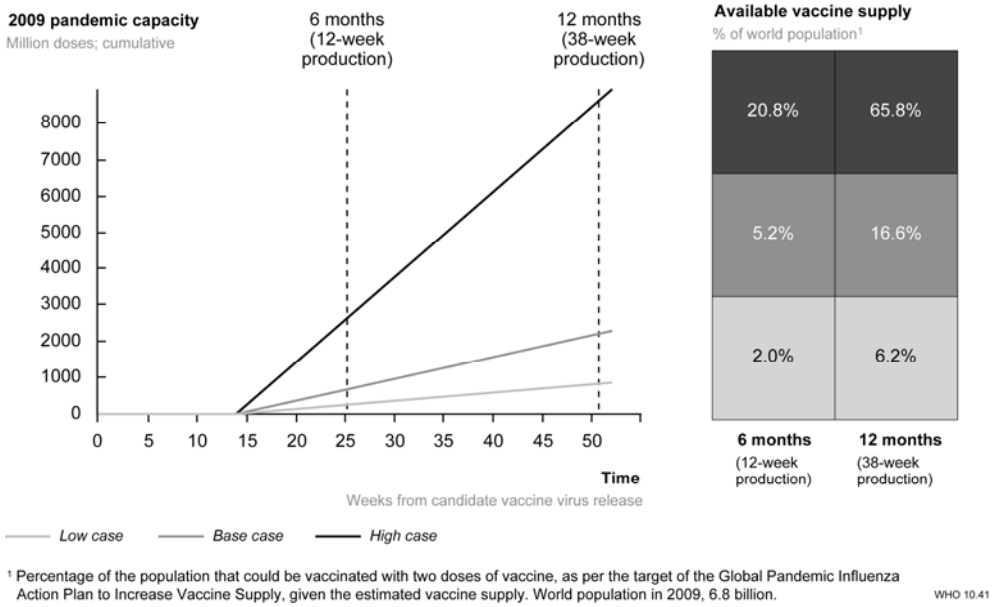
[3] 52 weeks broken down as follows: 14 weeks between the candidate vaccine virus becomes available to industry and the market release of the first dose, 38 weeks of production.

Figure 4. Scenarios for pandemic vaccine manufacturing capacity



Regardless of the conversion scenario, current pandemic capacity would be insufficient to achieve broad population coverage. Depending on the conversion scenario, 12 months after release of the candidate vaccine virus to manufacturers, there would be sufficient pandemic vaccine to immunize 6.2–65.8% of the world's population with two doses (Figure 5). Six months after release of the candidate vaccine virus, the number of doses produced would be sufficient to vaccinate only 2–20.8% of the world's population.

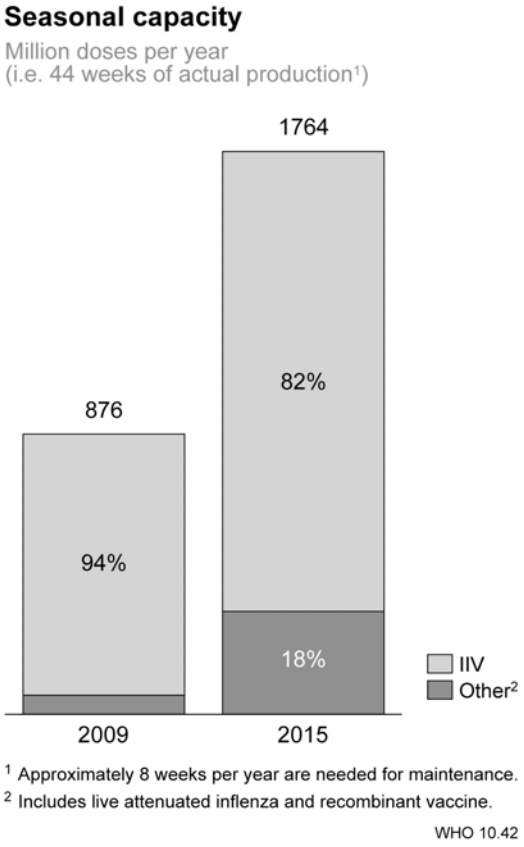
Figure 5. Pandemic vaccine production capacity in 2009 and supply available to cover the world's population



Updated estimate of future capacity

Seasonal vaccine manufacturing capacity is expected to grow in the near future and could reach approximately 1.8 billion doses per year by 2015[1] (Figure 6), 82% of which would be IIV and 18% other technologies (LAIV and recombinant). The growth in capacity will be due to the upgrading of existing manufacturing facilities or the building of new plants. Completion of these plans would result in 560–900 million doses of excess seasonal capacity over current seasonal demand.[2,3] Manufacturers indicated that such an excess could hinder the materialization of expansion plans or the shutting down of existing capacity.

Figure 6. Forecast of global seasonal vaccine manufacturing capacity



- With the increase in seasonal vaccine production capacity, the increase in pandemic capacity would be substantial. By 2015, pandemic capacity 1 year after release of the candidate vaccine virus for manufacturing could reach the following: Low case conversion scenario: 2620 million doses

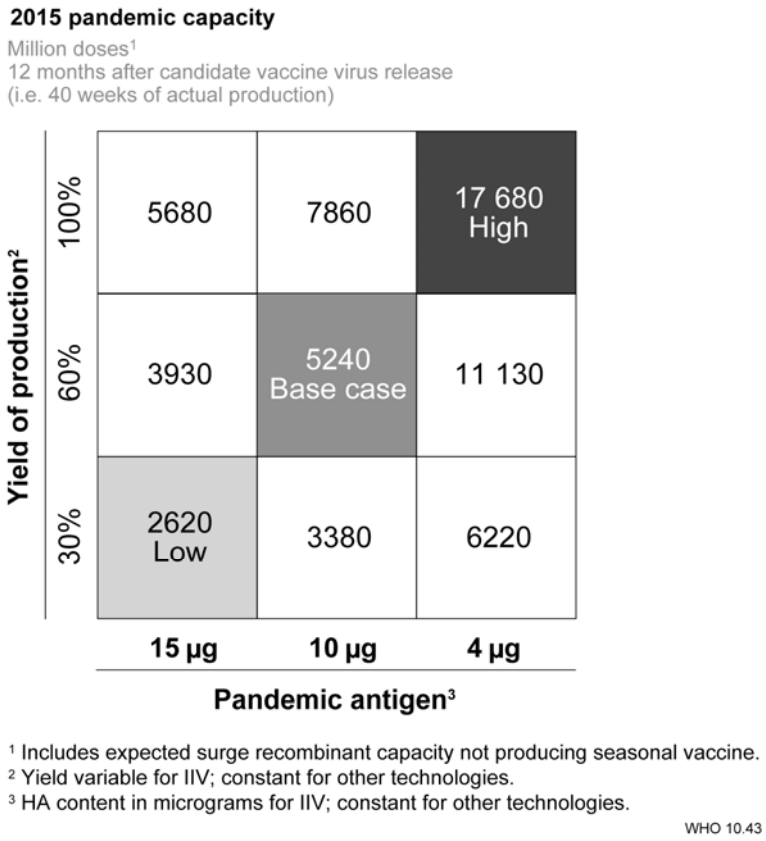
[1] From interviews with manufacturers in developed and developing countries.

[2] Accounting for the fact that most seasonal demand originates in the northern hemisphere and that a maximum of 35 weeks of production are required to manufacture vaccine for that hemisphere.

[3] Wyman O, International Federation of Pharmaceutical Manufacturers Association (IFPMA) WHO *Influenza vaccine supply and demand summary of findings.* March 2009.

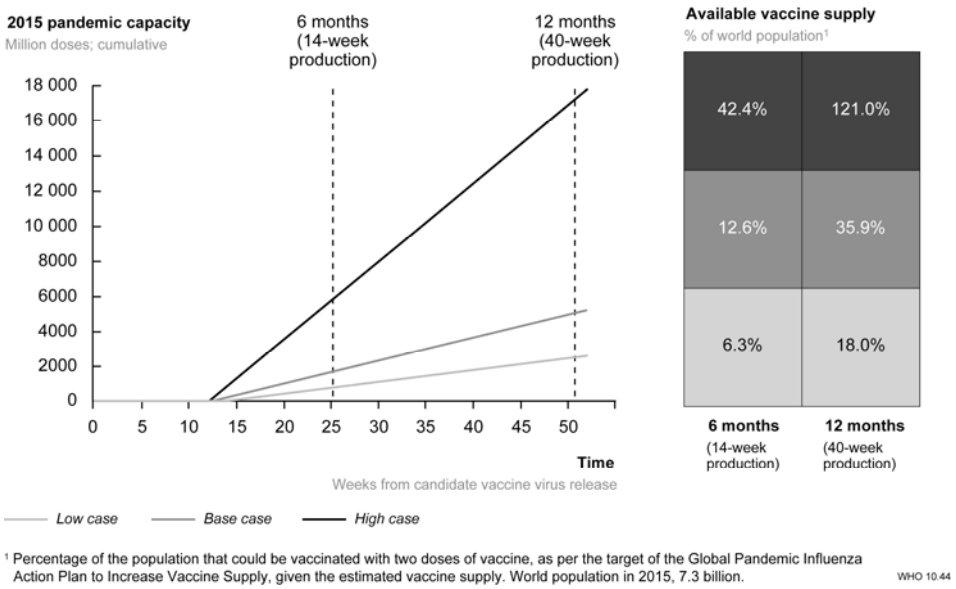
- *Base case* conversion scenario: 5240 million doses; and
- *High case* conversion scenario: 17 680 million doses (Figure 7).

Figure 7. Forecast pandemic production capacity



Despite the potential increase in production capacity by 2015, it would still be insufficient to produce enough doses to vaccinate the world's population within 6 months of release of the candidate vaccine virus. The available supply would be enough to cover 6.3–42.4% of the estimated world population (Figure 8).

Figure 8. Potential pandemic vaccine production capacity in 2015 and available supply to cover the world's population



[1] Percentage of the population that could be vaccinated with two doses of vaccine, as per the target of the Global Pandemic Influenza Action Plan to Increase Vaccine Supply, given the estimated vaccine supply. World population in 2015, 7.3 billion. WHO 10.44

Illustrative targets

Target 1: Cover 70% of the global population[1] with two doses of pandemic vaccine within 6 months of release of the candidate vaccine virus to manufacturers. This represents a total of approximately 10 billion doses.

Target 2: Cover 100% of the population with two doses of pandemic vaccine within 6 months of release of candidate vaccine virus. This represents a total of approximately 14 billion doses and is the target in the GAP.[2]

Rationale for target coverage of 70–100%

Experience with H5N1 and H1N1 suggests that the long-term target range should be 70–100% of the global population with two doses of vaccine:

> Most national pandemic preparedness plans reviewed set the vaccination target at 100% of the population.

[1] *United Nations population statistics, 2006 revision*. http://www.un.org/esa/population/publications/wpp2006/English.pdf.

[2] Global pandemic influenza action plan to increase vaccine supply. Geneva, World Health Organization, 2006 (WHO/IVB/06.13).

The literature on modelling suggests that coverage of 70–80% of the population could reduce pandemic spread.[1,2,3]

Expert advisory groups in two countries with the aim of vaccinating 100% of the population recognized that, in the event of a pandemic, vaccine demand might be significantly less than 100%: the Canadian Pandemic Influenza Committee considered it prudent to plan for 75% coverage,[4] and the United States President's Council of Advisors in Science and Technology assumed 80% in a recent report.[5]

Evidence on herd immunity (protecting one group from a disease by vaccinating another group) against influenza[6] suggests that coverage as low as 60% can reduce infection.[7]

Rationale for six-month time frame target

The GAP six-month time frame remains the most realistic planning assumption: as the primary technology (IIV) requires three months to first dose, a shorter time frame is not likely by 2015. A longer target time (over six months) between release of the candidate vaccine virus to manufacturers and the first dose might mean that vaccine became available too late to intervene before the second pandemic peak. In the 2009 pandemic, the second, more severe pandemic wave started in September 2009, approximately three months after release of the candidate vaccine virus to industry.[8]

Illustrative strategic options[9]

Even at the lowest proposed population coverage target (70%), there would be a sizeable gap relative to planned capacity by 2015 (Figure 9). To fill the gap between pandemic influenza vaccine manufacturing capacity and population coverage targets, various complementary strategic options could be considered.

[1] Goldstein E. et al. Reproductive numbers, epidemic spread and control in a community of households. *Mathematical Biosciences*, 2009; 221:11–25.

[2] Yang Y. et al. The transmissibility and control of pandemic influenza A (H1N1) virus. *Science*, 2009; 326:729–733.

[3] Germann T. et al. Mitigation strategies for pandemic influenza in the United States. *Proceedings of the National Academy of Sciences*, 2006; 103:5935–5940.

[4] Canadian pandemic influenza plan.2004. http://dsp-psd.pwgsc.gc.ca/Collection/H39-4-26-2004E.pdf.

[5] President's Council of Advisors on Science and Technology (PCAST) *Report to the President on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza*. http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST-Influenza-Vaccinology-Report.pdf 2010.

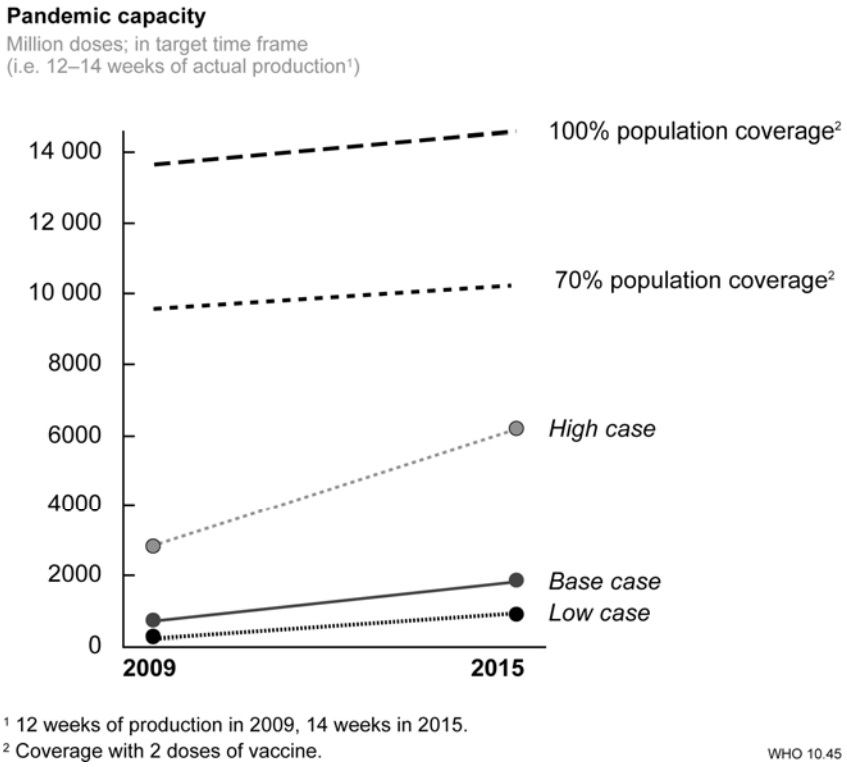
[6] Glezen (P) Herd protection against influenza. *Journal of Clinical Virology*, 2006; 37:237–243.

[7] Asllani I. & Ettkin A. A generic simulation model to manage a vaccination program. *Journal of Medical Systems*, Online First™, 2010, doi: 10.1007/s10916-009-9423-1.

[8] PCAST report August 2010 "Report to the President on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza".

[9] An overview of the costs of the strategic options described in this section, a detailed breakdown of all costs for each option, a description of the assumptions made and the sources of information used to make those assumptions are given in Annex 2.

Figure 9. Gaps between the scenarios of pandemic vaccine manufacturing capacity and the targets of 70% or 100% coverage with two doses



[1] 12 weeks of production in 2009, 14 weeks in 2015.
[2] Coverage with 2 doses of vaccine.

WHO 10.45

Strategic option 1: Increase seasonal demand[1]

Description: Provide support for increasing seasonal demand in order to improve the business case for maintaining and building capacity; this solution is proposed in the GAP. Without seasonal demand, pandemic vaccine production facilities remain idle between pandemics. Average seasonal vaccination rates throughout the world are low today, at 20% in high-income, 5% in middle-income and less than 1% in low-income countries.

Activities:

- Study the burden of seasonal influenza in low- and middle-income countries.
- Encourage prioritization of seasonal influenza by organizations such as the GAVI Alliance.
- Mobilize the public to follow seasonal recommendations, with marketing and promotion campaigns.
- Conduct national seasonal vaccination campaigns, including funding of vaccine.

Potential impact: New capacity of 0–630 million pandemic doses within six months for a population coverage of 0–4%, with two doses of vaccine.

[1] *Global pandemic influenza action plan to increase vaccine supply*. Geneva, World Health Organization, 2006 (WHO/IVB 06.13, 4.1).

This option, on its own, is not feasible to sustain the capacity needed to fill the gap. Vaccinating the world's population every influenza season would still not generate enough seasonal demand to fill the gap completely.

A more realistic expansion goal for seasonal coverage might be to increase seasonal vaccination from the average level within each income bracket to the highest achieved in any country within each income bracket. Reaching 48% for high-income countries, 24% for upper middle-income countries, 9% for lower middle-income countries and 4% for low-income countries would result in 655 million additional doses of seasonal demand.[1]

This increase in demand would help to reduce the excess capacity expected by 2015 (estimated at 560–900 million doses without additional demand); however, it is unclear whether this level of increased demand would stimulate new capacity expansion, given the already expected excess capacity. If new capacity were to be built to provide 655 million doses of new seasonal demand, the resulting capacity would be 630 million doses of pandemic vaccine within six months of release of the candidate vaccine virus in the base case scenario, of which 450 million doses would be supported by increased seasonal demand in low- and middle-income countries.

Feasibility: The feasibility of this option is low to moderate, as it would require a significant increase in coverage to reach the higher targets. This could be done by recommending universal coverage in high-income countries and driving demand in low- and middle-income countries, where the priority is low.

Costs:[2] The one-time cost would be about US$ 280 million, including the costs of studying burden of disease and marketing and promoting seasonal vaccination in low- and middle-income countries. These costs are equivalent to US$ 0.6 per pandemic dose.[3] The operating expenses would be about US$ 3.7 billion, to cover implementing national seasonal campaigns in low- and middle-income countries, including the costs of seasonal vaccine and vaccination. These costs are equivalent to US$ 8.3 per pandemic dose.

Strategic option 2: Build or expand capacity in countries that have government support or a business case to sustain production

Description: Establish sustainable local or regional manufacturing capacity in countries that do not have it. This option would be a natural extension of the WHO initiative to facilitate acquisition by vaccine manufacturers in developing countries of influenza vaccine production technologies.[4,5] Candidate new producers could also be supported to construct facilities with capacity that exceeds potential demand and that are subsidized. The new capacity would preferably be based on egg-IIV,

[1] As data on seasonal coverage in low-income countries are sparse, and current estimates indicate an average below 1%, for the purposes of this study, a mid-point between the current average and that in lower-middle-income countries was assumed.

[2] The costs included in the options do not include the cost of purchase and deployment of vaccine in the event of a pandemic.

[3] Based on the potential number of pandemic doses (450 million) that could be added by capacity built to satisfy seasonal demand in low- and middle-income countries.

[4] *Global pandemic influenza action plan to increase vaccine supply*. Geneva, World Health Organization, 2006 (WHO/IVB 06.13, 4.2.1).

[5] Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits. A62/5 Add.1 6.13.1.

egg-LAIV and recombinant technologies, as they are cost–effective, with the possibility of using IIV–LAIV conversion (strategic option 4) or adjuvants (strategic option 5) in the event of a pandemic.

Activities:

- Sustain support to complete current projects of the GAP grant programme.
- Extend the GAP grant programme by soliciting expressions of interest from countries based on ability to sustain local capacity.
- Establish partnerships with local manufacturers, select appropriate technology and transfer the technology necessary to manufacture the vaccine.
- Build production facilities.
- License or WHO prequalify the product.

Impact: If production can be established in two to seven more countries (apart from current GAP grantees), the additional capacity would be 40–160 million seasonal doses or 40–150 million pandemic doses within six months (allowing < 1–1% population coverage[1]).

A population of 40 million people was identified as the minimum size needed to sustain local production. This population would have a potential demand for 10 million doses of seasonal vaccine, assuming a 25% vaccination rate (the highest level achieved by any middle-income country[2]). This would provide minimally efficient scale for an influenza vaccine manufacturing facility producing approximately 10 million doses.

Twelve low- and middle-income countries with no GAP grants have populations above 40 million. Seven of these countries have a seasonal demand of over 200 000 doses, suggesting a potential seasonal market. Two of the seven counties have established vaccine manufacturing facilities (as evidenced by the existence of a member of the Developing Country Vaccine Manufacturer Network (DCVMN)[3] in the country). This suggests a potential two to seven additional facilities, producing 10–30 million doses each (depending on the population size). Building facilities in the two countries with a DCVMN member would result in a capacity of 40 million seasonal doses, while building in all seven countries would result in a capacity of 160 million seasonal doses.

Feasibility: Current GAP grantees are on target to reach their capacity goals, suggesting that this option is viable. The feasibility of pursuing this option in addition to existing grants would, however, be medium, because of the current low seasonal demand in these countries and their relatively limited experience with vaccine manufacture. Pursuit of strategic option 1 may improve the feasibility by increasing seasonal demand and improving the business case for continuous use of these facilities.

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[1] Coverage of population in 2015 with two doses of vaccine.

[2] International Federation of Pharmaceutical Manufacturers Association (IFPMA); Influenza Vaccine Supply International Task Force. *Provision of seasonal influenza vaccines in 157 countries (2004–2009)* http://www.ifpma.org/fileadmin/webnews/2010/pdfs/20100903_IVS226_IFPMA_IVS_seasonal_flu_vac_dose_distribution_study.pdf.

[3] http://www.dcvmn.com/.

Costs: The one-time cost for completing on-going GAP grant programme projects and for extending the programme to establish two to seven facilities, assuming use of the egg-IIV technology, would be US$ 125–490 million. These costs include the construction of new facilities, funding the clinical plan for registering a seasonal vaccine with multiple indications (children, adults, elderly), licensure of the product and training and administrative costs. The cost is equivalent to US$ 3.2 per pandemic dose. There would be no annual operating costs if the manufacturers sustainably operate the facilities between pandemics.

Strategic option 3: Subsidize idle capacity above seasonal demand levels

Description: Establish mechanisms to maintain capacity above seasonal demand levels so that influenza vaccine could be produced in the event of a pandemic. Subsidies could be sought for existing or planned capacity in order to prevent downsizing if strategic option 1 is not pursued and significant excess capacity remains.

Activities: Support the maintenance of excess capacity in existing facilities in exchange for access to that capacity at the time of a pandemic.

Impact: The impact of this option could be either moderate or high. Avoiding downsizing of existing capacity would keep 560–900 million doses of seasonal capacity that might otherwise be eliminated. It is unclear, however, whether subsidies are needed to maintain this capacity, as existing pre-purchase agreements for 1.2–1.4 billion pandemic doses might be enough to ensure the capacity remains.

Feasibility: The main challenge of this option is financial, as it would require continuous support, including operational maintenance of the facilities to produce at the time of a pandemic.

Costs: The operating expenses would be US$ 280–450 million to subsidize a potential excess capacity of 560–900 million doses. This cost is equivalent to US$ 0.4 per pandemic dose.[1] Existing pre-purchase agreements may already cover these costs.

Strategic option 4: Stimulate capacity to convert from IIV to LAIV

Description: Support IIV producers in converting their production to LAIV in the event of a pandemic, increasing their effective capacity by 10–20 times. IIV facilities built in the context of strategic option 2 could be considered prime candidates for such conversion.

Activities:

- Conduct pilot studies with manufacturers that use both technologies in order to assess the feasibility of conversion from IIV to LAIV.
- Establish commercial-scale capability to switch between technologies.
- License pandemic LAIV vaccine.
- Produce commercial batches each year (at least one per year) to maintain capability.

[1] 560–900 million doses of seasonal capacity are equivalent to approximately 0.7–1.1 billion pandemic doses within 6 months.

Impact: Converting all IIV manufacturers in low- and middle-income countries would increase pandemic capacity by 1.9 billion doses within six months of release of the candidate vaccine virus (allowing 13% coverage of the population in 2015 with two doses of vaccine). For the purpose of this estimate, $10^{7.5}$ plaque-forming units per dose and 10^{8} plaque-forming units per ml of yield were assumed. The impact of this option could be higher if lower doses or higher yields were obtained.

Converting the two manufacturers with current capability for both technologies (capacity of about 40 million seasonal doses) could result in 0.4 billion pandemic doses within six months. If it is assumed that producers in high-income countries continue to use IIV, converting the 12 additional middle-income country manufacturers (~150 million seasonal doses) with IIV capacity could add another 1.5 billion pandemic doses within six months.

Feasibility: The feasibility of this option is medium, despite its clear theoretical advantages, as it is still unproven on a commercial scale. One manufacturer is, however, preparing its facility to allow this option. Conversion requires manufacturers to establish capacity in both technologies and to license products under both production processes, assuming the costs associated with the preclinical and clinical programmes and regulatory filings. Establishing LAIV capacity may require additional equipment, e.g. ultrafiltration, diafiltration or freeze-drying, and all facilities may not have enough space for such expansion.

Costs: The one-time cost would be US$ 130–230 million to pilot the conversion in the two manufacturers with both technologies, add the necessary equipment to the other 12 manufacturers and support the preclinical, clinical and regulatory approval costs. The cost would be equivalent to approximately US$ 0.1 per pandemic dose, or US$ 0.17–0.10 per dose on the basis of 1.9 billion pandemic doses.

The operating expenses would be US$ 0.6–0.8 million to purchase small-scale commercial test batches from all the convertible facilities and personnel costs to inspect test production runs. The cost per dose would be negligible.

Strategic option 5: Expand the use of potent adjuvant technology

Description: Expand the use of vaccines with adjuvant in the event of a pandemic and support the necessary mechanisms to give producers access to potent adjuvants (oil in water).[1] The use of seasonal vaccines with adjuvant would be discouraged in this option, as replacement of the current seasonal IIV formulation (45 µg active ingredients) with IIV with a lower antigen content (11–23 µg active ingredients) would significantly decrease "surge" capacity during a pandemic.

Activities:

- Encourage high- and middle-income countries to adopt vaccines with adjuvant in the event of a pandemic, resulting in full use of existing capacity among manufacturers with such products. To this end, facilitate acceptance of products with adjuvants by national regulatory authorities and by the general public.

- Transfer technology to manufacturers that do not have the potent adjuvant technology.[1]

[1] *Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits* A62/5 Add.1 6.13.2.

- Extend grants to license pandemic vaccine with adjuvants.

- Produce commercial batches of adjuvant each year (at least one per year) to maintain capability.

Impact: Enable all IIV manufacturers to produce pandemic vaccine with six months of release of the candidate vaccine virus (allowing 30% coverage of the population in 2015 with two doses of vaccine).

Full use of the potent adjuvant technology by manufacturers with products with adjuvants (if demand exists) could produce an additional 2.2 billion pandemic doses above the base case scenario within six months by 2015. Use of the potent adjuvant technology by manufacturers that do not currently have such products could add another 2.1 billion pandemic doses within six months.

Feasibility: The feasibility of this option is medium to high, as some high-income countries have been reluctant to use vaccine with adjuvants if there is no need from the point of view of immunogenicity. The technology can, however, be transferred to most manufacturers of split IIV. IIV whole virion vaccines must undergo clinical testing.

Costs: The one-time cost would be US$ 230–420 million, which includes the cost of technology transfer to all manufacturers that acquire the technology (equipment in an existing building, set up and training), preclinical and clinical programmes to build a regulatory dossier and the licensing process. This cost is equivalent to US$ 0.1–0.2 per pandemic dose on the basis of the 2.1 billion pandemic doses that could be added by manufacturers that currently do not have the technology.

The operating expenses would be US$ 0.6–1 million per year for all the manufacturers acquiring the technology to produce one commercial batch of adjuvant. The costs per dose would be negligible.

Strategic option 6: Convert other biological capacity to pandemic vaccine production at the onset of a pandemic

Description: Support the manufacturers of other biological materials to prepare for converting their facilities to pandemic influenza vaccine production in case of a pandemic. The capacity could be converted from that for other vaccines, other proprietary biological agents and contract manufacturers. Production of influenza vaccine in cell-based and recombinant systems expands the potential for sharing capacity with manufacturers of other biological products. Existing facilities would have to be modified, influenza vaccine technology would have to be transferred, and the vaccines from these facilities would have to be licensed before the pandemic.

Activities:

- Identify manufacturers with compatible technologies to pilot-test conversion.

- Transfer technology and establish commercial-scale capability to switch from one technology to the other.

- License pandemic vaccine in convertible facilities.

- Produce commercial batches each year (at least one per year).

Impact: Significant capacity to produce other cell-based biological products exists globally, estimated at 3 million litres. For the recombinant technology, 5% of that capacity would have to be converted in order to produce 1 billion doses of pandemic vaccine within six months.

Feasibility: The feasibility of this option is low because of a number of potential technical and difficulties and issues of intellectual property. Recombinant influenza vaccines that are close to registration are produced in insect cells, whereas it is estimated that only a small portion of the current cell-based capacity that could feasibly be used is based on insect cells. The change from mammalian to insect cell culture in the same facility would have to be proven at commercial scale and might be less feasible.

Intellectual property and licensing issues might restrict the number of producers available to test and develop the conversion.

Production of cell-IIV vaccine in mammalian cell culture facilities is another possibility, but most cell culture facilities do not have the level of biosafety containment needed for vaccine production. Additionally, cell-based IIV vaccine production requires ultracentrifugation equipment that might not be available in most biological manufacturing facilities.

Estimated costs: The one-time cost would be US$ 38–94 million to pilot-test the conversion by two manufacturers, provide the necessary equipment and support preclinical, clinical and regulatory approval. The cost would be equivalent to US$ 0.04–0.09 per pandemic dose. This does not include licensing fees to transfer the technology to convertible facilities and depends on the number of facilities. If more facilities are needed to produce 1 billion pandemic doses, the one-time cost would increase.

The operating expenses would be US$ 4–9 million for production of a commercial vaccine batch produced in 10 000-litre bioreactors every year, so that two to three facilities could produce a combined 1 billion pandemic doses within six months. The operating expenses depend on the number of facilities. If more facilities are needed to produce 1 billion pandemic doses, the costs would increase. These costs are equivalent to ≤ US$ 0.01 per pandemic dose. This is the cost of making the facilities ready for conversion and not the cost of the vaccine itself.

Strategic option 7: Accelerate the development of new technologies

Description: Accelerate the development of new production technologies with a shorter time to first dose, more rapidly scalable capacity and broader cross-protection against virus strains. The most viable options would be recombinant platforms of production other than those already on the market. The ideal long-term solution would be production of a "universal" influenza vaccine that would provide protection against a wide range of influenza virus strains and subtypes.[1,2]

Activities: Extend grants to support research and development of full preclinical and clinical programmes for new influenza vaccine manufacturing technologies.

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[1] *Global pandemic influenza action plan to increase vaccine supply*. Geneva, World Health Organization, 2006 (WHO/IVB 06.13, 4.3.2).

[2] *Business plan for the Global Pandemic Influenza Action Plan to increase vaccine supply*. Geneva, World Health Organization, 2008.

Impact: While the potential impact of new technologies is high, it would take a long time, in view of the fact that the average time to develop a new biological product is more than 10 years. Although there is widespread support by governments and private investors for accelerating new technologies, an internationally funded programme might ensure that the intellectual property associated with these developments can be accessed by manufacturers in the developing world.

Feasibility: The feasibility of making available one recombinant technology (production in insect cells) within five years is high. The feasibility of technologies in early preclinical phases is low, given the uncertainty of research and development.

Costs: The estimated one-time cost of a development plan would be US$ 50–200 million. The total cost of this option would depend on the number of development programmes funded. Considerably more resources would be needed to bring such a product to market. In addition, the value of such funding is unclear, because governments and the private sector are already funding this type of research and development.

V. ACCESS, AFFORDABILITY AND EFFECTIVE DEPLOYMENT

Vaccines

Goal

> To develop mechanisms to ensure real-time access, based on public health need, to affordable pandemic vaccines by Member States without such access.[1]

Approach, limitations, assumptions and data sources

Approach and limitations

Lessons learnt from the pandemic (H1N1) 2009 and on-going outbreaks of H5N1 have provided information on issues related to access, affordability and effective deployment of pandemic vaccines by Member States. Several obstacles faced by Member States in gaining access to vaccine were identified, reviewed and analysed further, as these are considered to be critical. Obstacles associated with WHO allocation of donated vaccine and in-country logistics (transfer of vaccines from the point of entry to vaccination sites) were not analysed.

The study also did not address the establishment of an international stockpile of H5N1 vaccine or other influenza vaccines. Options for doing so were prepared in response to a request to the Director-General in resolution WHA60.28 (subparagraph 2(2)) and shared with Member States in February 2009.[2] Further to the recommendations of the Strategic Advisory Group of Experts on immunization, the stockpile was to contain 150 million doses, assuming that this number were to be donated.[3] The nominal cost of establishing the stockpile (including materials and transport, storage,

[1] Document A62/5 Add.1, section 6.11 Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits.

[2] *Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology* (February 2009) http://www.who.int/csr/disease/influenza/H5N1_Stockpile_Design_Feb2009.pdf (accessed 26 November 2010).

[3] http://www.who.int/wer/2008/wer8301.pdf.

management and replenishment) was estimated to be US$ 70–880 million.[1] The recommendations made by the Strategic Advisory Group of Experts on immunization in 2007 are to be updated in the light of lessons learnt from pandemic (H1N1) 2009. If the pandemic is caused by a strain of virus similar to current H5N1 viruses, an H5N1 vaccine stockpile could allow real-time access to some pandemic vaccine. It would, however, have no value if a future pandemic is caused by a strain from a different subtype, as was the case in pandemic (H1N1) 2009. Further information is provided in the *Report by the Director-General, pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits*[2] and in *Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology.*[1]

Assumptions

Countries with the following characteristics were assumed to have access to supply: countries with domestic production capacity, those with pre-purchase agreements (e.g. contracts between countries and manufacturers to ensure the supply of a specific volume of vaccine in the case of a pandemic) and countries classified as high-income. All other countries were assumed to be at risk of lacking access to supply. It was assumed that pre-purchase agreements would be satisfied before a supply was released to other countries. All the calculations are based on the use of two doses of vaccine per person, and the cost estimates for the strategic options are based on the 2015 targets.

Data sources

review of 119 national pandemic preparedness plans and 82 national H1N1 deployment plans to identify trends in populations targeted for vaccine coverage;

recommendations of the Strategic Advisory Group of Experts on immunization;

interviews with vaccine manufacturers in high-income and developing countries and countries with pre-purchase agreements;

an extensive search of the press to identify the size of vaccine pre-purchase agreements, doses received under those agreements and the timing of receipt;

sources that defined the size of the target population groups (e.g. number of health-care workers by country);[3] and

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[1] See Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology (February 2009) http://www.who.int.csr/disease/influenza/H5N1_Stockpile_Design_Feb2009.pdf, page 25/47 (accessed 26 November 2010).

[2] *Report by the Director-General, pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits.* A/PIP/IGM/13, Annex 4 pp. 37–38 and 44–47.

[3] Based on a population model covering 176 countries developed by O. Wyman with data from WHO *World health statistics (2008)*, the International Labour Organization (ILO) Labour Statistics database (LABORSTA 2008), World Bank *World development indicators* (2006 Ed.), the United Nations Population Database (*World population prospects: 2006 revision*), the United Nations survey of crime trends (*Eighth United Nations survey on crime trends and the operations of criminal justice systems*, 31 March 2005) and the global prevalence of adult obesity (International Association for the Study of Obesity, December 2008) http://www.iotf.org/database/documents/GlobalPrevalenceofAdultObesityMarch08v4pdf.pdf. For countries for which data were not available for certain segments, estimates were created by extrapolating from countries with similar income levels for which the population sizes were known.

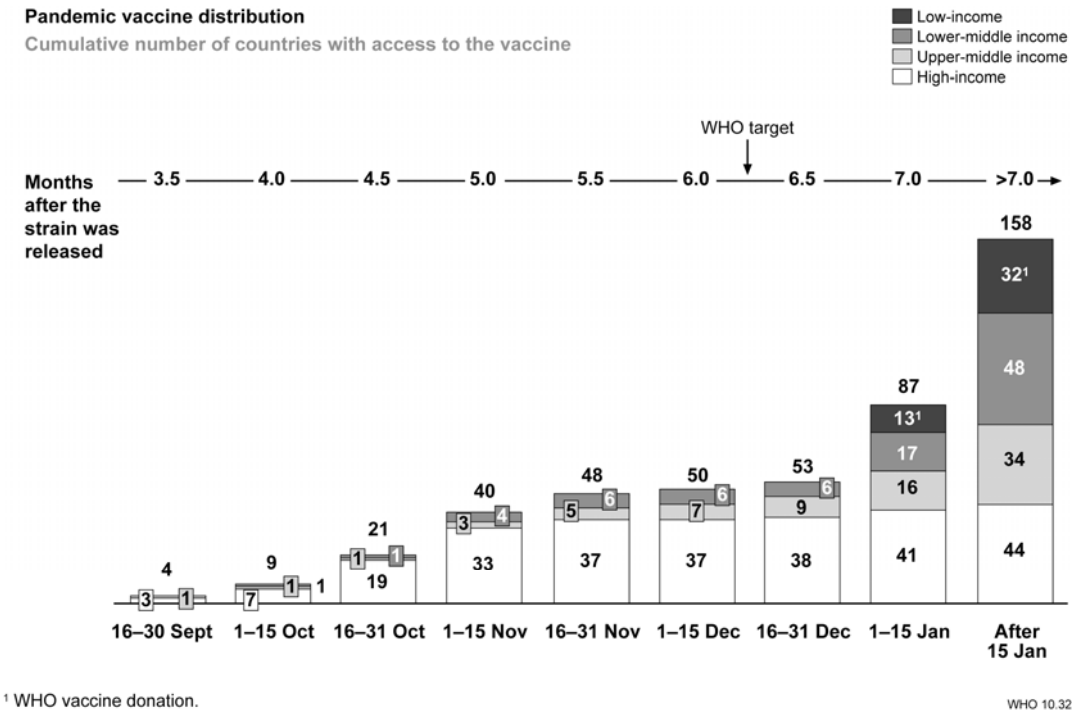
Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology.[1]

Current state

Time line and volume of H1N1 vaccines deployed by WHO

High-income countries received doses within 3.5 months of release of the candidate vaccine virus to manufacturers.[2] A similar time line was achieved by middle-income countries with local production capacity. Low-income countries received the first doses of H1N1 vaccine approximately seven months after release of the candidate vaccine virus to manufacturers (Figure 10).[3] The available public information indicated that most doses provided to low-income countries were donated through WHO.[4]

Figure 10. Time line of country access to H1N1 pandemic vaccine (2009–2010)



[1] See Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology (February 2009) http://www.who.int.csr/disease/influenza/H5N1_Stockpile_Design_Feb2009.pdf, page 25/47 (accessed 26 November 2010).

[2] *Pandemic (H1N1) 2009 media monitoring/communications surveillance*. Geneva, World Health Organization, 2009.

[3] *WHO H1N1 pandemic vaccine deployment update, 27 September 2010*. http://www.who.int/csr/disease/swineflu/h1n1_vaccine_deployment_update20100927.pdf (last accessed 27 January 2011).

[4] *Urgent support for developing countries' response to the H1N1 influenza pandemic*. WHO, United Nations Office for the Coordination of Humanitarian Affairs, and United Nations System Influenza Coordination, 2010.

Obstacles to access and effective deployment

Lack of available supply: If a pandemic were to occur at the time of writing, pre-purchase agreements (see Annex 3.1.1 for further details) would fully commit the majority of the vaccine supply available in the first six months after release of the candidate vaccine virus.[1] This constitutes a critical impediment to the availability of vaccine for countries without access.

Pre-purchase agreements were identified for 19 high-income countries, including 10 countries with local production (Table 6). Most of the pre-purchase agreements identified were contracted after the H5N1 outbreaks and allowed countries to provide 50–100% of their populations with two doses of vaccine.[2] This represents commitments for 1200–1400 million doses of pandemic vaccine. Assuming that these agreements are served first, they would fully engage all production capacity in the first 7–8 months after release of the candidate vaccine to manufacturers (in a base case capacity scenario). Countries without access would therefore not receive any vaccine within the six-month target time frame.[3]

An additional eight countries do not have pre-purchase agreements but have local vaccine production capacity (including four middle-income countries). Local demand during a pandemic would probably absorb much of local production. Pre-purchase agreements and local vaccine production capacity would give 27 countries direct access to vaccine.

Of the 146 low- and middle-income countries analysed, 142, representing approximately 4200 million people,[4] did not have pre-purchase agreements or local manufacturing facilities and were categorized as having limited or no access to pandemic vaccine (Table 6). By 2015, eight new manufacturers in middle-income countries are expected to begin producing vaccine, mostly as a result of the GAP programme. The effect will be to reduce the population without access to approximately 2400 million.[5]

[1] Based on 1.2–1.4 billion doses of pre-purchase agreement volumes and a total base case pandemic capacity of approximately 260 million doses per month (note that time to first dose is 14 weeks).

[2] Two of the 19 pre-purchase agreements provide two doses to 30–40% of the countries' populations.

[3] *Global pandemic influenza action plan to increase vaccine supply*. Geneva, World Health Organization, 2006 (WHO/IVB/06.13).

[4] World Bank income class (September 2010 revision), press search on pre-purchase agreements and WHO document *Update on A(H1N1) pandemic and seasonal vaccine availabilit*y, July 2009. Population estimates based on United Nations Department of Economic and Social Affairs, Population Division*. World Population Prospects: 2006 Revision,* New York, 2007 (ST/ESA/SER.A/261/ES).

[5] Effect of 11 grants to manufacturers in developing countries as part of the GAP, which will increase the number of doses of trivalent vaccine by over 200 million per year by 2015. Friede M., Palkonyay L., Alfonso C., Pervikov Y., Torelli G, Wood D, Kieny MP. *Overview: WHO initiative to increase global and equitable access to influenza vaccine in the event of a pandemic: supporting developing country production capacity through technology transfer*. Vaccine, *in press*, 2011.

Table 6. Countries with limited or no access to pandemic influenza vaccine, 2009

Number of countries, 2009

		Country income level			
		High	Upper middle	Lower middle	Low
Country access to vaccine	No local production or pre-purchase agreement	27	45	53	44
	Local production without pre-purchase agreement	4	2[2]	2[2]	
	Pre-purchase agreement	19[1]			

Identified as countries without access to supply

1 Including 10 countries that have local production.

2 By 2015, 4 more upper-middle-income countries and 4 more lower-middle-income countries will have local production.

WHO 10.33

Lack of national deployment plan or funds to operationalize the plan: The review of 119 national pandemic preparedness plans showed that 91% of Member States included use of vaccine during a pandemic; however:

- only 61% of the plans set priorities for population target groups for vaccination,
- only 40% of the plans defined national guidelines for the logistics of vaccine distribution,
- only 25% of the plans had national guidelines for vaccine storage,[1]
- only 42% of the plans outlined the financial resources required during a pandemic and
- only 8% of Member States conducted pandemic simulation exercises to test their plans before pandemic (H1N1) 2009.

Limited national regulatory and contracting capacity: The limited capacity of national regulatory authorities includes:

- limited legal capacity to assess rapidly the acceptability of the terms in legal donation agreements, such as exceptional liability and indemnification clauses;

[1] *Comparative analysis of national pandemic influenza preparedness plans*. Geneva, World Health Organization (draft October 2010).

- limited capacity of national regulatory authorities, including delays in authorizing use and importation of pandemic vaccine through either provisional approvals for emergencies or normal regulatory processes;

- limited or no harmonization of regulatory approvals that would allow countries to recognize authorizations granted by other national regulatory authorities;

- limited or no harmonization of the technical manufacturing data required for approvals; and

- requirements to approve pandemic vaccine on the basis of batches or lots.

Limited logistics and infrastructure: The logistical obstacles experienced during the pandemic (H1N1) 2009 that caused delays in deployment are listed below. The situation would have been exacerbated in the case of an extreme pandemic with greater demand for logistics.

- limited cold-packing capacity at manufacturers' sites;

- lack of cold storage infrastructure (e.g. in Europe, only one airport, Paris Charles De Gaulle, had sufficient cold storage capacity to host large vaccine shipments);

- limited space available on commercial aircraft; and

- lack of airport infrastructure and sufficient land transport in recipient countries to unload and dispatch the required volumes of vaccine.

Affordability of vaccines

The main finding of this study is that the first constraint to access to pandemic vaccine by countries without access is pre-purchase agreements rather than the price of the vaccine. As explained above, existing pre-purchase agreements fully commit the majority of vaccine supply available in the first six months after release of the candidate vaccine virus. This constitutes a critical impediment to the availability of vaccine for countries without access. In this study the price per dose (excluding deployment cost) of pandemic vaccine was estimated at US$ 3. This price assumes the use of tiered pricing for low income countries which is consistent with existing practice for other vaccines.[1]

Illustrative targets

Targets were established according to how much (quantity) and when (time frame) affordable pandemic vaccines will be available to countries without access. More details of the target groups are given in Annex 3.1.

[1] http://www.who.int/immunization_financing/options/en/briefcase_pricingtiers.pdf.

Quantity targets for vaccines

Target 1: Health-care workers: Countries have access to sufficient pandemic vaccine to cover their health-care workers, representing roughly 0.3% of a country's population (Table 7).[1]

In 2009, this represented 14 million people, or a total of 28 million doses, for countries without access and consumed 4% of base case production capacity.[2] By 2015, the advent of new manufacturers in developing countries will have reduced the number of countries without access. This target will require a total of 16 million doses for countries without access and consume 1% of future estimated base case production capacity.

Target 2: Essential personnel and pregnant women: Countries have access to sufficient pandemic vaccine to cover health-care workers, essential personnel and pregnant women, representing approximately 5.5% of a country's population.

In 2009, this represented 213 million people, or a total of 426 million doses, for countries without access, and consumed 60% of base case production capacity.[3] By 2015, the advent of new manufacturers in developing countries will have reduced the number of countries without access; this target will require a total of 276 million doses for countries without access and consume 15% of future estimated base case production capacity.

Target 3: Essential personnel and populations at risk: Countries have access to sufficient pandemic vaccine to cover the groups designated as priorities in their pandemic preparedness plans: health-care workers, essential personnel and populations at risk, representing roughly 13.7% of a country's population.[4]

In 2009, this represented 569 million people, or a total of 1138 million doses, for countries without access, and consumed 159% of base case production capacity. By 2015, the advent of new manufacturers in developing countries will reduce the number of countries without access. This target will require a total of 668 million doses for countries without access, and will consume 36% of future estimated base case production capacity.

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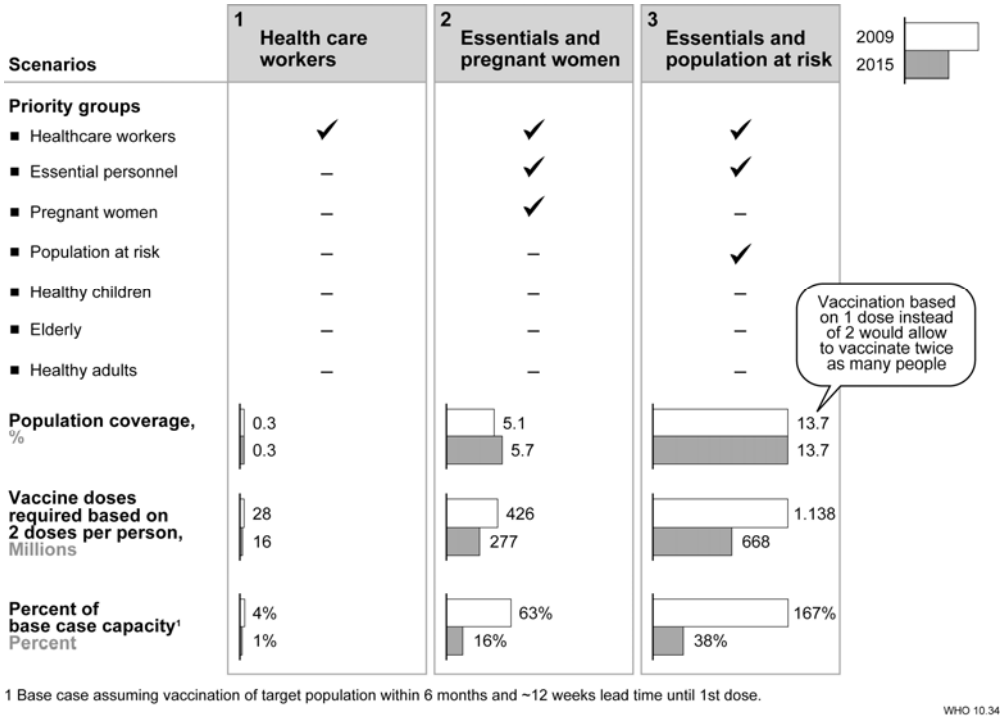
[1] Based on a population model covering 176 countries developed by O. Wyman with data from WHO *World health statistics (2008)*, the International Labour Organization (ILO) Labour Statistics database (LABORSTA 2008), World Bank *World development indicators* (2006 Ed.), the United Nations Population Database (*World population prospects: 2006 revision*), the United Nations survey of crime trends (*Eighth United Nations survey on crime trends and the operations of criminal justice systems*, 31 March 2005) and the global prevalence of adult obesity (International Association for the Study of Obesity, December 2008). http://www.iotf.org/database/documents/GlobalPrevalenceofAdultObesityMarch08v4pdf.pdf). For countries for which data were not available for certain segments, estimates were created by extrapolating from countries with similar income levels for which the population sizes were known.

[2] Base case capacity, assuming vaccination of target population within 6 months and ~12 weeks' lead time until release of first dose.

[3] Assuming vaccination of target population within 6 months and about 12 weeks' lead time until release of first dose.

[4] Based on a population model covering 176 countries developed by O. Wyman with data from WHO *World health statistics (2008)*, the International Labour Organization (ILO) Labour Statistics database (LABORSTA 2008), World Bank *World development indicators* (2006 Ed.), the United Nations Population Database (*World population prospects: 2006 revision*), the United Nations survey of crime trends (*Eighth United Nations survey on crime trends and the operations of criminal justice systems*, 31 March 2005) and the global prevalence of adult obesity (International Association for the Study of Obesity, December 2008). http://www.iotf.org/database/documents/GlobalPrevalenceofAdultObesityMarch08v4pdf.pdf).

Table 7. Potential targets for access to pandemic vaccines



Rationale for quantity targets, definition of population groups: The Strategic Advisory Group of Experts on immunization recommended that health-care workers be the first priority for vaccination against the pandemic (H1N1) 2009 virus. The Group recommended that other groups should include pregnant women, populations at risk, healthy children, elderly people and healthy adults, although the order of priority is for countries to decide.[1]

Countries identified their priorities for vaccination in one of two ways. In national pandemic preparedness plans (drafted principally to address H5N1) they identified health-care workers, populations at risk and essential personnel as priorities. In H1N1 national deployment plans, all countries eligible for WHO vaccine donations assigned the highest priority to health-care workers, followed in most cases by pregnant women, populations at risk and healthy children. (See Annex 3.1 for additional details.)

Time frame targets for vaccines

Target 1: Real-time access

Countries without direct access through domestic production or pre-purchase agreements are guaranteed to receive pandemic vaccine at the same time as countries with access, by a mechanism in which a certain percentage of real-time production output is reserved. For example, during the

[1] Strategic Advisory Group of Experts on Immunization (SAGE). *Report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic.* 7 July 2009. Weekly Epidemiological Record 2009; 84(30); 301-304. http://www.who.int/wer/2009/wer8430.pdf.

pandemic (H1N1) 2009, two manufacturers committed themselves to set aside 10% of their real-time vaccine production for provision to WHO for the benefit of developing countries.

Target 2: Access within a fixed period

Countries without direct access will receive enough pandemic vaccine to vaccinate their target populations no later than the end of a specified time, e.g. all health-care workers to be vaccinated within six months.

Strategic options

Strategic options pursued to increase capacity will also improve access in the long term, by increasing both the absolute volume of vaccine doses available and the number of countries with local manufacturing capacity. Until capacity targets are achieved, the strategic options outlined below would give increased access to pandemic vaccine by countries without such access. See Annex 3.1 for detailed cost calculations for all strategic options.

Strategic option 1: Establish new pre-purchase agreements

Establish a pooled pre-purchase agreement to ensure that sufficient quantities of pandemic vaccine are available for countries without access. The agreement could be established by an international agency on behalf of the countries without access. The agreement terms could be similar to those in existing pre-purchase agreements. Key terms would include: price per dose (based on a tiered pricing scheme so that lower-income countries pay less than higher-income countries), guaranteed payment, quantity and time of availability.[1,2]

Activities:

- Establish pooled pre-purchase agreements between governments of recipient countries that currently lack access (or an international agency on their behalf) and vaccine manufacturers.

- Purchase and deploy pre-contracted vaccine to countries without access at the time of a pandemic.

Feasibility: It is estimated that current pre-purchase agreements will fully engage most production capacity for the first seven to eight months after release of the candidate vaccine virus to manufacturers. This option would require governments with existing pre-purchase agreements or local vaccine production capacity to reconsider their pandemic requirements so that a portion of future capacity could be re-allocated to countries without access. The feasibility of reaching quantity target levels 2 and 3 is low, given the amount of existing capacity that would have to be used.

[1] WHO immunization financing briefcase: key concepts: tiered pricing. http://www.who.int/immunization_financing/options/en/briefcase_pricingtiers.pdf (accessed 24 November 2010).

[2] Asian Development Bank. *Immunization financing in developing countries and international vaccine market.* 2001. http://www.adb.org/Documents/Books/Immunization_Financing/default.asp (accessed 24 November 2010).

Strategic option 2: Expand existing pre-purchase agreements

Expand the volumes of existing pre-purchase agreements held by countries to include vaccine for countries without access. As in option 1, expansion of pre-purchase volume agreements could be pooled and held by an international agency on behalf of countries without access.

Activities:

- Establish agreements to expand existing pre-purchase agreements between countries with current agreements and vaccine manufacturers. The revised pre-purchase agreements should clearly specify the volume that is contracted on behalf of countries without access.

- Purchase and deploy pre-contracted vaccine at the time of a pandemic to countries without access.

Feasibility: The governments of high-income countries with existing pre-purchase agreements would have to be willing to expand the volume of their agreements (paid either by them or by other funding sources). The expansion would extend the time over which their pre-purchase contracts are satisfied but would give access to pandemic vaccine to countries without such access.

Estimated additional pre-purchase requirements: Depending on the size of the existing pre-purchase agreements held by high-income countries, this option would require expansion of existing pre-purchase agreements by the following aggregate amounts by 2015 in order to ensure access to countries without such access:

- quantity target 1: one additional pre-purchased dose for each 74 doses currently pre-purchased

- quantity target 2: one additional pre-purchased dose for each 4.3 doses currently pre-purchased

- quantity target 3: one additional pre-purchased dose for each 1.7 doses currently pre-purchased.

Impact: If sufficient vaccine production capacity becomes available, both strategic options could allow real-time access, to meet the quantity targets set out for 2015 (16–668 million doses).

Estimated costs

The costs for strategic options 1 and 2 are similar. They will depend on the terms existing pre-purchase agreements, which are structured in various ways. The costs shown below are estimated on the basis of the following terms: no up-front payment, an on-going fee to reserve capacity and a one-time payment to purchase and deploy vaccine at the time of a pandemic. In estimating the costs, US$ 3 was used as the purchase price per dose of pandemic vaccine.

Annual costs to reserve capacity:[1]

- quantity target 1: US$ 10 million
- quantity target 2: US$ 140 million
- quantity target 3: US$ 335 million

One-time cost for purchasing and deploying vaccine:[2]

- quantity target 1: US$ 70 million
- quantity target 2: US$ 1155 million
- quantity target 3: US$ 2795 million

Antiviral medicines

Goal

To establish effective, feasible mechanisms to ensure sustainable, real-time access of Member States, on the basis of public health need, to affordable influenza antiviral medicines.

Approach, limitations, assumptions and data sources

Approach and limitations

The demand for antiviral medicines in the event of a pandemic will depend in part on the severity of the pandemic, as this will affect demand for such medicines. As the severity of a future pandemic cannot be predicted, the quantity targets proposed here are based on the experience of the past 10 years in managing human H5N1 infections (severe but infrequent) and the pandemic (H1N1) 2009 (widespread but less severe).

Quantity targets are proposed for two groups of Member States:[3] group 1, 72 low- and lower-middle-income countries eligible for GAVI Alliance support;[4] and group 2, 105 countries, comprising those in group 1 plus all other countries defined as least developed,[5] low- or lower-middle income.[1]

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[1] Estimate based on an annual fee of US$ 0.5 per dose to reserve capacity. Source: public information on pre-purchase agreements made by the United Kingdom.

[2] The cost to purchase and deploy vaccine at the time of the pandemic is estimated at US$ 4.2 per dose: US$ 3 to purchase vaccine and US$ 1.2 for deployment. Figures are based on the report *Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology* (February 2009), and interviews with manufacturers; WHO H1N1 deployment data; and press searches. Further details of the assumptions are outlined in Annex 3.

[3] The rationales for these groupings were, for group 1, the GAVI Alliance country list was used as part of the background for distribution of oseltamivir stocks by WHO in 2009, and, for group 2, least developed and lower-middle-income countries are generally eligible for tiered pricing of essential medicines (see for example http://www.gilead.com/pdf/access_fact_sheet.pdf (accessed 25 January 2011).

[4] http://www.gavialliance.org/support/who/eligible/index.php (accessed 25 January 2011).

[5] http://www.unohrlls.org/en/ldc/related/62/ (data as of 2009; accessed 20 January 2011).

The selection of antiviral medicines was limited to those that are globally available and for which there is sufficient evidence of efficacy and safety for WHO to offer specific recommendations for use.[2,3] The medicines that meet these criteria are amantadine, rimantadine, oseltamivir and zanamivir. Other medicines and associated medical supplies and equipment were not considered, although they may be required for effective clinical management of (severe) illness. Nevertheless, the principles and options described here could be applied to the wider range of products.

Estimates of the prices of antiviral treatment courses were derived from publically available information on retail prices. The actual price to be paid will be determined by negotiation and may depend on scale, market (country) and other factors.

The cost of in-country logistics (i.e. distribution of antiviral medicines to the point of clinical use) and of developing and maintaining in-country distribution were not considered, and issues related to intellectual property were not assessed in detail.

Assumptions

- Access to both classes of antiviral medicine (adamantanes and neuraminidase inhibitors) is considered, as the susceptibility to antiviral medicines of future strains cannot be predicted. See Annex 3 for a summary of information on the available antiviral medicines.

- Population data are for 2009; no assumptions were made about future population growth.

- Development and deployment of a pandemic vaccine, as set out above, will be achieved. Thus, the demand for antiviral medicines will be highest in the first 8–10 months of a pandemic but will diminish once vaccines are deployed to protect populations from infection.

Data sources

These findings are based on existing data and guidance, including:

- 119 national pandemic preparedness plans, which were reviewed to identify national needs and plans for antiviral use;

- previously developed WHO guidance and planning documents;

- data on medicines prescriptions from IMS Health HQ Ltd;[4] and

[1] http://data.worldbank.org/about/country-classifications/country-and-lending-groups (accessed 1 May 2009).

[2] *WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A(H5N1) virus*. http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html (accessed 18 January 2011).

[3] *WHO guidelines for pharmacological management of pandemic influenza A(H1N1) 2009 and other influenza viruses*. http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html (accessed 18 January 2011).

[4] Provided by IMS Health HQ Ltd, United Kingdom.

- United Nations world population data,[1] World Bank economic data[2] and data on least-developed country status.

Extensive use was made of public information sources, including from manufacturers, national governments and health agency web sites and reports. When appropriate, such information was verified by direct communication with manufacturers, health agencies and others.

Current state

Background to influenza antiviral medicines

The four antiviral medicines within the scope of this study fall into two classes: adamantanes and neuraminidase inhibitors.

The adamantanes (amantadine and rimantadine) were first used for the treatment of influenza in the 1960s, but products in this class are not currently used against seasonal influenza viruses or pandemic (H1N1) 2009, as all currently circulating viruses are resistant to them. In the past, amantadine has been more widely available than rimantadine. Current manufacturing capacity for these medicines is unknown, as some manufacturers no longer market their products.

The class of neuraminidase inhibitors (oseltamivir and zanamivir) was developed in the 1990s, and all currently circulating virus strains are sensitive to this class.[3] Oseltamivir, which is taken orally, has been used more widely than zanamivir,[4] which is administered only by inhalation (see Annex 3 for further information).

These medicines do not contain viruses or virus-derived materials; however, both an initial demonstration of their usefulness against the new virus (as shown by the WHO Collaborating Centre in the United States in April 2009[5]) and continuous testing of viruses for antiviral susceptibility[6] are part of the global public health pandemic response.

The development of neuraminidase inhibitors in particular, which coincided with the emergence of human H5N1 infections as a pandemic threat, led to a resurgence in interest in influenza antiviral medicines as a public health tool. These medicines have two key public health uses:

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[1] *World population prospects: the 2008 revision*. New York, Population Division, Department of Economic and Social Affairs, United Nations Secretariat, 2009. http://www.un.org/esa/population/publications/wpp2008/wpp2008_text_tables.pdf (accessed 26 January 2011).

[2] http://data.worldbank.org/about/country-classifications/country-and-lending-groups (accessed 1 May 2009).

[3] During the period 2007–2009, the pre-pandemic seasonal H1N1 influenza virus strain developed resistance to oseltamivir, but this strain has been displaced by pandemic (H1N1) 2009.

[4] Information from IMS Health HQ Ltd database.

[5] *Drug susceptibility of swine-origin influenza A (H1N1) viruses.* 2009. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5816a6.htm (accessed 25 January 2011).

[6] *Update on oseltamivir-resistant pandemic A (H1N1) 2009 influenza virus: January 2010.* http://www.who.int/wer/2010/wer8506.pdf (accessed 25 January 2011).

- treatment of patients with severe illness or at risk of developing severe illness, including prophylaxis in settings where the risk of infection is high or where the risk for serious illness is high (e.g. with H5N1 infections); and

- prevention of infection in the community, perhaps at the start of an outbreak to limit and contain spread.

Through formal, independent reviews of clinical evidence and expert consultations, WHO reviewed the use of antiviral medicines for both human H5N1 infections[1] and pandemic (H1N1) 2009.[2] WHO's recommendations focus on the public health use of these medicines to treat or prevent severe influenza-related illness or death as a priority. Different recommendations were made for H5N1 and pandemic (H1N1) 2009, reflecting the different risks for severe disease from infection:

- WHO recommends that all patients with H5N1 infections be treated with antiviral medicines, as should other people at high risk of exposure to the infection ("post-exposure prophylaxis"). An adamantane may be used in addition to a neuraminidase inhibitor or when the latter are not available. These recommendations take into account the potential severity of the disease.

- For pandemic (H1N1) 2009, WHO recommends administration of antiviral medicines (neuraminidase inhibitors) for patients presenting with severe or deteriorating illness and other infected patients at high risk of developing severe illness. WHO does not generally recommend use for other patient groups or for prophylaxis. These recommendations take into account the widespread nature of epidemics and the fact that most patients experience a mild, self-limiting illness. In January 2010, oseltamivir was added to the WHO Model List of Essential Medicines[3] on the basis of evidence of its potential benefit in specific patient groups and the expected prevalence of pandemic (H1N1) in coming seasons. As a consequence, oseltamivir is currently the first choice of many countries for stockpiling and for treatment of severe illness.

Access and affordability

Antiviral drug supply and procurement was addressed in 96 of the 119 (87%) national pandemic preparedness plans reviewed.[4] Of these, 51 provided information on expected sources on antiviral medicines, as shown in Figure 11.

Under its prequalification programme, WHO has called for expressions of interest for prequalification of oseltamivir- and zanamivir-based medicines. As a result, several products, including from two manufacturers in India, have been prequalified. (See Annex 3 for a list of WHO prequalified medicinal products.)

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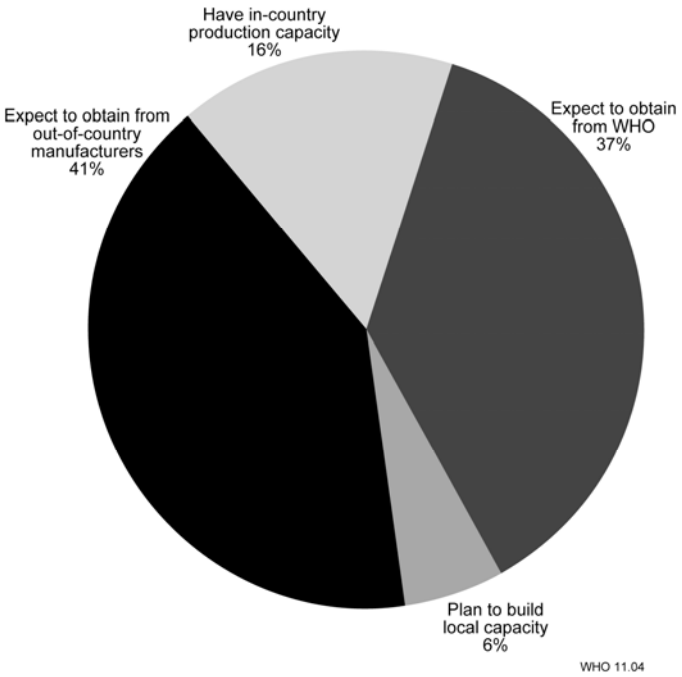
[1] *WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A(H5N1) virus*. http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html (accessed 18 January 2011).

[2] *WHO guidelines for pharmacological management of pandemic influenza A(H1N1) 2009 and other influenza viruses*. http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html (accessed 18 January 2011).

[3] http://www.who.int/selection_medicines/committees/expert/emergency_session/unedited_Emergency_report.pdf (accessed 14 January 2011).

[4] *Comparative analysis of national pandemic influenza preparedness plans* (unpublished draft, 2011).

Figure 11. Antiviral drug sources identified in national pandemic preparedness plans of 51 countries



Deployment

Before the 2009 influenza pandemic, WHO had a stockpile of 5 million treatment courses of oseltamivir, donated by the manufacturer, Hoffman-La Roche (Roche). In May 2009, after the emergence of the new H1N1 influenza virus in April 2009, WHO distributed over 3 million treatment courses of oseltamivir from its stockpile. Upon subsequent requests from Member States during the 2009 pandemic, further supplies were distributed (Figure 12). Roche made a further donation in 2009 of 5 million adult treatment courses and 650 000 paediatric treatment courses of oseltamivir. The WHO stockpiles as at January 2011 are shown in Table 8.

Figure 12. Distribution of oseltamivir to Member States during pandemic (H1N1) 2009

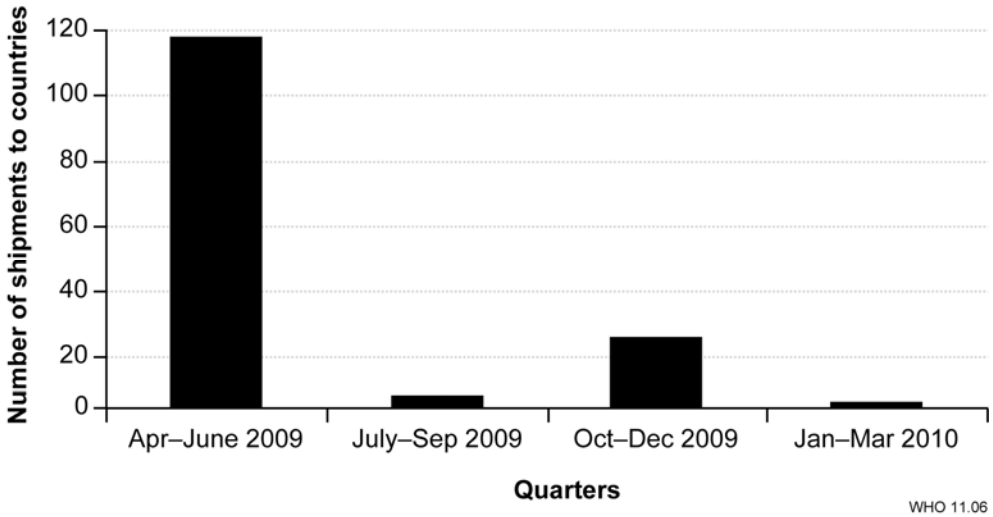


Table 8. Status of WHO stockpiles, January 2011

Donations	Deployed in 2009–2011 (millions of treatment courses)	Remaining stocks (millions of treatment courses)	Comments
2005–2006	3.7	1.3	Shelf-life expires on or before August 2011
2009	0.01	5.64	Includes 650 000 paediatric (capsule) treatment courses

A further 0.9 million treatment courses, which comprise the Association of Southeast Asian Nations (ASEAN) contingency stock, are available to specified countries in south-east Asia.[1]

At least 40 countries have national stockpiles of antiviral medicines, sufficient to cover 5%–50% of their populations[2]. During the 2009 influenza pandemic, relatively little of this stock is reported to have been used.[3] Information on deployment during the 2009 pandemic from other sources is limited. Information on distribution through commercial supply chains for some countries is available from IMS Health HQ Ltd.

Obstacles to access and affordability

Cost and shelf-life

Cost is inevitably an obstacle to access, as even the older (generic) adamantanes cost US$ 1.6–37 per treatment course, and the neuraminidase inhibitors cost US$ 6.5–26.

All medicines have a finite shelf-life, defined after extensive stability testing. Over time, stocks will have to be disposed of and replaced,[4] both of which carry a cost. The shelf-life of existing stocks might be extended on a national basis, but the medicines must be tested under appropriate regulatory conditions, which also carries a cost.

Lack of local manufacture

Although there are some local manufacturers, the absence of broader, more geographically diverse manufacturing capability and capacity (and consequent dependence on international commercial markets) is a constraint to access and affordability. Contributing factors include:

[1] http://www.aseansec.org/index2008.html (accessed 26 January 2011).

[2] Information derived from a variety of public sources.

[3] For example, the United Kingdom Health Protection Agency reported that 1 million antiviral treatments were collected by patients in England between July 2009 and February 2010, representing 2% of the population. *Epidemiological report of pandemic (H1N1) 2009 in the UK*. http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1284475321350 (accessed 17 January 2011). Data were also obtained from the United States.

[4] See, for example, a notice by the United States Food and Drug Administration on expiry of oseltamivir stocks at http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm154962.htm (accessed 17 January 2011).

- lack of regular (seasonal influenza) demand in many countries, resulting in low incentive to manufacture (including generics), poor familiarity with the products and lack of supply (distribution) chains;
- intellectual property protection of some products, which limits the freedom to manufacture and supply in many countries; and
- the need for specialized technology and know-how.[1]

Operational constraints

A number of other factors contribute to low access or demand including:

Stockpile management:

- The paediatric suspension formulation of oseltamivir has a shorter shelf-life and is less suitable for stockpiling.
- While 92% of the 119 national pandemic preparedness plans reviewed by WHO[2] provided some information on use of antiviral medicines, only 62% had considered their distribution, and only 30% had considered storage requirements.

Purchase: Not all countries have issued market authorizations for available products.

Use and national distribution:

- Laboratory capacity is low in 114 countries (see section III). As discussed here, effective surveillance and laboratory diagnosis are important in guiding use of antiviral medicines, including when they should be used.
- In countries where influenza antiviral medicines have not been in regular use, there is lack of familiarity with these medicines.
- For antiviral medicines to be beneficial, they should be administered early in the course of illness. They must therefore be available at the point of care (e.g. primary care sites, hospitals and other health-care facilities).
- The currently available medicines (and formulations) do not meet some of the most urgent clinical needs. Many of the presentations and formulations are not suitable or easy to use in small children, and there are no licensed injectable preparations for use in the most seriously ill patients.

Some of these and other constraints are covered in the Interagency Guidelines on Drug Donations,[3] including market authorization and shelf-life, identification as "essential medicines", language of

[1] For example, chemical synthesis of neuraminidase inhibitors involved hazardous reactions, and zanamivir manufacture required formulation for inhalation and production of inhalation devices.

[2] *Comparative analysis of national pandemic influenza preparedness plans* (unpublished draft, 2011).

[3] *Interagency guidelines on drug donations* revised 1999. http://whqlibdoc.who.int/hq/1999/who_edm_par_99.4.pdf (accessed 19 January 1999).

product labelling, shipping and disposal costs. One barrier to donation might be products and needs that do not fully meet these guidelines.

Illustrative quantity targets

Quantity targets have been established on the basis of two possible periods of use as an influenza pandemic develops.

Early response: An important consideration in response measures during the early stages of a pandemic is that a vaccine is unlikely to be available for the first several months. Antiviral agents are particularly important during this period, for reducing anxiety and treating illness. It is also possible (but not certain) that rapid containment could be initiated. Antiviral agents will therefore be needed to prevent illness in people at risk of infection and to reduce the spread of infection. During this early period, when uncertainty and public concern may be high, all countries are likely to want access to antiviral medicines.

Sustained response: In the event that a new virus spreads globally in a pandemic, it is likely that there will be increased demand for antiviral medicines for the treatment of clinical cases (and possibly also for prevention of infection), so as to reduce severe illness and mortality. As the new virus may be expected to circulate for one to two years, and vaccines may not be fully deployed until after one or two epidemic waves, there will be a continuous exceptional demand for antiviral medicines.

Illustrative quantity targets are described for these two periods of use. For each target, two quantities are shown: quantities to cover target populations in group 1 (72 countries) and group 2 (105 countries) (see above). Thus, in implementing a programme to increase access to antiviral medicines, two choices must be made: the number of countries to be covered by the programme and whether to plan for early response only or for support throughout the pandemic (early response plus sustained response).

Target 1: Early response

A global stockpile of 3 million treatment courses is available for deployment to Member States or regions first affected by an outbreak with pandemic potential, for the purpose of rapid response and to limit the initial spread of the outbreak.[1] It is assumed that this stockpile would be used in any country or region where antiviral medicines are not immediately available and where an urgent response is necessary to meet international public health needs. Although an operation of this type was not attempted for the pandemic (H1N1) 2009, because of the rapid initial spread of the virus, a future pandemic might start under different circumstances.

In addition to the global stockpile, sufficient antiviral medicine should be available for immediate distribution to countries (group 1 or 2) to ensure that they have access to some antiviral medicines at the start of a potential pandemic. This amount has been estimated as treatment courses for 0.2% of the population (see rationale below).

Stockpiles of antiviral medicines for use in early response must be established, and the medicines must be physically available before an international emergency or pandemic. As the drug susceptibility profile of a new pandemic virus cannot be predicted, two classes of antiviral medicine should ideally

[1] *WHO interim planning guidance for rapid containment of the initial emergence of pandemic influenza* (draft, 2009).

be available for early response, i.e. a neuraminidase inhibitor (oseltamivir or zanamivir) and an adamantane (amantadine or rimantadine). This would represent a total of 18 million treatment courses (9 million of each class of antiviral medicine) to provide a global stockpile and to cover group 1 countries only. If the scope is extended to group 2, the target would be 26 million treatment courses (13 million of each class of antiviral medicine) (Table 9).

Table 9. Treatment courses of each class of antiviral medicine required for early response

	Group 1 countries	Group 2 countries
No. of countries	72	105
Population (billions)	2.95	4.85
Global stockpile (millions of treatment courses)	6	6
Additional stock for country distribution (millions of treatment courses)	12	20
Target total (millions of treatment courses)	18	26

Target 2: Early response plus sustained response

The aim of target 2 is to ensure sufficient courses of antiviral treatment for the early response described under target 1, plus a quantity sufficient to allow all countries to treat (within appropriate guidelines) people seeking medical care. This represents 2.25% of the population, as set out in more detail under "rationale" below.

Unlike target 1, physical stockpiles of antiviral medicines are not required to meet target 2 requirements, as, on the basis of current production figures, the quantities could be provided by manufacturers at the time of a pandemic with existing global manufacturing capacity. This would reduce costs and address the disadvantages of stockpiling, such as finite shelf-life and the need to stockpile both classes of antiviral medicine. Pre-purchase agreements with manufacturers of antiviral agents might be necessary in order to ensure real-time access to the necessary quantities when required (Table 10).

Table 10. Treatment courses required for sustained response (in addition to target 1)

	Group 1 countries	Group 2 countries
No. of countries	72	105
Population (billions)	2.95	4.85
No. of treatment courses of antiviral agents required (millions)	66	109

These quantity targets are within the maximum global manufacturing capacity for oseltamivir, although this scale of manufacture would take up to 12 months to achieve from its current (seasonal) levels. (See Annex 3 for a summary of information on available antiviral medicines.)

Rationale for quantity targets

Target 1: This quantity target has two components:

- A global stockpile for rapid response and to limit the spread of an outbreak. Since 2006, WHO has had available a stockpile of 3 million treatment courses of oseltamivir, earmarked for rapid response. This quantity is consistent with two international expert assessments, which concluded that a stockpile of 1–3 million treatment courses should be sufficient for potential containment of an outbreak.[1,2]

- Sufficient antiviral medicines to meet treatment needs of high priority. The quantity proposed in target 1 is based on experience of the 2009 influenza pandemic. WHO was able to make available to 72 countries (on the basis of public health needs assessed at the time[3]) 3.7 million treatment courses, representing coverage of 0.2% of the population, which appears to have been sufficient as WHO is not aware of any requests for support from Member States that could not be met.

The quantity proposed is further validated by an analysis of the reported numbers of hospitalizations of patients with pandemic (H1N1) 2009 infection in the first 12 months of the pandemic. In most countries with adequate surveillance and reporting systems, the number was 10–50 per 100 000 population (i.e. 0.05%).[4] In addition, previous modelling analyses showed that the number of hospitalized patients in the event of a pandemic would represent 0.1–0.2% of the population.[5] Thus, a population coverage of 0.2% would be sufficient to meet the most urgent treatment needs and is consistent with both previous estimates and actual experience of the 2009 pandemic.

Although this quantity target is described as having two components (early response stockpile and material for immediate country distribution), the material could be regarded as a single stockpile to be distributed appropriately, depending on actual response needs. A more severe pandemic could have a different pattern from that in 2009, leading to different priorities for response.

Target 2: Target 2 is based on the quantity of antiviral medicine needed to treat all patients seeking care (and is in accordance with relevant WHO and national guidelines). The figure of 2.25% of the target populations is consistent with two approaches to estimating treatment needs. The target is consistent with an estimate of the (median) quantities of antiviral medicines actually distributed in upper-middle and high-income countries during the 2009 pandemic. In developing this target, the distribution of antiviral medicines in upper-middle- and high-income countries through established

[1] M. J. Longini, A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. Cummings, and M. E. Halloran, (2005) "Containing pandemic influenza at the source," *Science*, vol. 309, no. 5737, pp. 1083-1087.

[2] Ferguson NM, Cummings DA, Cauchemez S, Fraser C, Riley S, Meeyai A, Iamsirithaworn S, Burke DS (2005) Strategies for containing and emerging influenza pandemic in Southeast Asia. *Nature*, 2005. 437(7056):209-14.

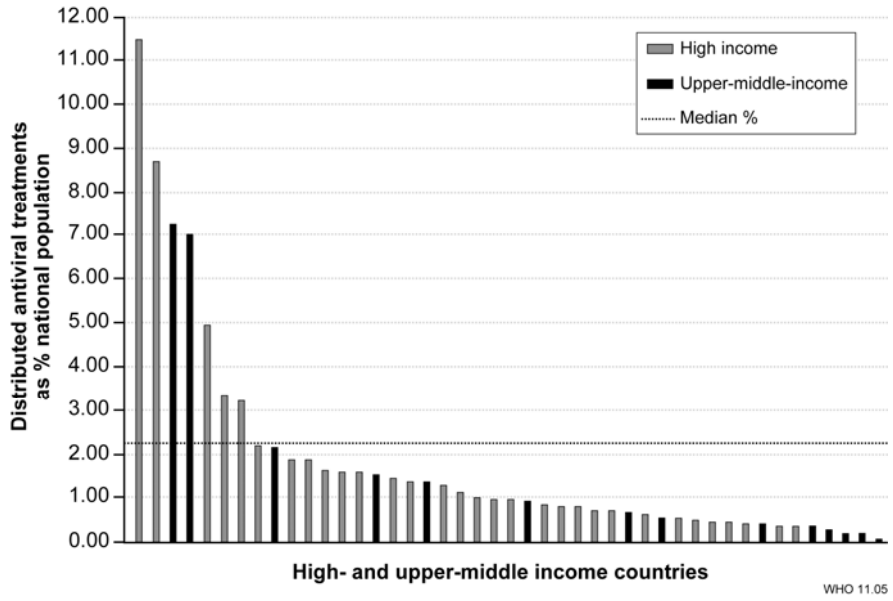
[3] The list of recipient countries was based on the GAVI Alliance list of eligible countries but included Mexico, which was the first country affected by the pandemic, and excluded India, which had national manufacturing capacity for oseltamivir that had been prequalified by WHO.

[4] Data extracted from reports from Member States.

[5] See for example Meltzer MI, Cox NJ, Fukuda K. The economic impact of pandemic influenza in the United States: priorities for intervention. *Emerging Infectious Diseases*, 1999; 5:659–671.

supply chains[1] was estimated. Figure 13 illustrates the quantities of antiviral medicine that were distributed in these countries.[2] The (median) volume distributed represented 2.25% of the populations of these countries. This figure is also consistent with estimates of primary care consultation rates for seasonal influenza of up to 2% of population,[3,4] although higher figures were used in some recent planning assumptions.[5]

Figure 13. Distribution of antiviral medicines, April 2009 – October 2010, in high- and upper- middle-income countries



Strategic options

The two broad strategies for facilitating and improving affordable access are diversification of manufacture and direct procurement and deployment, within which there are several complementary options.

Strategic option 1: Diversification of manufacture

[1] The extent to which material distributed from national stockpiles is included in these data is uncertain, but, as this affects only a few countries, it is unlikely to alter the median distribution quantity significantly.

[2] Data on medicines distributed through commercial supply chains from IMS Health Inc. The quantities of medicines released from national stockpiles were derived from a range of public information sources.

[3] Fleming D. The impact of three influenza epidemics on primary care in England and Wales. *Pharmacoeconomics*, 1996; Suppl 3:38–45.

[4] Pitman RJ, Melegaro A, Gelb D, Siddiqui MR, Gay NJ, Edmunds WJ. Assessing the burden of influenza and other respiratory infections in England and Wales. *Journal of Infection*, 2007; 54:530–538.

[5] *Pandemic influenza preparedness and mitigation in refugee and displaced populations. WHO guidelines for humanitarian agencies*. 2nd Ed. Geneva, World Health Organization, 2008. http://www.who.int/diseasecontrol_emergencies/HSE_EPR_DCE_2008_3rweb.pdf (accessed 18 January 2011).

The development, production and deployment of antiviral medicines rely primarily on a market economy. The contribution of the pharmaceutical industry to access and affordability, through such mechanisms as facilitated access to technology, intellectual property and lower prices, is important. Recent examples of mechanisms that involved industry participation include technology transfer and facilitating local and regional generic manufacture.

Technology transfer, whereby a company holding intellectual property rights, other know-how or capability, makes these available to interested parties to allow them to manufacture the product, may increase capacity (both quantity and geographical coverage) and reduce prices. It can take the form of:

- local manufacture (under sub-licence), undertaken by both Roche and GlaxoSmithKline, which granted manufacturing sub-licences to manufacturers in India and China, respectively;[1,2]

- sale of active pharmaceutical ingredient (API), also referred to as "bulk drug substance" for local secondary manufacture, which is an example of partial technology transfer and has been practised by Roche for oseltamivir; and

- a patent pool, which is a variation of local manufacture under licence. In this approach, licences to the intellectual property are pooled, and technology transfer is managed through a third party. For example, UNITAID is establishing a voluntary patent pool for medicines to reduce prices and ensure the availability of AIDS medicines in developing countries.[3] This option may be more appropriate for future products.

Facilitating local and regional generic manufacture: There are no intellectual property barriers to local production of products for which there is no intellectual property protection and in countries in which patent holders have elected not to seek protection. Investment in local manufacturing capacity and expertise would be an option in such cases, although transfer of know-how may be required.

Activities:

- *Negotiation with industry*: For manufacture in countries in which patent protection exists, agreements must be established with pharmaceutical companies for access to intellectual property and know-how and for tiered pricing structures.

- *Development of national manufacturing and distribution capacity*: In order for transferred technology to be effectively and sustainably used, capacity for primary (active pharmaceutical ingredient) and secondary (finishing) manufacture and effective deployment of medicines are needed.

- *Development of (medicines) regulatory capacity*: Countries with no regulatory or approval systems for medicines will have to put in place processes to provide assurance of the quality and

[1] Reddy D. Responding to pandemic (H1N1) 2009 influenza: the role of oseltamivir. *Journal of Antimicrobial Therapy*, 2010; 65 Suppl 2: pp35-40 http://jac.oxfordjournals.org/content/65/suppl_2/ii35.full.pdf+html (accessed 20 January 2011).

[2] See http://www.gsk.com/policies/GSK-on-pandemic-preparedness-dev-countires.pdf (accessed 25 January 2011).

[3] http://www.unitaid.eu/en/The-Medicines-Patent-Pool-Initiative.html (accessed 21 January 2011).

safety of medicines, market authorizations and post-market surveillance (adverse event reporting). The WHO prequalification programme[1] may support this activity.

Feasibility: There are many precedents for most aspects of the above option, and it represents a low-cost solution for industry, as the aim is to make medicines available in markets where there is currently low access. Establishing successful local (manufacturing) capacity requires capital investment, sustained support and market demand.

Impact: This option may increase global capacity, reduce local dependence on international markets, allow development of local or regional capacity and reduce prices. The purchase and stockpiling of active pharmaceutical ingredients may overcome the finite short life of finished products (as different criteria apply to active pharmaceutical ingredients) and reduce costs by use of local secondary manufacture.

Strategic option 2: Direct procurement and deployment

Another approach to increasing access and deployment of antiviral medicines is direct procurement (by purchase or donation) from manufacturers. This can be achieved by:

- *Donation of medicines by manufacturers to form global or regional stockpiles*: Antiviral medicines distributed to Member States during the 2009 influenza pandemic were obtained by WHO as direct donations from manufacturers.

- *Purchase of medicines to form global or regional stockpiles*: The ASEAN stockpile of 0.9 million treatment courses of oseltamivir and other medical supplies was established in this manner.[2]

- *Establishment of a global fund for medicines purchase*: UNITAID[3] was established on this model. It guarantees purchase of products from specific manufacturers, thereby increasing supply, promoting the development of needed products, creating a sustainable market and reducing prices.

- *Flexible purchasing options*: Roche and GlaxoSmithKline have offered tiered pricing[4,5] for oseltamivir and zanamivir, respectively, whereby lower market prices are offered to lower-income countries. The Roche "Tamiflu Reserve Program"[4] also includes staged payment and storage options.

[1] See http://apps.who.int/prequal/default.htm (accessed 21 January 2011).

[2] http://www.wpro.who.int/media_centre/press_releases/pr_20060503.htm (accessed 12 January 2011).

[3] http://unitaid.eu/ (accessed 12 January 2011).

[4] Reddy D. Responding to pandemic (H1N1) 2009 influenza: the role of oseltamivir. *Journal of Antimicrobial Therapy*, 2010; 65 Suppl 2 pp 35-40. http://jac.oxfordjournals.org/content/65/suppl_2/ii35.full.pdf+html (accessed 20 January 2011).

[5] See http://www.gsk.com/policies/GSK-on-pandemic-preparedness-dev-countires.pdf (accessed 25 January 2011).

Activities:

- The primary requirement is availability of funds for procurement (resource mobilization).
- All medicines purchased by United Nations organizations must be approved under the WHO prequalification programme.
- Mechanisms must be in place to manage, store, distribute and replenish stocks.
- Criteria to ensure equitable access must be defined.

Feasibility: Success will be determined by the availability of funds (or donations in kind). Stockpiling has the disadvantage that medicines have a finite shelf-life and must be properly destroyed and replaced. Reliance on purchase in time of need is based on the assumption that medicines are available and can be distributed rapidly. Drug donations to countries should be managed in accordance with interagency guidelines.[1]

Impact: These options would increase access to antiviral medicines.

Costs:

For the indicative costs set out below, a purchase price of US$ 6.5 for a treatment course of oseltamivir was used, on the basis of the estimated price of this drug for a low-income country. A purchase price of US$ 1.6 was used for a treatment course of amantadine, on the basis of the lowest published price. The costs are based on the "procurement and deployment" option described above, on the grounds that technology transfer costs would be reflected in the final (local) market price of the product.

The costs of developing and maintaining in-country distribution were not considered, although distribution is essential for effective use of antiviral medicines, as patients presenting with illness must be treated immediately.

The costs of accessing antiviral medicines under this strategic option are summarized in Table 11.

[1] *Interagency guidelines for drug donations*. http://whqlibdoc.who.int/hq/1999/who_edm_par_99.4.pdf (accessed 12 January 2011).

Table 11. Costs of accessing antiviral medicines based on the strategic option of procurement and deployment

Target[1]	Cost (US$ million)		
	One-time cost[2]	Replacement and operating costs[3] (per annum)	Surge cost at time of a pandemic[4]
Early response in 72 countries (For each of 2 antiviral medicines, a 3 million treatment course stockpile, plus additional medicine to treat 0.2% of population.)	~82	~11	Not applicable
Early response in 105 countries	~118	~16	Not applicable
Early plus sustained response in 72 countries (as 1, plus coverage of 2.25% of population with one antiviral medicine)	~82	~11	~462
Early plus sustained response in 105 countries	~118	~16	~763

[1] On the assumption that both classes of antiviral agent are included for early response. If adamantanes are not included, the "one-time cost" and the "operating expenses" will be reduced by 20–25%.

[2] Based on US$ 6.5 per treatment course plus US$ 0.5 per course for international distribution. Does not allow for the fact that 5 million treatment courses are already available as a WHO stockpile (which accounts for US$ 40 million in this column).

[3] Based on US$ 0.05 per course for storage and maintenance plus annual re-purchase (one seventh of the stock) to maintain a stockpile within the shelf-life.

[4] Based on price of oseltamivir.

Diagnostic reagents and test kits

Goal

To ensure that Member States have access to the diagnostic reagents and test kits necessary for identifying cases of pandemic influenza.

Approach, limitations, assumptions and data sources

Approach

Two purposes were considered for the use of influenza diagnostic tests: a public health and a clinical purpose. In the public health purpose, confirmation of influenza virus infection by laboratory analysis permits the identification of outbreaks and characterization of the viruses. It is in this way that new viruses with pandemic potential are identified. In the clinical purpose, confirmation of influenza virus infection and characterization of the virus contribute to clinical management; however, as described below, such testing is not necessary for all patients.

The reagents and test kits necessary for both of these purposes may by provided by either the public sector (non-commercial) or on a commercial basis from manufacturers.[1] Provision of public sector non-commercial diagnostic reagents and test kits by WHO Collaborating Centres and other laboratories under their terms of reference[2] is described below. Access to commercially provided equipment, technology platforms, diagnostic reagents and test kits sold for use in the laboratory, which are integral to laboratory diagnostic capacity, are included in the scope and costs described in section III. Access to rapid diagnostic test kits[3] for use outside a laboratory is discussed below.

Limitations

To date, few data are available on the efficacy and cost–benefits of rapid diagnostic tests for influenza, and WHO has been able to provide only limited guidance on their use.[4]

Issues of intellectual property rights associated with such products were not analysed in detail.

Estimated prices for diagnostic kits were derived from publically reported retail prices.[5] The price that Member States pay for commercial diagnostic kits will likely be determined by negotiation and may depend on scale, the market (country) and other factors.

Quantity targets and their costs were not determined for this goal, as rapid diagnostic tests for influenza are at too early a stage of development and commercialization for a meaningful assessment.

Assumptions

It was assumed that Collaborating Centres will continue to provide reagents and test kits on the same basis and in accordance with their WHO terms of reference.

Specific testing for influenza virus infection is not necessary (and is not cost-effective) for every patient. Testing can be restricted to a sample of patients in order to identify and monitor outbreaks and epidemics, or to specific patients when additional information is needed for clinical management. More frequent sampling and testing will be needed at the start of an outbreak in order to confirm the presence of influenza virus in the community and to provide samples for characterization of the virus; as an epidemic develops, the frequency of such sampling will probably diminish.

[1] *Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits. Outcome of the resumed intergovernmental meeting* (A62/5 Add.1 paragraph 6.4). http://apps.who.int/gb/ebwha/pdf_files/A62/A62_5Add1-en.pdf (accessed 19 January 2011).

[2] http://www.who.int/csr/disease/influenza/influenzanetwork/en/index.html (accessed 26 January 2011).

[3] For an example of such a product, see http://www.bd.com/ds/productCenter/256050.asp (accessed 19 January 2011).

[4] *Use of influenza rapid diagnostic tests.* http://apps.who.int/tdr/publications/tdr-research-publications/rdt_influenza/pdf/rdt_influenza.pdf (accessed 19 January 2011).

[5] Most information was found for Japan, the United Kingdom and the United States.

Data sources

The conclusions are based on existing data and guidance and extensive use of public information sources, including from manufacturers.

Current state

Background to influenza diagnosis

Methods for diagnosing influenza infection include clinical diagnosis, laboratory tests and rapid diagnostic kits at the point of care.

Clinical diagnosis is based entirely on clinical symptoms reported by individual patients, which form the basis for defining influenza-like illness. It is also the first source of information for surveillance. As many pathogens can cause influenza-like illness, clinical diagnosis of influenza is most reliable when combined with knowledge of currently circulating viruses (i.e. laboratory-based surveillance data).

Laboratory tests can be used to detect influenza virus in clinical specimens and also to characterize the virus.[1] Laboratory tests are the most reliable method for confirming an influenza virus infection, and it is only in a laboratory that viruses can be fully characterized.

Rapid diagnostic kits for use at the point of care are tests for screening for influenza that can be used outside a laboratory. As they are often used at the time and place of patient consultation, they are described as "point-of-care" tests. Results can generally be obtained within 15 minutes, but the tests give only limited information on the virus and are much less reliable than laboratory methods for detecting the virus.

Role of the WHO Network in influenza diagnosis in National Influenza Centres

The WHO Global Influenza Surveillance Network is a global alert mechanism for the emergence of influenza viruses with pandemic potential (see also Annex 3). Characterization of new viruses by WHO Collaborating Centres or National Influenza Centres provides the information necessary for preparation of laboratory reagents and protocols to detect and characterize the viruses. Sharing of this information allows all members of the Network to establish diagnostic capability. A critical aspect of the operation of the Network is that its members can conduct tests in a consistent matter. This is achieved by sending reagent kits and panels from one of the Collaborating Centres, so that all laboratories have access to a common set of reagents. Reference standards[2] are also sent from a Collaborating Centre, so that if a National Influenza Centre elects to procure or prepare its own

[1] Some laboratory tests allow detection of antibodies to influenza virus (serology tests). These are used to show past infection with influenza virus, primarily to assess the extent of spread in a population and vaccine efficacy.

[2] Reference standards are materials that are used as benchmarks to calibrate or validate tests and reagents. For an example of such materials, see information from the National Institute for Biological Standards and Control at http://www.nibsc.ac.uk/services/reference_standards/biological_reference_materials.aspx (accessed 25 January 2011).

reagents[1] (on the basis of information shared on the Network), the locally developed methods and reagents can be validated against shared standards.[2]

Use of rapid diagnostic tests at the point of care

Rapid diagnostic tests are potentially useful in outbreak and epidemic response, as results can be obtained rapidly, and no laboratory facilities are required for their use. Rapid tests could be used for diagnosing influenza in several ways:

- *to support clinical diagnosis*: Rapid diagnostic tests could guide the treatment of patients by providing a test result at the point of initial presentation. Both WHO and manufacturers advise, however, that these tests should not be relied upon for this purpose, as they are much less sensitive than laboratory methods, and many infections will be missed.[3]

- *for outbreak alert and response*: Use of rapid diagnostic tests as part of an outbreak investigation could provide rapid confirmation of influenza infection, although follow-up laboratory investigations are essential for characterizing the viruses.

- *for surveillance*: Use of rapid diagnostic tests in routine surveillance could provide rapid assessment but would have to be complemented by specific laboratory-based diagnosis. As above, follow-up laboratory investigations are essential for characterizing the viruses, particularly for emerging strains.

Development of rapid diagnostic tests

Rapid diagnostic tests generally contain, as a component of their manufacture, virus products (proteins or antigens) and other materials (antibodies). These virus components are not strain-specific, so the manufacture of such tests may not have to rely on access to new strains. In order to confirm the usefulness of rapid diagnostic tests in a pandemic, it would be necessary to demonstrate their ability to detect a new virus.

Access and affordability of rapid diagnostic tests

Rapid diagnostic tests are available from commercial vendors in some high-income countries. Their availability to low- and middle-income countries has not been evaluated. A brief Internet search found 39 rapid diagnostic tests from major manufacturers, at a price ranging from US$ 9 to US$ 39 per test. The price of the same test varied from US$ 30.7 (in the United Kingdom) to US$ 9 (in the Philippines).

[1] This is possible for some reagents; others, such as antisera, are harder to reproduce locally and are usually provided by a collaborating centre.

[2] WHO Collaborating Centres provide all National Influenza Centres with a kit of diagnostic reagents, containing polyclonal sera, monoclonal antibodies and viral antigens for the relevant influenza strains. These kits are updated and distributed annually to ensure standardized analysis of current strains and submission of antigenic variants to WHO Collaborating Centres for detailed analysis. http://www.who.int/csr/disease/influenza/surveillance/en/ (accessed 24 January 2011).

[3] A positive result can be relied on as confirmation of influenza infection, but a negative result does not exclude influenza as the diagnosis.

Obstacles to access to rapid diagnostic tests

- purchase price;
- intellectual property considerations and know-how for in-country development. While the reagents and virus strains used may not be subject to intellectual property constraints, the technologies for producing rapid diagnostic tests may be proprietary.
- regulatory requirements: In some countries, the use of such rapid diagnostic tests is subject to regulatory review and approval.[1]

Obstacles to the use of rapid diagnostic tests, even where they are available, include lack of a clear rationale and cost–benefit of use and insufficient sensitivity and specificity.

Strategic options for rapid diagnostic tests

If access to commercially produced rapid diagnostic tests should be considered valuable for public health, the options for access would be similar to those described for antiviral medicines. These include purchase by individual countries from international manufacturers; local manufacture after licensing (where required) and technology transfer; and local product development, whereby a local manufacturer develops its own reagents and applies the generic technology.

VI. SUSTAINABLE FINANCING, SOLIDARITY MECHANISMS AND OTHER APPROACHES

Goal

To establish sustainable financing mechanisms for pandemic influenza preparedness and response.[2]

Approach, assumptions, data sources and limitations

Approach

The costs of the options described above were used as the basis for estimating potential financial needs over the next five years. Examples were gathered of relevant financing mechanisms used to raise funds for health (e.g. those of UNITAID, the Global Fund to Fight AIDS, Tuberculosis and Malaria and the GAVI Alliance), and potential funding mechanisms for pandemic influenza preparedness were identified on the basis of these models. When possible, illustrative quantified estimates were made. The estimates are illustrative; additional analysis would be needed to determine the amounts that might be raised.

[1] For example, in the United States, professional use of non-laboratory test kits requires approval from the Food and Drug Administration. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124202.htm (accessed 21 January 2011).

[2] See document A62/5 Add.1, Annex, paragraph 6.14 on sustainable and innovative financing mechanisms.

Assumptions

It was assumed that pandemic influenza preparedness will continue to be a priority for WHO Member States, with expected gaps in available financing to meet projected needs. No assumptions were made about the feasibility, set-up costs or operating costs of potential financing models for pandemic influenza preparedness. Further detailed analyses of various options will be conducted on the basis of the preferences of Member States.

Data sources and limitations

The sources for all cost estimates included reports from WHO, other reports in the public domain and expert interviews.

Current state

Financing for pandemic influenza preparedness, including the response to pandemic (H1N1) 2009

Current financing for pandemic influenza preparedness includes funding to support both seasonal preparedness and vaccines and preparedness for future pandemic events. Funding is provided at country, regional and global levels and covers various types of costs. Funding by Member States includes that of their national laboratory and surveillance systems, that for procurement of vaccines and regular financial support for laboratories in the WHO Network in their countries (National Influenza Centres, WHO Collaborating Centres for influenza, Essential Regulatory Laboratories and H5 Reference Laboratories) and that for research and development of seasonal influenza vaccines and influenza medicines. Funding for activities can be provided by Member States, multilateral organizations, development banks, philanthropic organizations, private sector institutions, nongovernmental organizations and private citizens.

No sustainable financing mechanisms are currently in place to fund a number of elements of the pandemic influenza preparedness benefit-sharing system,[1] the aim of which is to increase global pandemic preparedness and response capacity, particularly in developing countries. Ad hoc contributions are unpredictable by nature and therefore unsustainable; they cannot support long-term activities that could strengthen national and global capacity and preparedness to respond to influenza and other pandemics.

At the outset of the pandemic (H1N1) 2009, the Director-General called for global solidarity to ensure that countries in need would have access to pandemic-related supplies, including vaccines, antiviral agents and other life-saving pharmaceutical and non-pharmaceutical products. In September 2009, the total cost of the H1N1 response for developing countries was projected to be US$ 1480 million.[2] By June 2010, at least US$ 536 million had been mobilized.[2]

[1] See document A62/5 Add.1, Annex, section 6.

[2] *Urgent support for developing countries' responses to the H1N1 influenza pandemic*. WHO, OCHA, UNSIC, 2009. http://www.reliefweb.int/rw/RWFiles2009.nsf/FilesByRWDocUnidFilename/VDUX-7XFNC6-full_report.pdf/$File/full_report.pdf.

Projected resource requirements for pandemic preparedness

Tables 12–14 summarize the estimated costs of the strategic options identified in the previous sections. Readers should review the actual sections to gain the full picture of each option, including impact, feasibility and other considerations. Depending on the decisions taken by Member States, multiple funding sources and mechanisms may be required.

Table 12. Laboratory and surveillance capacity-building[1]

Target	Strategic option	Cost (US$ million)		
		One-time	Operating expenses	Surge cost at time of pandemic[2]
Indicator-based surveillance				
1. All reach capacity level 3.	1. In-country capacity for all countries	~ 4–7	~ 10–15	~ 30–74
	2. In-country capacity for larger countries, support to access external capacity for smaller countries	~ 4–7	~ 10–15	~ 30–74
2. All reach capacity level 3, and at least 20% reach capacity level 4.	1	~ 5–7	~ 10–15	~ 30–74
	2	~ 5–7	~ 10–15	~ 30–74
3. All reach capacity level 3, and at least 40% reach capacity level 4.	1	~ 7–10	~ 12–18	~ 30–74
	2	~ 7–10	~ 12–18	~ 30–74
Event-based surveillance				
1. All reach capacity level 2, and at least 50% reach capacity level 3.	1. In-country capacity for all countries	~ 1	~ 13–20	~ 74–221
	2. In-country capacity for larger countries, support to access external capacity for smaller countries	~ 1	~ 13–20	~ 74–221
2. All reach capacity level 3.	1	~ 1–2	~ 29–44	~ 74–221
	2	~ 1-2	~ 29–44	~ 74–221
3. All reach capacity level 3, and at least 20% reach capacity level 4.	1	~ 2–3	~ 29–44	~ 74–221
	2	~ 2–3	~ 29–44	~ 74–221

Laboratory analysis and surveillance				
1. All countries reach capacity level 3.	1. Build or support laboratory capacity to achieve recognition as a national influenza centre.	~ 7–11	~ 10–16	~ 56–169
	2. Build or support laboratory capacity for larger countries; support access external capacity for smaller countries.	~ 5–7	~ 9–13	~ 56–169
2. All countries reach capacity level 4.	1	~ 10–14	~17–26	~ 56–169
	2	~ 6–9	~ 13–20	~ 56–169
3. All countries reach capacity level 4; at least 20% reach capacity level 5; at least one collaborating centre per region.	1	~ 20–30	~ 25–38	~ 56–169
	2	~ 17–26	~ 22–32	~ 56–169
Virus sample shipping				
1. All countries reach capacity level 2.	2. Expand WHO influenza specimen shipping project to all countries without adequate in-country shipping capacity.	Not applicable	< 1	~ 1–3
2. All countries reach capacity level 3.	1. Support in-country capacity-building for all countries.	~ 1	~ 1	~ 1–3

[1] Estimated costs are rounded to the nearest US$ 1 million; these estimates are preliminary and should be validated in further studies.

[2] Operating expenses in a pandemic year: these are substantially higher than the costs in the column "Operating expenses", which are for a non-pandemic year.

Table 13. Expanding global influenza vaccine production capacity

Strategic option	Cost (US$ million)[1]		
	One-time	Operating expenses	Surge cost at time of pandemic[2]
1. Increase seasonal demand	~ 280	~ 3720	Not applicable
2. Build or expand capacity in countries that have government support or a business case to sustain production	~125–490	0	Not applicable
3. Subsidize idle capacity above seasonal demand levels	~ 330–770 (new capacity)	~280–450 (existing capacity) ~ 370–1470 (new capacity)	Not applicable
4. Stimulate capacity to convert IIV to LAIV	~ 130–230	< 1	Not applicable
5. Expand use of potent adjuvant technology	~ 230–420	< 1	Not applicable
6. Convert other biological capacity to pandemic vaccine production at onset of pandemic	~ 38–94	~ 4–9	Not applicable
7. Accelerate development of new technologies	~ 50–200 per development programme	0	Not applicable

[1] Estimated costs rounded to nearest US$ 5 million; these estimates are preliminary and should be validated in further studies.

[2] Costs include those to establish vaccine manufacturing capacity but not the purchase or deployment of vaccine in the event of a pandemic.

Table 14. Access, affordability and effective deployment

Target	Strategic option	Cost (US$ million)[1]		
		One-time[2]	Operating expenses	Surge cost at time of pandemic
Vaccines				
1. Health-care workers	1. Establish new pre-purchase agreements. 2. Expand existing pre-purchase agreements.	Not applicable	~ 10	~ 70
2. Essential personnel and pregnant women	1 2	Not applicable	~ 140	~ 1155
3. Essential personnel and populations at risk	1	Not applicable	~ 335	~ 2795

Antiviral agents				
	1. Early response in 72 countries	~ 82	~ 11	Not applicable
	1. Early response in 105 countries	~ 118	~ 16	Not applicable
	2. Early plus sustained response in 72 countries	~ 82	~ 11	~ 462
	2. Early plus sustained response in 105 countries	~ 118	~ 16	~ 763

[1] Estimated costs rounded to nearest US$ 5 million; these estimates are preliminary and should be validated in further studies for antiviral agents, costs are not rounded.

[2] Assuming pre-purchase agreement terms are similar to those of existing pre-purchase agreements and that the key terms include no up-front payment.

Potential funding sources and mechanisms

National governments provide a substantial share of the pandemic influenza financing that benefits their own countries directly. This is likely to continue to be the main financing mechanism for improving national public health systems, including pandemic influenza preparedness. National sources of health funding are largely derived from general taxation revenues and national health or social insurance schemes.

Countries use various mechanisms to generate further funds for health, some of which might be applied to pandemic influenza preparedness. For example, mandatory levies on certain products and tax-based systems are used to support health. The Thai Health Promotion Foundation (ThaiHealth), established in 2001, raises approximately US $35 million per year from a 2% Government excise tax on tobacco and alcohol. The funds are used to provide grants for a range of health promotion projects. The WHO *World health report on health financing* (2010) cites several other examples.[1] Gabon imposed a 1.5% levy on the post-tax profits of companies that handle remittances and a 10% tax on mobile phone operators. Between them, the two taxes raised the equivalent of US$ 30 million for health in 2009. Similarly, for many years, the Government of Pakistan has been taxing the profits of pharmaceutical companies to finance part of its health spending.

Additional financing for pandemic influenza is derived from international sources. A call for global solidarity at the outset of pandemic (H1N1) 2009 resulted in a global resource pool, which is not sustainable given the time-limited nature of the event. Potential funding mechanisms described in this section focus on international sources and focus specifically on mechanisms that would be predictable and sustainable.[2]

[1] *World health report*. Geneva, World Health Organization, 2010, p. 29.

[2] These mechanisms are to be applied in the broader global health financing environment. As a result, in assessing the feasibility of any of these mechanisms, it is important to consider the relative priority that donors and national governments give to pandemic influenza risk.

Overview of funding mechanisms

A number of funding mechanisms are currently used in global health, some of which (through adaptation, replication or direct integration) may be relevant to pandemic influenza preparedness (See Annex 4 for further details of the mechanisms.) The types of funding mechanism to be considered include:

- *Mechanisms to raise funds or resources*, including levies on products or services, subscriptions and assessments, endowment funds, debt relief, loans and cash donations. In defined cases, in-kind donations may further supplement cash donations.

- *Mechanisms to better match the timing of fund availability or to improve risk management and reduce costs* by passing risk onto those who are better able to pool it or hedge against it; these mechanisms include the issuance of bonds, and insurance.

Examples of mechanisms relevant to pandemic influenza preparedness are described below, with illustrative applications. All the funding amounts are illustrative; further analysis would be needed to assess the amounts that might be raised in practice. None of the mechanisms described is exclusive; several could be pursued in parallel.

Mechanisms to raise funds

Mandatory levies on products or services assessed by governments and collected through the national tax system can be raised from products or services that are either related or unrelated to the goal. Examples include the United States National Vaccine Injury Compensation Program, Brazil's Provisional Contribution on Financial Transactions, the airline solidarity levy used to support UNITAID (in participating countries) and the proposed Currency Transaction Development Levy.

Example 1: The United States National Vaccine Injury Compensation Program was created in 1988 to compensate people for vaccine-related injury or for death claims for covered vaccines. This programme is funded through a levy of US$ 0.75 per dose on certain vaccines sold in the United States. A total of US$ 235 million was raised in 2009.[1] The total assets of the fund as at 30 September 2010 were US$ 3200 million.[2]

Example 2: UNITAID is an international facility for the purchase of drugs and diagnostics to be used in the treatment of HIV/AIDS, malaria and tuberculosis**.** Participating countries raise funds through either a solidarity levy on airline tickets purchased in the country or from voluntary contributions to the development budget. Those countries that rely on the airline ticket levy calculate the amount from a formula based on economy or business class travel, amounting to €1 for an economy-class fare to €40 for a business-class fare.[3] In 2009, countries using the solidarity levy (Chile, France, Madagascar, Mauritius, Niger and the Republic of Korea) generated US$ 170 million for UNITAID, with France

[1] *Budget of the United States Government: Appendix fiscal year 2011* (detailed budget estimates by agency for Department of Health and Human Services) http://www.gpoaccess.gov/usbudget/fy11/pdf/appendix/hhs.pdf. (accessed 15 February 2011).

[2] Unaudited balance sheet; ftp://ftp.publicdebt.treas.gov/dfi/tfmb/dfivi0910.pdf.

[3] http://www.brookings.edu/~/media/Files/Projects/globalhealth/healthsnapshots/airline.pdf. (accessed 15 February 2011).

contributing US$ 160 million of that amount.[1] The total UNITAID revenue in 2009 was over US$ 300 million.

Example 3: Voluntary levies have been applied to other consumer and industry activities, such as air travel and mobile phone use. The UNICEF Check Out for Children, an alliance between Starwood Hotels & Resorts and UNICEF, invites guests to add US$ 1 (or local currency equivalent) to their bill upon check out, as a donation to UNICEF.

Applying a similar model to pandemic influenza preparedness: The United States National Vaccine Injury Compensation Program raises money at national level. A similar model might be applied to seasonal influenza vaccine to raise money at global level. As for UNITAID, Member States could choose whether to participate. The model could be applied to sales of seasonal influenza vaccine at a fixed levy per dose (Table 15 shows levies of US$ 0.01, 0.05 and 0.10 per dose) or at a percentage of the price per dose. The levy could be designed to be sensitive to local consumer purchasing power as well as to the needs of industries in the early stages of development.

Table 15. Funds available from applying a levy to sales of seasonal influenza vaccine

No. of seasonal vaccine doses per year (millions)	Levy per dose (US$)	Funds available (US$ million)		
		After 1 year	After 3 years	After 5 years
500	0.01	5	15	25
	0.05	25	75	125
	0.10	50	150	250
750	0.01	8	23	38
	0.05	38	113	188
	0.10	75	225	375
1000	0.01	10	30	50
	0.05	50	150	250
	0.10	100	300	500

Subscriptions and assessments are fees charged to public and private sector entities for participation in networks or multilateral organizations. Examples include subscriptions assessed by the Network of Medical Councils of the South-East Asia Region, the Joint Commission on Accreditation of Healthcare Organizations, the Joint Commission International and the Health InterNetwork Access to Research Initiative.

Applying a similar model to pandemic influenza preparedness: As part of their terms of reference in the WHO Network, collaborating centres and essential regulatory laboratories generate various products of benefit to users (e.g. manufacturers and researchers). These include candidate vaccine viruses, reference reagents, vaccine potency reagents, high-growth reassortant influenza viruses and influenza reference viruses. A possible mechanism for raising funds would be to apply either a yearly subscription fee or a per-product user fee on these products. Table 16 shows the subscription rates that could be charged to various users; they could vary by type of user, for example by some measure of income.

[1] *UNITAID annual report 2009.* http://www.unitaid.eu/images/NewWeb/documents/AR09/unitaid2009ar_web%20spreads.pdf. (accessed 15 February 2011).

Table 16. Funds available from charging a subscription to the WHO Network

Country income classification	No. of institutions	Annual subscription (US$ million)	Funds available (US$ million)		
			After 1 year	After 3 years	After 5 years
Low	20	0.01	0.2	0.6	1.0
		0.10	2	6	10
	40	0.01	0.4	1.2	2.0
		0.10	4	12	20
High	20	1.00	20	60	100
		10.00	200	600	1000
	40	1.00	40	120	200
		10.00	400	1200	2000

Alternatively, Member States themselves could subscribe. Table 17 shows possible subscription rates for Member States, which could also vary by income level.

Table 17. Funds available from charging a subscription to the WHO Network

World Bank income class	Number of participating Member States	Annual subscription (US$ million)	Funds available (US$ million)		
			After 1 year	After 3 years	After 5 years
High	50	0.10	5	15	25
		0.25	13	38	63
		0.50	25	75	125
		1.00	50	150	250
Upper-middle	47	0.10	5	14	24
		0.25	12	35	59
		0.50	24	71	118
		1.00	47	141	235
Lower-middle	54	0.10	5	16	27
		0.25	14	41	68
		0.50	27	81	135
		1.00	54	162	270
Low	42	0.10	4	13	21
		0.25	11	32	53
		0.50	21	63	105
		1.00	42	126	210

Based on data from the World Bank and the Organisation for Economic Co-operation and Development, September 2010.

A number of ***global health initiatives*** have been created to address major global health problems and to increase voluntary cash support by governments, industry and other donors. Examples include the Global Fund to Fight AIDS, Tuberculosis and Malaria and GAVI. Mechanisms to replenish voluntary contributions are unsustainable by nature; however, many of the global health initiatives have been able to generate funds over the past 10 years.

Examples: At October 2010, the GAVI Alliance had US$ 10 600 million in donor commitments and US$ 4500 million in cash receipts from 1999–2009.[1] The Global Fund to Fight AIDS, Tuberculosis and Malaria received US$ 18 200 million in cash donations out of a pledged total of US$ 28 600 million for the period 2001–2015.[2]

Applying a similar model to pandemic influenza preparedness: Approaches similar to those used by these organizations could be used to generate funds for specific pandemic influenza preparedness projects. Table 18 shows how much could be raised if influenza-specific donations amount to 1%, 5% and 10% of average annual donations to GAVI and the Global Fund.

Table 18. Funds available from donations

Organization	Average annual donations (US$ million)	Donations that might similarly be raised for influenza (%)	Funds available (US$ million)		
			After 1 year	After 3 years	After 5 years
GAVI Alliance	410	1	4	12	21
		5	21	62	103
		10	41	123	205
Global Fund	1200	1	12	36	60
		5	60	180	300
		10	120	360	600

In-kind donations are voluntary donations of products and services by governments, industry and other donors. They are typically used in emergencies, although experience with neglected tropical diseases demonstrates that long-term agreements for donations with companies can be secured.[3] Examples of in-kind contributions include antiviral drugs and vaccines during the pandemic (H1N1) 2009, WHO management of a number of long-term pharmaceutical in-kind contributions for neglected tropical diseases, the Pool for Open Innovation against Neglected Tropical Diseases and the international WHO H5N1 stockpile of vaccine donations. In-kind product donations must be accompanied by financial support for any ancillary products (e.g. syringes).

Example: During the pandemic (H1N1) 2009, an estimated US$ 536 million was mobilized to support developing countries, through donors, loans and vaccine manufacturer donations and discounts, of which an estimated US$ 382 million was in the form of multilateral in-kind donations and vaccine

[1] See GAVI Alliance web site http://www.gavialliance.org.

[2] See Global Fund to Fight AIDS, Tuberculosis and Malaria web site http://www.theglobalfund.org/documents/pledges_contributions.xls.

[3] Merck has contributed ivermectin for onchocerciasis control for over 30 years.

deployment costs.[1] A number of countries also contributed cash for or made in-kind donations of supplies of personal protection equipment.

Applying a similar model to pandemic influenza preparedness: WHO has created structures for in-kind contributions that could be used in the future. Under clear criteria, vaccines, medicines, personal protection equipment and diagnostic kits could be donated. Attention is required to ensure longer-term sustainability, and rules must be established for emergencies, such as pandemics.

Debt relief is partial or total waiving of loans, directly by the lender or indirectly via a third party. As part of the arrangement, the funds allocated to a country to repay the debt can be redirected to support a public good (e.g. health services). Examples include the Global Fund Debt2Health initiative, the World Bank Investment Partnership for Polio and the Heavily Indebted Poor Countries debt-relief programme. Debt-for-health swaps can take up to two years to negotiate and implement.

Example 1: Debt2Health is a partnership between creditors and grant recipient countries in which the Global Fund to Fight AIDS, Tuberculosis and Malaria facilitates agreements to increase recipient countries' investment in health through debt conversion. Under this agreement, creditors forego repayment of a share of their claims on the condition that the recipient country invests in health through Global Fund-approved programmes. Germany was the first creditor to join Debt2Health, with a commitment of US$ 290.2 million for 2008–2010.

Applying a similar model to pandemic influenza preparedness: A similar mechanism could be used to fund specific pandemic influenza preparedness projects that benefit a country that is ready to repay a loan or to pool funds for a global effort to address pandemic influenza preparedness. For example, a country may be ready to repay a loan of US$ 100 million. The creditor would agree to forego 50% of that amount, and US$ 50 million would either be used by the country to pay for pandemic influenza preparedness projects or contributed to a pooled fund at global level, which would be used for pandemic influenza preparedness.

Table 19 shows how much funding could be made available for influenza programmes on the assumption of 25%, 50% and 75% discounts during loan cancellation.

Table 19. Funding that could be made available for influenza programmes on the assumption of 25%, 50% and 75% discounts during loan cancellation

Loan (US$ million)	Discount from loan cancellation (%)	Funds available (US$ million)		
		After 1 year	After 3 years	After 5 years
10	75	3	8	13
	50	5	15	25
	25	8	23	38
100	75	25	75	125
	50	50	150	250
	25	75	225	375

[1] *Urgent support for developing countries' responses to the H1N1 influenza pandemic*. WHO, United Nations Office for the Coordination of Humanitarian Affairs, United Nations System Influenza Coordination, 2010.

Example 2: The World Bank, the Bill & Melinda Gates Foundation, Rotary International and the United Nations Foundation together comprise the Investment Partnership for Polio, a third-party donor that pays off all or part of a country's loan upon successful completion of its poliomyelitis eradication programme. The long-term, low-interest loans are funded through the International Development Association. The partnership was established in 2003 with a trust fund of US$ 25 million from the Bill & Melinda Gates Foundation and US$ 25 million from Rotary International and the United Nations Foundation.[1] The International Development Association's generous loan terms mean that each donor dollar is converted to US$ 2.50–3.00 for affected countries to fight poliomyelitis. The total amount of funding for the partnership was US$ 316.37 million in the period 2003–2009.[2]

Applying a similar model to pandemic influenza preparedness: A similar mechanism might be applied to raising funds for pandemic influenza preparedness. Table 20 shows how much funding might be obtained for influenza programmes on the assumption of influenza-specific donations amounting to 1%, 5% and 10% of the average annual funding of the Investment Partnership for Polio.

Table 20. Funds that could be made available to Pandemic influenza preparedness using the model for the Investment Partnership for Polio

Average annual partnership funding (US$ million)	Estimated funds unlocked (US$ million)	Donations that might similarly be unlocked for influenza (%)	Funds available (US$ million)		
			After 1 year	After 3 years	After 5 years
45	124	1	1	4	6
		5	6	19	31
		10	12	37	62

Mechanisms to better match the timing of needs and to fund availability or to improve risk management and reduce costs

These mechanisms are not exclusive to the fund-raising mechanisms described in the previous section. Member States might voluntarily participate in one or more of these activities.

Bonds are financial instruments that allow their buyers and sellers to change the timing of their cash flow. A bond seller receives a lump-sum payment, the price of the bond, from buyers. In return, the seller commits to pay back the amount, with interest, in regular instalments over a longer period. Examples of bond sellers include the International Finance Facility, issuers of Catastrophe bonds, Diaspora bonds, global development bonds and the Product Development Partnership Financing Facility.

Example 1. In 2006, the GAVI Alliance, the United Kingdom and seven other donor States established the International Financing Facility for Immunization, which sells bonds to raise money for childhood vaccination. The bonds are guaranteed by participating Member States. Effectively, the private sector

[1] United Nations Foundation web site. http://www.unfoundation.org/press-center/press-releases/2003/financial-innovation-will-buy-polio-vaccine.html.

[2] Global Polio Eradication Initiative Annual Report 2009. http://www.polioeradication.org/content/publications/AnnualReport2009_ENG.pdf. (accessed 15 February 2011).

raises the cash for immediate use, and the public sector repays it in the future. To date, the Facility has sold over US$ 2000 million of these bonds to investors, which will be paid back with interest by the donors over the next 3–5 years. Donors have so far committed US$ 5300 million over the next 20 years to fund this effort. Bonds backed by donor countries with good credit ratings reduce both the risk of default (non-payment) and the interest rate charged.

Applying a similar model to pandemic influenza preparedness: This mechanism could be an effective way of paying for major capacity-building (e.g. for upgrading a laboratory and surveillance network). The seller of a bond (e.g. governments, banks) could raise funds on the financial markets, depending on what is required. The interest rate would depend strongly on the amount borrowed, the duration of the bond and the credit worthiness of the potential borrowers.

Example 2: The World Bank established the MultiCat Program in 2009 as a platform through which national governments could issue catastrophe bonds, which function as insurance against catastrophic costs. The sellers of these bonds (e.g. national governments) pay investors interest, as on a normal bond, and the proceeds of the sale of the bond are held in a "special-purpose vehicle". In the event of a predefined catastrophe, such as an earthquake or hurricane of specific magnitude, the interest payments cease and the special-purpose vehicle pays out to the seller (e.g. the national government, which can then use it for event-related costs). If the specified event does not occur, the special-purpose vehicle pays out to the investors, who thus recuperate their principal. The first issuance of these MultiCat bonds raised US$ 290 million, which would be received by the Government of Mexico in the event of a hurricane or earthquake.

Applying a similar model to pandemic influenza preparedness: This mechanism could be applied to finance surge costs for pandemic influenza preparedness. For example, individual countries could issue bonds in the near term in order to finance purchase of vaccines when a pandemic emerges. Bond premium payments could be met by a combination of national governments, foundations and other contributors. The price of such an option, including up-front costs would depend on, inter alia, the creditworthiness of the potential borrowers and the probability of the event.

Private donors, such as insurance companies and other corporations, might find such a facility beneficial, because increasing access to vaccine in the case of a pandemic could decrease the risk for global spread and, therefore, global financial losses. More analysis is needed to assess the financial impact of such a mechanism in the event of a pandemic.

Insurance allows its users to finance future costs, which are uncertain but potentially high, by making small, regular payments.

Example 1: The Caribbean Catastrophic Risk Insurance Facility insures 16 participating Caribbean governments against hurricanes, earthquakes and excessive rainfall. Countries paid membership fees totalling US$ 21 million in 2010 and receive financing when an insured disaster strikes, while the World Bank and the Caribbean Development Bank bear some financial risk for payouts. For example, Haiti's annual premium was US$ 385 500, and it received US$ 7.7 million within two weeks of the earthquake in January 2010.[1]

[1] *CCRIF Annual report (2010).* http://www.ccrif.org/sites/default/files/publications/CCRIF_Annual_ReportSeptember272010_0.pdf. (accessed 15 February 2011).

Applying a similar model to pandemic influenza preparedness: This mechanism could be effective for paying surge expenses at the time of a pandemic, such as for purchase of vaccines, medicines and other commodities. The agreed definition of the event has a substantial influence on the price of the insurance payment terms. If this option is seen as viable, extensive work must be done to determine the definition and payment terms.

Example 2: The World Bank Catastrophe Risk Deferred Drawdown Option is a contingent capital arrangement that guarantees countries access to a credit line of up to 0.25% of gross domestic product (up to US$ 500 million), in exchange for a 0.25% initial fee and committed repayment terms. In 2008, Costa Rica became the first country to use this facility, establishing a US$ 65 million revolving credit line (with an initial fee of US$ 162 000) for use in case of a declared national state of emergency. This insurance is in effect subsidized by the World Bank, whose terms for the contingent capital provided are lower than those demanded by the private market.

Applying a similar model to pandemic influenza preparedness: This mechanism could be applied to pandemic influenza by a variety of options, including expanding existing Catastrophe Risk Deferred Drawdown Option facilities to cover pandemic influenza risk or developing a new, subsidized mechanism to reduce the cost of such arrangements. In the case of a pandemic, the facility would require access to enough money to cover the credit lines extended. As with the Caribbean Catastrophic Risk Insurance Facility, the agreed definition of an event will affect the price of insurance. If this option is seen as viable, further work is needed to define the terms and determine the price range.

Revolving funds use income to finance continuing operations. The initial capital may be generated by any number of national or international sources. Income could come from a service fee charged to fund participants. A fund of this type could be used to buy goods for participants at cheaper prices by consolidating procurement, as well as contributing to better multi-country planning.

Example: Created in 1979 by the WHO Regional Office for the Americas (the Pan-American Health Organization; PAHO), the PAHO Revolving Fund for the purchase of vaccines, syringes and related supplies requires interested countries to forecast their annual needs for certain products; the Fund then issues a comprehensive bid solicitation for the products, thereby securing reduced prices through bulk procurement. The Revolving Fund invoices countries for the purchase cost and adds a 3% service charge. The current capitalization of the Fund is US$ 145 150 000.

Applying a similar model to pandemic influenza preparedness: This mechanism could be used or replicated to ensure bulk purchases of vaccines at pre-negotiated prices, either in advance or at the time of a pandemic. Various funding sources (e.g. national governments, the international mechanisms outlined above) could be used to establish the fund. Some degree of reimbursement and a service fee could be charged to ensure sustainability.

Implementing potential financing mechanisms

A number of principles should be considered in implementing these or any other financing mechanisms for pandemic influenza preparedness.

Competition for global health funds: As the previous examples illustrate, many financing mechanisms are in use for global health. In assessing the feasibility of any potential financing mechanism, it is important to consider the relative priority and urgency placed by donors and national governments on the risk for pandemic influenza.

Balance of funding sources: Given the amount of funds required and the various funding flow requirements (e.g. one-time, operating and surge funding) for pandemic influenza preparedness, no single funding source or mechanism is likely to provide a comprehensive solution. A mix of funding sources and mechanisms will probably be required.

Necessity for political negotiation and agreements: Most of these mechanisms require multilateral agreements, both to generate funds and to manage and disburse them. The time required for these negotiations must be considered in the overall time line for setting up a functioning mechanism.

Building new mechanisms versus using existing ones: For all possible mechanisms, certain decisions will be required, about whether to establish pandemic influenza preparedness-specific mechanisms or to use existing mechanisms to take advantage of organizations, infrastructure and systems already in place.

Mechanisms to hold, manage and disburse funds: While not discussed above, a management model required for an international pool of funds will have to be developed further. As multiple mechanisms might have to be pursued in parallel, due consideration should be given to the need for a centrally coordinated mechanism to manage, disburse and monitor funds and contracts effectively.

ANNEX 1

Laboratory and surveillance capacity-building

1.1 Laboratory and surveillance capacity elements, levels and components

Table A1.1. Elements and levels of indicator-based surveillance capacity

Capacity level	Influenza-like illness surveillance sites	Severe acute respiratory illness surveillance sites	Central infrastructure
1 Ad-hoc indicator based surveillance	None	None	None
2 At least one sentinel site for influenza-like illness surveillance	1 per country	None	1 epidemiologist with equipment
3 Multiple sentinel sites with broad population coverage; at least one site for severe acute respiratory illness	1 per 10 million population	1 per country	1 epidemiologist with equipment
4 Widespread national coverage for both influenza-like illness and severe acute respiratory illness	1 per 3 million population	1 per 10 million population	1 epidemiologist with equipment
Shared central infrastructure (e.g. strategic option 2 for small States)	As for levels 1–4	As for levels 1–4	None

Table A1.2 is based on self-reported, non-influenza-specific data from Member States reported to WHO, pursuant to the International Health Regulations (2005), in response to a survey on core capacities sent to all Member States (data as at October 2010, not publicly available). To estimate total costs, the countries in each region that did report were assumed to be representative of the countries in the region that did not report.

Table A1.2. Estimated levels of indicator-based surveillance capacity, 2009

WHO region	Level 1	Level 2	Level 3	Level 4	Data not available	Number of countries in region
Africa	0	9	12	2	23	46
Americas	0	8	7	2	18	35
Eastern Mediterranean	1	8	5	3	4	21
Europe	4	6	11	8	24	53
South-East Asia	0	7	1	2	1	11
Western Pacific	1	9	2	8	7	27
All	6	47	38	25	77	193

Table A1.3. Elements and levels of event-based surveillance capacity

Capacity level	Reporting networks	Central infrastructure
1 Ad hoc event-based surveillance	None	None
2 Basic central reporting system in place, and health worker sector has formal reporting	Health worker formal reporting for unusual influenza	Basic infrastructure (e.g. telephone hotline, SMS, e-mail)
3 School and employer sector and animal health worker sector have formal reporting	Health worker, school, employer and animal health worker formal reporting of unusual influenza	Basic infrastructure (e.g. telephone hotline, SMS, e-mail)

4 All three sectors have formal reporting, and central media monitoring is in place	Health worker, school, employer and animal health worker reporting of unusual influenza	Basic infrastructure (e.g. telephone hotline, SMS, e-mail) Media and rumour monitoring
Shared central infrastructure (e.g. strategic option 2 for small States)	As for levels 1–4	None

Table A1.4 is based on self-reported, non-influenza-specific data from Member States reported to WHO, pursuant to the International Health Regulations (2005), in response to a survey on core capacity sent to all Member States (data as at October 2010, not publicly available). To estimate total costs, the countries in each region that did report were assumed to be representative of the countries in the region that did not report.

Table A1.4. Estimated levels of event-based surveillance capacity, 2009

WHO region	Level 1	Level 2	Level 3	Level 4	Data not available	Number of countries in region
Africa	2	20	1	0	23	46
Americas	1	12	3	1	18	35
Eastern Mediterranean	1	13	3	0	4	21
Europe	0	22	6	1	24	53
South-East Asia	0	9	0	1	1	11
Western Pacific	2	16	1	1	7	27
All	6	92	14	4	77	193

Table A1.5. Elements and levels of laboratory analysis and surveillance capacity

Capacity level	Human resources	Equipment and operations	Reagents and disposables
1 No access to polymerase chain reaction testing	None	None	None
2 Access to polymerase chain reaction testing but not to influenza-specific laboratories	Training for shared support staff	Basic office equipment: computer, printer, mobile phone, vehicle Basic operating costs Basic laboratory equipment (e.g. pipettes)	Sampling kit Polymerase chain reaction kits for shared laboratories Laboratory consumables
3 Access to influenza-specific laboratories with limited capacity	1 administrator 1 technician Training	Basic office equipment: computer, printer, mobile phone, vehicle Basic operating costs Basic laboratory equipment: (e.g. pipettes), refrigerator, incubator, inverted microscope Polymerase chain reaction unit	Sampling kits Polymerase chain reaction kits Laboratory consumables
4 Access to influenza laboratories that meet terms of reference for a WHO National Influenza Centre	1 administrator 3 technicians Training	Basic office equipment: computer, printer, mobile phone, vehicle Basic operating costs Basic laboratory equipment (e.g. pipettes), refrigerator, incubator Polymerase chain reaction unit Inverted microscope	Sampling kits Polymerase chain reaction kits Laboratory consumables Antiserum and other reagents

5 Access to influenza laboratories that meet terms of reference for a WHO National Influenza Centre with capacity to support other countries	1 administrator 7 technicians Training	Basic office equipment: computer, printer, mobile phone, vehicle Basic operating costs Basic laboratory equipment (e.g. pipettes), refrigerator, incubator, inverted microscope Polymerase chain reaction unit Ultra-low freezer	Sampling kits Polymerase chain reaction kits Laboratory consumables Antiserum and other reagents
Shared central infrastructure (e.g. strategic option 2 for small States)	Sample transport	Basic office equipment: computer, printer, mobile phone, vehicle Transport costs	Sampling kits

Table A1.6 is based on data collected by WHO for preparing the *WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009* (draft document not yet publicly available).

Table A1.6. Estimated levels of laboratory analysis and surveillance, 2009

WHO region	Level 1	Level 2	Level 3	Level 4	Level 5	Number of countries in region
Africa	9	15	12	3	7	46
Americas	5	6	15	7	2	35
Eastern Mediterranean	1	12	4	4	0	21
Europe	3	2	10	34	4	53
South-East Asia	3	1	1	6	0	11
Western Pacific	13	0	3	8	3	27
All	34	36	45	62	16	193

Table A1.7 Elements and levels of virus sample shipping capacity

Capacity level	In-country capacity	Available capacity
1 No access to virus sample shipping	None	None
2 Virus sample shipping is possible with assistance from abroad	Varied	Contract with courier to provide shipping personnel, dry ice and packaging from abroad when needed
3 Country has in-country capacity for shipping virus samples	Dry-ice machine Airport personnel and air carriers trained to carry infectious substances Trained in-country personnel	All available in-country

Table A1.8 is based on analyses conducted within the WHO influenza specimen shipping project in 2009, from a survey of courier companies and expert interviews. The findings refer only to capacity linked to that project.

Table A1.8. Estimated levels of virus sample shipping capacity, 2009

WHO region	Level 1	Level 2	Level 3	Number of countries in Region
Africa	1	32	13	46
Americas		22	13	35
Eastern Mediterranean	5	5	11	21
Europe	4	2	47	53
South-East Asia	3	4	4	11
Western Pacific	8	11	8	27
All	21	76	96	193

1.2 Average estimated running costs of the WHO Global Influenza Surveillance Network

The main components of the WHO Network are:

- National Influenza Centres;
- H5 Reference Laboratories;
- WHO Collaborating Centres;
- Essential Regulatory Laboratories;
- global coordination of the Global Influenza Surveillance Network by WHO, including the influenza virus traceability mechanism, training and support, and provision of some supplies from both WHO headquarters and the WHO regional offices; and
- shipping within the Network.

Table A1.9 summarizes the average estimated global costs for the WHO Network (costs per element are described in subsequent sections). As the average costs are based on information from low- and lower-middle-income countries, the range of global costs may be broad; therefore, "lower" and "upper" bounds are shown. The estimates for National Influenza Centres in particular may be low because the data from which they were derived were for low- and lower-middle-income countries.

Table A1.9. Summary costs of the WHO Global Influenza Surveillance Network

Element	Number	Cost (US$ millions)		
		Estimated average global cost	Lower bound on cost estimate	Upper bound on cost estimate
National Influenza Centres	136	22	18	25.5
H5 Reference Laboratories	11	1.8	1.6	2
Collaborating Centres	6	18	9	36
Essential Regulatory Laboratories	4	4	3.2	4.8
WHO global and regional coordination		10	9	12
Shipping		0.7	0.6	0.9
Total		56.5	41.4	81.2

The assumptions on which these costs were based are described below.

1.2.1 National Influenza Centres

The average annual operating cost of a National Influenza Centre is US$ 162 000 per year, ranging from US$ 130 000 (25th percentile) to US$ 187 000 (75th percentile).

Table A1.10. Average annual operating costs for a National Influenza Centre

Cost component	Capacity-building activity	Assumptions	Assumption source	Annual cost mean (range)[1] (US$)
Human resources	Employ administrative staff	One administrator per laboratory, with salary equivalent to clerical officer	2,3	5000 (2100–7100) per administrator
		Benefits equal 25% of salary cost		
		No training required		
	Employ technical staff	3 technicians with salary equivalent to medical officer	2,3	8400 (3600–12 000) per technician
		Benefits equal 25% of salary cost		
	Train technical staff	Technical training appropriate for capacity level of laboratory, including, as appropriate: collecting specimens, biosafety, basic virology testing and diagnostics, rapid diagnostic tests, polymerase chain reaction subtyping	2	2000 (840–3250) 1550 (650–2000) 2200 (920–2800) 60 (25–800) 1920 (1420–2420)
		Advanced training at collaborating centre		3100 (600–3600)
		Training trainers, specimen collection, biosafety, shipping and transport		3100 (600–3600)
Equipment and operations	Purchase and maintain equipment	Equipment, as appropriate for laboratories of different capacity levels, including: basic office equipment, mobile, office equipment, vehicle	2	2600 (2100–2800) 3300 (3000–3600)
		Laboratory equipment for basic analysis		10 800 (9700–12 000)
		Polymerase chain reaction machine		1650 (1500–1800)
		Ultra-low freezer		
	Provide operational support	Support for facilities, utilities, telephone, Internet, transport and miscellaneous overheads, as appropriate for level and capabilities of laboratory	2	≤ 30 000 per year average (25 000–35 000)
Reagents and disposables	Purchase reagents, such as polymerase chain reaction kits, immunofluorescence reagents and disposables, such as sample kits and laboratory supplies	Cost includes reagents usually purchased by laboratory and also reagents usually provided by WHO Network (e.g. Collaborating Centres), as appropriate for laboratories of different capacity levels	2,3	86 000 (80 000–90 000) per year for laboratory meeting full terms of reference for National Influenza Centre and processing 1000 clinical samples per year

Cost component	Capacity-building activity	Assumptions	Assumption source	Annual cost mean (range)[1] (US$)
		Reagents include primers and polymerase chain reaction reagents, laboratory supplies, sampling kits, immunofluorescence kits and virus culture material		
		1000 samples per month average volume		
		Costs are constant across regions		

1. 25th–75th percentile of low- and middle-income countries.

2. *WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009* (draft document not yet publicly available).

3. *WHO-CHOICE and the global immunization vision and strategy costing model*. http://www.who.int/bulletin/volumes/86/1/07-045096.pdf (accessed 19 November 2010).

1.2.2 H5 Reference Laboratories

The estimated costs are similar to those for National Influenza Centres.

1.2.3 WHO Collaborating Centres

Four Collaborating Centres provided data. The estimated costs for core activities (including routine operating expenses, reagents and other materials supplied to National Influenza Centres) under the WHO terms of reference were reported to be US$ 1.5–6 million (average, US$ 3 million). These laboratories are, however, integrated into larger institutions, so that it is difficult to identify specific costs for the WHO Network. All Collaborating Centres have specific terms of reference to provide additional services, the cost of which may vary by collaborating centre and year to over US$ 50 million per year.

1.2.4 Essential Regulatory Laboratories

The limited data indicate that the average annual cash operating cost for an Essential Regulatory Laboratory is approximately US$ 1 million, ranging from US$ 0.8 million to US$ 1.2 million.

1.2.5 Global and regional coordination

The costs include:

- quality assessment infrastructure (based on the external quality assessment programme budget);
- central costs for meetings, site visits and training;
- central and regional coordination teams; and
- Influenza Virus Traceability Mechanism (IVTM)

The annual operating costs are approximately US$ 10 million, ranging from US$ 9 million to US$ 12 million globally.

1.2.6 Shipping

Shipping varies widely by country, depending on local circumstances, but may include:

- training laboratory personnel in packaging and dealing with customs authorities, environmental health departments and carrier companies;
- purchase of essential equipment, such as dry-ice machine and shipping material; and
- contracts with courier companies.

Data from the WHO Shipping Fund Project indicate that the average annual estimated cost per low- and lower-middle-income country is US$ 3250 (range, US$ 2500–4000) for 173 countries that have virus sample shipping capacity. For 21 countries without this capacity, the costs are higher, as shipments must be arranged individually rather than on annual contracts; the cost is estimated to be US$ 7500 (range, US$ 6000–9000) per country.

1.3 Cost components, unit costs and data sources

When possible, the costs associated with the components of these capacities are estimated from existing sources, such as the 2005 Global Immunization Vision and Strategy costing exercise.[1] These cost estimates were supplemented by budgetary data from the Global Influenza Programme, interviews and input from global and national experts (e.g. directors of National Influenza Centres and Collaborating Centres) and outside data sources as appropriate.

[1] http://www.who.int/bulletin/volumes/86/1/07-045096.pdf.

Table A1.11. Laboratory and surveillance cost components

Indicator-based surveillance					
Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range mean (range)[a]	Annual cost range mean (range)[a]
Influenza-like illness sentinel sites	Train sentinel site workers on influenza-like illness	US$ 160 per worker, one-time cost for 1-day training, including per diem, travel, materials and instructor time	Global Immunization Vision and Strategy (GIVS) costing data[b]	160 (70–205) US$ per worker	50 (20–60) US$ per worker
		US$ 50 per worker per year, including employee turnover and periodic refresher training for trained staff			
		10 workers per influenza-like illness site	WHO expert guidance	1600 (700–2050) US$ per site	500 (200–600) US$ per site
	Add support personnel per surveillance site to ensure proper reporting is maintained	One third of a full-time equivalent per surveillance site for reporting officer, either shared among three sites and dedicated to influenza or one third of responsibility for existing worker; registered nurse salary for one third of a full-time equivalent per surveillance site for area manager, with at least one for countries with at least three influenza-like illness sites; nursing director salary	GIVS costing data[b]	No one-time cost, training included in training figures above	2070 (900–3000) US$ per site
					1750 (750–2500) US$ per site
		Benefits equal 25% of salary cost			
	Purchase and maintain essential equipment and supplies for reporting influenza-like illness	Computer, printer, copier and other equipment dedicated to reporting influenza-like illness at each site	GIVS costing data[b]	4500 (3500–5900) US$ per site	3200 (2400–4400) US$ per site
		Stationery required to carry out duties			
		Annual maintenance and replacement of equipment, assuming 5-year useful life and 15% maintenance			
Severe acute respiratory illness sentinel sites	Conduct training in severe acute respiratory illness for sentinel site workers	US$ 155 per worker, one-time cost for 1-day training, including per diem, travel, materials and instructor time	GIVS costing data[b]	155 (65–200) US$ per worker	50 (20–60) US$ per worker
		US$ 50 per worker per year, including employee turnover and periodic refresher training for trained staff		2300 (1000–3000) US$ per influenza-like illness site	750 (200–600) US$ per influenza-like illness site
		15 workers per site			

Indicator-based surveillance					
Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range mean (range)[a]	Annual cost range mean (range)[a]
	Add support personnel per surveillance site to maintain proper reporting	Assume that the severe acute respiratory illness site is also an influenza-like illness site; therefore, cost of personnel is included in influenza-like illness cost above			
	Purchase and maintain essential equipment and supplies for reporting	Assume that the severe acute respiratory illness site is also an influenza-like illness site and that influenza-like illness equipment and supplies can be used for reporting severe acute respiratory illness; therefore, cost of equipment and maintenance is included in influenza-like illness cost above			
Central infrastructure	Employ epidemiologist	One epidemiologist per country, with salary equivalent to medical specialist Benefits equal 25% of salary cost	GIVS costing data[b]		8400 (3600–12 000) US$ per country
	Train epidemiologist	One epidemiologist per country, with basic public health education but requires influenza-specific training Training involves extensive course at WHO collaborating centre, similar to laboratory training, at same cost for all countries Refresher training every 3 years	WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009[c]	7750 (6500–9000) US$ per country (range based on travel costs)	2600 (2170–3000) US$ per country (range based on travel costs)
	Purchase and maintain essential equipment and supplies for central site	Computer, printer, copier and other equipment Stationery required to carry out duties Annual maintenance and replacement of equipment, assuming 5-year useful life and 15% maintenance	GIVS costing data[b]	4500 (3500–5900) US$ per country	3200 (2400–4400) US$ per country

Indicator-based surveillance

Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range mean (range)[a]	Annual cost range mean (range)[a]
Technical assistance	As needed, support establishment of basic field reporting and central analysis infrastructure	Salary and per diem of one full-time consultant (e.g. WHO P3 or P4 level equivalent based on WHO daily rate, and 20 days per month) For countries currently at level 2 or 3, one full-time consultant for 2 months For countries currently at level 1, one full-time consultant for 12 months	WHO consultants daily rate[d] GIVS in-country per diem rates[b]	8800 (6500–11 000) US$ per full-time consultant per month	

[a] Range, 25th–75th percentile of low- and middle-income countries.

[b] See http://www.who.int/bulletin/volumes/86/1/07-045096.pdf (accessed 19 November 2010).

[c] *WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009* (draft document not yet publicly available).

[d] As of 1 January 2010.

Event-based surveillance

Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range (25th, 50th, 75th percentile of low- and middle-income countries)	Annual recurring cost range (25th, 50th, 75th percentile of low- and middle-income countries)
Central infrastructure	Establish and maintain central reporting capacity	Cost of telephone hotline, SMS and e-mail interface Administrative capacity borne by host entity (e.g. National Influenza Centre, national surveillance centre)	Benchmarked on basis of multiple carriers in developed and developing countries	600 (400–800) US$ per country	600 (400–800) US$ per country
	Employ media and rumour monitor	One media and rumour monitor per country Salary equivalent to public relations officer Benefits equal 25% of salary cost Training equivalent to 1-month course at regional hub (assume 75th percentile of per diem)	Public health assistant salary costs from WHO-CHOICE[a]	24 000 (19 000–29 000) US$ per country	22 000 (18 000–27 000) US$ per country

Event-based surveillance					
Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range (25th, 50th, 75th percentile of low- and middle-income countries)	Annual recurring cost range (25th, 50th, 75th percentile of low- and middle-income countries)
	Purchase and maintain equipment for media and rumour monitor	Computer, printer, copier and other equipment Stationery required to carry out duties Annual maintenance and replacement of equipment, assuming 5-year useful life and 15% maintenance	GIVS costing data[b]	4500 (3500–5900) US$ per country	3200 (2400–4400) US$ per country
Health worker reporting network	Develop and distribute educational material to health worker network	Basic network building costs borne by International Health Regulations capacity-building Material preparation cost equivalent to approximately 1 month cost of medical officer Printing and distribution costs equal cost of printing and distributing two-page brochure and poster Material distributed to 70% of health workers	GIVS costing data[b] Number of health workers from *World Health Statistics 2010*[c]	700 (300–1000) US$ per country	0.85 (0.5–1.05) US$ per health worker Cost per country varies by number of health workers
School and employer networks	Develop and distribute educational material to school and employer networks	Basic network building costs borne by International Health Regulations capacity-building Material preparation cost equivalent to approximately 1 month cost of medical officer Printing and distribution costs equal cost of printing and distributing two-page brochure and poster Material distributed to 25% of all teachers and 10% of all employers	GIVS costing data[b] UNESCO Institute for Statistics, primary and secondary school teachers; accessed 22 November 2010 ILO LABORSTA database Table 2A subcode 2 (employers); accessed 22 November 2010	700 (300–1000) US$ per country	0.85 (0.5–1.05) US$ per teacher or employer Cost per country varies by number of teachers and employers

Event-based surveillance					
Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range (25th, 50th, 75th percentile of low- and middle-income countries)	Annual recurring cost range (25th, 50th, 75th percentile of low- and middle-income countries)
Animal health network	Develop and distribute educational material to animal health worker network and other farming community leaders	Basic network building costs borne by International Health Regulations capacity-building Material preparation cost equivalent to approximately 1 month cost of medical officer Printing and distribution costs assume distribution of educational materials to approximately one person (e.g. animal health worker, farming community leader) per 1500 population	Expert estimates, as data not available	700 (300–1000) US$ per country	500 (400–600) US$ per 1 million population
Technical assistance	As needed, support establishment of basic central infrastructure and expansion of reporting networks	Salary and per diem of one full-time consultant (e.g. WHO P3 or P4 level equivalent based on WHO daily rate and 20 days per month) For all countries receiving assistance, assume one full-time consultant for 1 month, in addition to assistance for indicator-based surveillance	WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009[d] GIVS in-country per diem rates[b]	8800 (6500–11 000) US$ per full-time consultant per month	

[a] See http://www.who.int/choice/en/ (accessed 19 November 2010).

[b] See http://www.who.int/bulletin/volumes/86/1/07-045096.pdf (accessed 19 November 2010).

[c] *World Health Statistics 2010* http://www.who.int/whosis/whostat/2010/en/ (accessed 19 November 2010).

[d] *WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009* (draft document not yet publicly available).

Laboratory analysis and surveillance

Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range mean (range)[a]	Annual cost range mean (range)[a]
Human resources	Employ administrative staff	One administrator per laboratory, with salary equivalent to clerical officer Benefits equal 25% of salary cost No training required	WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009[b] GIVS costing data[c]		5000 (2100–7100) US$ per administrator 5000 (2100–7100) US$ per country
	Employ technical staff	No technicians at level 1 or 2, one at level 3, three at level 4 and seven at level 5 Salary equivalent to medical officer Benefits equal 25% of salary cost	WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009[b] GIVS costing data[c]		8400 (3600–12 000) US$ per technician
	Train technical staff	Technical training appropriate for capacity level of laboratory, including, as appropriate, collecting specimens, biosafety, basic virology testing and diagnostics, rapid diagnostic tests, polymerase chain reaction subtyping Advanced training at collaborating centre Training trainers, specimen collection, biosafety, shipping and transport Annual cost equivalent to 20% of one-time cost	WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009[b]	10 000 (4200–13 000) 7750 (3250–10 000) 11 000 (4600–14 000) 300 (125–390) 9600 (7100–12 100) 15 500 (13 000–18 000) 15 500 (13 000–18 000) US$ per laboratory, depending on capacity level	2000 (840–3250) 1550 (650–2000) 2200 (920–2800) 60 (25–800) 1920 (1420–2420) 3100 (600–3600) 3100 (600–3600) US$ per laboratory per year, depending on capacity level

Laboratory analysis and surveillance

Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range mean (range)[a]	Annual cost range mean (range)[a]
Equipment and operations	Purchase and maintain equipment	Equipment, as appropriate, for laboratories of different capacity levels, including: basic office equipment, including mobile, office equipment, vehicle	WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009[b]	17 000 (14 000–19 000)[a]	2600 (2100–2800)
		Laboratory equipment for basic analysis			3300 (3000–3600)
		Polymerase chain reaction machine		22 000 (19 800–24 200)[d]	10 800 (9700–12 000)
		Ultra-low freezer		72 000 (65 000–79 000)	1650 (1500–1800)
				11 000 (9900–12 100)	
		Maintenance 15%		All in US$ per laboratory	All in US$ per laboratory per year
	Provide operational support	Support for facilities, utilities, telephone, Internet, transport and miscellaneous overheads, as appropriate for level and capabilities of laboratory	WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009[b]		Up to 30 000 US$ per year average (24 000–36 000 US$) per country
Reagents and disposables	Purchase reagents such as polymerase chain reaction kits, immunofluorescence reagents and disposables such as sample kits and laboratory supplies	Assume cost includes reagents usually purchased by laboratory and reagents usually provided by the WHO Network (e.g. Collaborating Centres), as appropriate for laboratories of different capacity levels	WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009[b]		89 000 (81 000–99 000) US$ per year for laboratory meeting full terms of reference for National Influenza Centre and processing 1000 clinical samples per year
		Reagents include primers and polymerase chain reaction reagents, laboratory supplies, sampling kits, immunofluorescence kits and virus culture material			
		Assume 1000 samples per month average volume for National Influenza Centre	Consultation with National Influenza Centre and collaborating centre budgets		
		Assume costs are constant across regions			

Laboratory analysis and surveillance					
Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range mean (range)[a]	Annual cost range mean (range)[a]
Technical assistance	Run quality assurance infrastructure	Assume current external quality assessment programme continues with 20% increase in costs	External quality assessment programme budget		US$ 250 000 globally, increasing by approximately 20% per year
	Other programme support	Assume central cost for meetings, site visits and central or regional coordination team	WHO expert opinion		US$ 6–8 million per year globally

[a] Range from 25th to 75th percentile of low- and middle-income countries.

[b] *WHO action plan for building influenza laboratory capacity in response to the pandemic A(H1N1) 2009.* (Draft document not yet publicly available).

[c] See http://www.who.int/bulletin/volumes/86/1/07-045096.pdf (accessed 19 November 2010).

[d] Range assumes prices vary by ± 10%.

Virus sample shipping					
Cost component	Capacity-building activity	Assumptions	Assumption source	One-time cost range	Annual recurring cost
Country capacity	Cost of establishing and maintaining in-country capacity	Requirements of each country will differ; they can include training of shipping personnel and dealing with customs authorities, environmental health departments and carrier companies	WHO Shipping Fund Project expert assumptions	8000 (6400–9600) US$ per country	3250 (2600–3900) US$ per country
		Purchase of essential equipment such as dry-ice machine and shipping material			
	Expand access to WHO Shipping Fund to countries with no access	All costs of expanding capacity covered by annual recurring costs	WHO Shipping Fund Project expert assumptions		7500 (6000–9000) US$ per country
	Run WHO Shipping Fund project	Includes central coordination	WHO Shipping Fund expert assumptions		500 000 (400 000–600 000) US$ globally

ANNEX 2

Expanding global influenza vaccine production capacity

2.1 Seasonal-to-pandemic capacity conversion factors

Seasonal capacity was determined from information collected from manufacturers and public sources and expressed as theoretical vaccine output in a full year of production, consisting of 44 weeks of actual production and 8 weeks of downtime for plant maintenance. Seasonal trivalent vaccine capacity was then converted into monovalent pandemic vaccine capacity in the scenarios described in the text. As technologies differ, different conversion factors were used for each. Table A2.1 gives the "effective conversion factors" for each scenario for 2009 and 2015. Effective conversion factors are the average of the factors for each technology, weighted by the proportion that each technology contributes to total capacity.

Table A2.1. Effective conversion factors for changing seasonal trivalent vaccine capacity to monovalent pandemic vaccine capacity

Scenario	Effective conversion factor	
	2009	2015[a]
Low case	1.12	1.39
Base case	2.99	3.02
High case	11.86	10.77

Account taken of the different mix of technologies in 2009 and 2015; individual conversion factors for each technology are not given in order to preserve the confidentiality of the information.

[a] In addition to conversion of seasonal into pandemic capacity, 440 million additional surge pandemic capacity per year (44 weeks of production) are assumed for 2015; this capacity does not involve seasonal production.

2.2 Strategic options

Table A2.2 gives a combined overview of the costs associated with each strategic option described in the text. Tables A2.3–A2.9 give a detailed breakdown of all the costs considered for each option, with the assumptions made and the sources of information on which they are based.

The cost estimates for strategic options were defined as follows:

- The activities required to implement the strategic options were defined.
- Activities were categorized by the type of costs they incur:
  - one-time costs incurred to put in place the strategic option;
  - operating expenses incurred annually to maintain the mechanism in place; and
  - strategic options to expand vaccine manufacturing capacity, excluding surge costs at the time of a pandemic.
- Each activity was broken down into types of costs and specific cost items. Assumptions were made for each cost item, allowing an estimate of the total cost of each strategic option.
- Total costs above US$ 100 million were rounded to the nearest multiple of 5. All costs above US$ 1 million were rounded to the nearest million. Costs below US$ 1 million were not rounded to the first significant digit, and costs per dose were expressed in US$ with either one decimal or rounded to the first significant digit if below US$ 0.10.

Table A2.2. Overview of total costs per strategic option

Strategic option	Total one-time cost (US$ million)	One-time cost per pandemic dose (US$)	Total operating expenses (US$ million)	Operating expenses per pandemic dose (US$)	Surge cost at time of a pandemic (US$ million)	Surge cost per dose at time of a pandemic (US$)
1	~280	~0.6	~3720	~8.3		
2	~125–490	~3.2	–	–		
3	–	–	~280–450	~0.4		
4	~130–230	~0.1	~0.6–0.8	Negligible		
5	~230–420	~0.1–0.2	~0.6–1	Negligible		
6a	~38–94	~0.03–0.06	~4–9	~0.01		
7	~50–200	–	–	–		

[a] Costs do not include technology licensing fees, which may be significant.

Table A2.3. Cost assumptions for strategic option 1: Increase seasonal demand

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
1. Conduct studies of burden of seasonal flu disease in low- and middle-income[a] countries	One-time	Cost of studies for 5 years, covering 5.6 billion people	US$ 5 million per study Five studies for every billion people	Global Pandemic Influenza Action Plan to increase vaccine supply (GAP) business plan	~140 for low- and middle-income countries (~28 per year)
2. Encourage prioritization of seasonal influenza by key organizations (e.g. GAVI Alliance)	–	–	–	–	–
3. Mobilize the public to follow seasonal recommendations, with marketing and promotion campaigns	One-time	Cost of marketing vaccine	US$ 0.7, 0.3, 0.1 per person in high-, medium- and low-income countries, respectively[b]	GAP business plan United Nations population statistics	~139 for low- and middle-income countries (~272 in total)
	Operating expenses	Cost to sustain coverage	US$ 0.1, 0.04, 0.01 per person in high-, medium- and low-income countries, respectively	GAP business plan United Nations population statistics	~18 for low- and middle-income countries (~38 in total)

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
4 Conduct national seasonal vaccination campaigns, including funding of vaccine	Operating expenses	Cost of administering vaccine	US$ 15, 5, 0.5 per person in high-, medium- and low-income countries, respectively	GAP business plan United Nations population statistics	~2309 for low- and middle-income countries (~5162 in total)
	Operating expenses	Cost of vaccine	US$ 8, 3, 3 per person in high-, medium- and low-income countries, respectively	Average 2010 seasonal vaccine price WHO and Bill & Melinda Gates Foundation report on H5N1 stockpile,[c] feedback from selected manufacturer interviews; assumes use of tiered pricing for lower-income countries (should be confirmed) if average price per dose for higher-income countries is ~US$ 8–10 per dose. Determining exact price per dose would require more detailed analysis with manufacturers and stakeholders	~1395 for low- and middle-income countries (~2916 in total)

[a] Middle income countries include lower middle- and higher middle-income countries.

[b] Seasonal uptake in high-income countries, 190 176 million people; middle-income, 461 478 million people; low-income, 3424 million people.

[c] WHO and Bill & Melinda Gates Foundation report *Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology*. February 2009.

Table A2.4. Cost assumptions for strategic option 2: Build or expand capacity in countries that have government support or a business case to sustain production

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
1. Sustain support for completing current projects within the GAP grant programme	One-time	Cost of completing current projects	US$ 50–100 million	GAP grant programme estimates	50–100
2. Extend GAP grant programme by soliciting expressions of interest from countries that could sustain local capacity	One-time	Cost of grant administration and grantee training	1–2% of one-time costs for building, preclinical and clinical programmes, licensing and filing	GAP grant programme estimates	1–9

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
3. Establish partnerships with local manufacturers, select appropriate technology and transfer technology to manufacture vaccine	Not applicable	Not applicable	Costs included in building budget	Interviews with manufacturers in developing countries	Not applicable
4. Build production facilities	One-time	Cost of building facilities	Two to seven facilities IIV technology US$ 1.4–1.5 per IIV dose[a] LAIV capacity could be built for ≤ US$ 0.4 per dose	Interviews with manufacturers in developing countries Interviews with manufacturing experts	55–267
5. License or WHO prequalify product	One-time	Cost of preclinical programme (preclinical trials of safety and efficacy)	Two to seven facilities One set of trials per facility US$ 0.6–1 million per set of trials	Technology transfer team from WHO Vaccine Formulation Laboratory, University of Lausanne	1–7
		Cost of clinical programme (clinical trials of safety and immunogenicity)	Two to seven facilities Seven trials needed (adults, elderly and five for children) One set of trials per facility US$ 1–2 million per trial	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	14–98
		International licensing fee	Two to seven facilities One product per facility One licence per product US$ 330 000 for international licensing fee per product	European Medicines Agency	0.7–2
		Local licensing fee	Two to seven facilities One product per facility One licence per product ~US$ 15 000 for local licensing fee per product	China State Food and Drug Administration	0.03–0.1
		Consultants and administrative work for filing	Two to seven facilities One filing dossier per facility ~US$ 1 million per dossier	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	2–7

[a] Capital expenditure per dose of seasonal trivalent dose; total building costs calculated on the basis of theoretical facility output during 44 weeks of production.

Table A2.5. Cost assumptions for strategic option 3: Subsidize idle capacity above seasonal demand levels

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
1. Support maintenance of excess capacity in existing facilities in exchange for access to that capacity at time of a pandemic	Operating expenses	Annual fee to pre-contract capacity	US$ 0.5 per dose per year 565–897 million doses of estimated excess capacity[a]	Public information on selected pre-purchase agreements Manufacturer interviews GAP business plan	282–448

[a] Rounded in the text to 560–900 million doses.

Table A2.6. Cost assumptions for strategic option 4: Stimulate capacity to convert from IIV to LAIV.

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
1. Conduct pilot studies with manufacturers using both technologies to assess feasibility of IIV to LAIV conversion	One-time	Manufacturing experts to train personnel and support the pilot studies	Two manufacturers ~2 months of training and piloting by two experts for each manufacturer US$ 13 000 per month per expert	WHO senior consultant at maximum pay band	~0.1
		Cost of pilot lot	Two manufacturers Pilot lot size, 1000 eggs 30 doses per egg US$ 1 per dose Pilot lots produced off-season (no opportunity costs)	Interviews with manufacturers in developing countries GAP business plan	~0.06
2. Establish commercial-scale capability to switch between technologies	One-time	Cost of equipment	12 additional manufacturers US$ 200 000 per manufacturer to add ultrafiltration equipment	Interviews with manufacturing experts	~2
		Cost of pilot lot	12 manufacturers Training, support and pilot lot costs as above	Interviews with manufacturing experts GAP business plan	~1
3. License pandemic LAIV vaccine	One-time	Cost of preclinical programme (preclinical trials of safety and efficacy)	All 14 manufacturers One set of trials per manufacturer US$ 0.6–1 million per set of trials	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	8–14

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
		Cost of clinical programme (clinical trials of safety and immunogenicity)	14 manufacturers Seven trials needed (adults, elderly and five for children) One set of trials per manufacturer US$ 1–2 million per trial	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	98–196
		International licensing fee	14 manufacturers One product per manufacturer One licence per product US$ 330 000 for international licensing fee per product	European Medicines Agency	~5
		Local licensing fee	14 manufacturers One product per manufacturer One license per product ~US$ 15 000 for local licensing fee per product	China State Food and Drug Administration	~0.2
		Consultants and administrative work for filing	14 manufacturers One filing dossier per manufacturer ~US$ 1 million per dossier	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	~14
4. Produce commercials batches each year (at least one per year) to maintain capability	Operating expenses	Cost of purchase of a test batch per year	14 manufacturers Batch of 1000 eggs 30 doses per egg ~US$ 1 per dose Test batch produced off-season (no opportunity costs)	Interviews with manufacturers in developing countries GAP business plan	~0.4
		Cost of inspecting test batch manufacture	One to two full-time equivalents US$ 200 000 per full-time equivalent (fully loaded costs)	WHO	0.2–0.4

Table A2.7. Cost assumptions for strategic option 5: Expand the use of potent adjuvant technologies

Activity	Type of cost	Cost items	Assumptions	Source	Cost range (US$ million)
1. Encourage high- and middle-income countries to adopt vaccines with adjuvant in the event of a pandemic, resulting in full use of existing capacity by manufacturers of such products	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
2. Transfer technology to manufacturers that do not have the potent adjuvant technology	One-time	Cost of setting up MF-59-like capability	23 egg- or cell-IIV manufacturers US$ 1–2 million for purchase of equipment, set up and training costs per manufacturer	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	23–46
3. Extend grants to license pandemic vaccine with adjuvant	One-time	Cost of preclinical programme (preclinical trials of safety and efficacy)	23 manufacturers One set of trials per manufacturer US$ 0.6–1 million per set of trials	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	14–23
		Cost of clinical programme (clinical trials of safety and immunogenicity)	23 manufacturers Seven trials needed (adults, elderly and five for children) One set of trials per manufacturer US$ 1–2 million per trial	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	161–322
		International licensing fee	23 manufacturers One product per manufacturer One licence per product US$ 330 000 international licensing fee per product	European Medicines Agency	~8
	One-time	Local licensing fee	23 manufacturers One product per manufacturer One licence per product ~US$ 15 000 for local licensing fee per product	China State Food and Drug Administration	~0.3

Activity	Type of cost	Cost items	Assumptions	Source	Cost range (US$ million)
		Consultants and administrative work for filing	23 manufacturers One filing dossier per manufacturer ~US$ 1 million per dossier	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	~23
4. Produce commercials batches of adjuvant each year (at least one per year) to maintain capability	Operating expenses	Cost of production of a test batch of adjuvant per year[a]	23 manufacturers Three full-time equivalents per manufacturer working for 4 weeks US$ 30 000 per full-time equivalent per year (fully loaded costs) Batch of 50 litres of MF-59-like adjuvant Negligible materials costs[b] Test batch produced off-season (no opportunity costs)	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	~0.2
		Cost of inspecting test batches manufacture	Two to four full-time equivalents US$ 200 000 per full-time equivalent (fully loaded costs)	WHO	0.4–0.8

[a] As the adjuvant and the vaccine can be produced and released separately, there is no need to produce vaccine with the adjuvant for batch testing; a test batch of adjuvant alone would suffice.

[b] If all the test batch of adjuvant is to be packed in vials, the material costs would not be negligible.

Table A2.8. Cost assumptions for strategic option 6: Convert other biological capacity to pandemic vaccine production at the onset of a pandemic

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
1. Identify manufacturers with compatible technology to pilot-test conversion process	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
2. Transfer technology and establish commercial-scale capability to switch from one technology to the other	One-time	Cost of developing process	Two to three facilities[a] with capacity to produce a total of 1 billion doses of pandemic within 6 months US$ 10–15 million for technical development (average contract manufacturing organization for process development)	Interviews with biological manufacturing experts	20–45

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
3. License pandemic vaccine in convertible facilities	One-time	Cost of preclinical programme (preclinical trials of safety and efficacy)	Two to three facilities One set of trials needed US$ 0.6–1 million per set of trials	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	1–3
		Cost of clinical programme (clinical trials of safety and immunogenicity)	Two to three facilities Seven trials needed (adults, elderly and five for children) US$ 1–2 million per trial	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	14–42
		International licensing fee	Two to three facilities One license needed US$ 330 000 for international licensing fee per product	European Medicines Agency	~0.7–1
		Local licensing fee	Two to three facilities One licence needed ~US$ 15 000 for local licensing fee per product	China State Food and Drug Administration	~0.03–0.05
		Consultants and administrative work for filing	Two to three facilities One filing dossier needed ~US$ 1 million per dossier	Technology transfer team of WHO Vaccine Formulation Laboratory, University of Lausanne	~2–3
4. Produce commercial batches each year (at least one per year)	Operating expenses	Cost of production of a test batch per year	Two to three facilities US$ 2–3 million per batch (estimated contract manufacturing organization batch price for 10 000 litres; time-based pricing model)	Interviews with biological manufacturing experts	4–9
		Cost to inspect test batch manufacture	One to two full-time equivalents US$ 200 000 per full-time equivalent (fully loaded costs)	WHO	0.2–0.4

[a] Facilities with 50 000–75 000 litres of cell culture capacity (45 µg doses and 300 doses per litre) assumed; if smaller facilities are used, all the costs would increase in proportion to the number of facilities used.

Table A2.9. Cost assumptions for strategic option 7: Accelerate the development of new technologies

Activity	Type of cost	Cost item	Assumptions	Source	Cost range (US$ million)
1. Extend grants to support research and development of full preclinical and clinical programmes for new influenza vaccine manufacturing technologies	One-time	Cost of supporting a product development project	US$ 50–200 million per programme (range of influenza vaccine programme costs) Excludes production facility building costs	Interviews with funding agencies and manufacturers Public information on United States Government grants	50–200

ANNEX 3

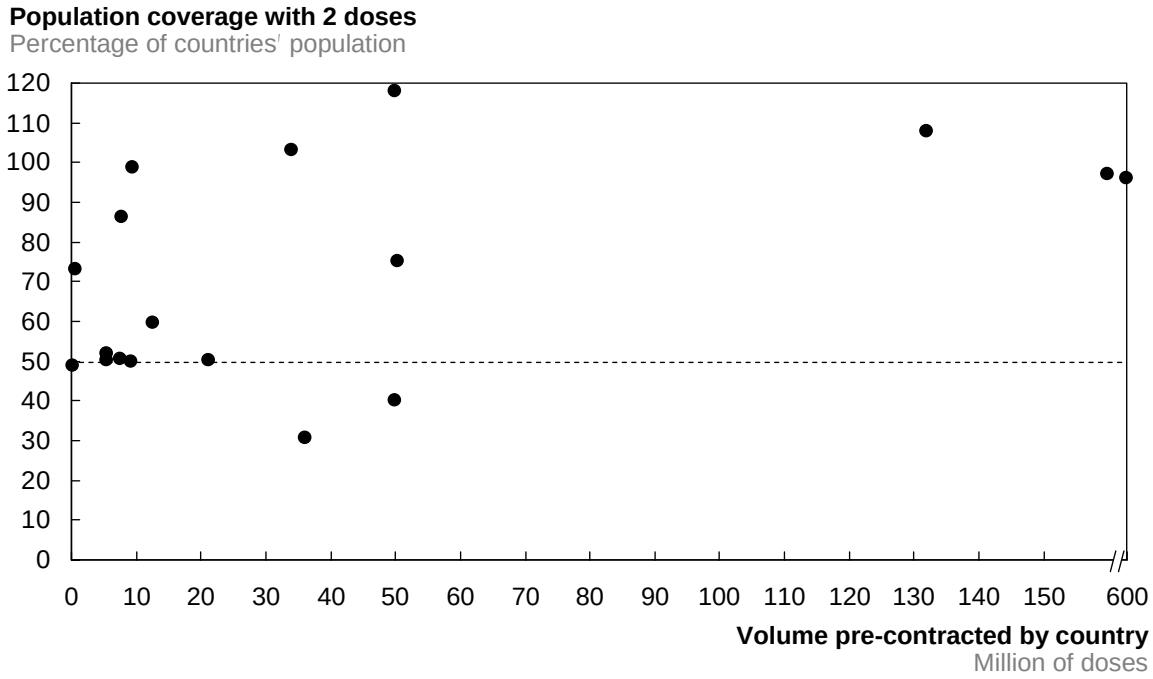
Access, affordability and effective deployment

3.1 Vaccines

3.1.1 Pre-purchase agreements

Pre-purchase agreements are contracts between countries and manufacturers that ensure a supply of pandemic vaccine at the time of a pandemic. These contracts usually specify the type of product (with some flexibility for different strains), the quantity supplied, the speed of delivery, the price and other contractual terms. Figure A3.1 shows the volume pre-contracted and the population coverage with two doses in the 19 high-income countries that currently have a pre-purchase agreement. Usually, the volume pre-contracted was sufficient to cover 50–100% of the population with two doses, and many contracts include options to extend to 100% coverage.

Figure A3.1. Overview of existing pre-purchase agreements (before pandemic (H1N1) 2009)



3.1.2 Definition of population target groups

The population groups presented in the section on potential targets are:[1,2,3]

[1] Wyman O. *Working paper for the SAGE H5N1 working group – estimating the size of the essential personnel population segment in developing countries.*

[2] *Comparative analysis of national pandemic influenza preparedness plans.* Geneva, World Health Organization (unpublished draft, October 2010).

[3] Executive summaries of 82 H1N1 national deployment plans.

- health-care workers: includes health workers with direct patient contact and public health workers;[1]
- essential personnel: includes emergency responders (police, fire, ambulance), military, key government officials and essential services workers (utilities, transport, communications);
- populations at risk: adults and children over 6 months with underlying diseases, such as cardiovascular, pulmonary, metabolic or renal disease or who are immunocompromised;[2]
- pregnant women: all pregnant women;[3]
- healthy children: all healthy children under 15 years of age;
- elderly: people over 65 years of age;[4]
- healthy adults: all healthy adults aged 15–65 years; and
- avian influenza risk groups (in national pandemic preparedness plans only): includes farmers, poultry farm workers and veterinary and livestock workers.

3.1.3 Approach to calculating access targets

Potential targets were defined and quantified by the following approach:

1. Review of existing target group prioritization from SAGE for H1N1,[5] national pandemic preparedness plans (mainly focused on H5N1)[6] and H1N1 national deployment plans.[7] This analysis is summarized in Figure A3.2.

[1] Some national pandemic preparedness plans also include laboratory workers, and some plans classify health-care workers as essential personnel.

[2] National pandemic preparedness plans include all people over 65 years (elderly), and some plans add children and pregnant women to this group.

[3] Pregnant women are included in populations at risk in some pandemic preparedness plans.

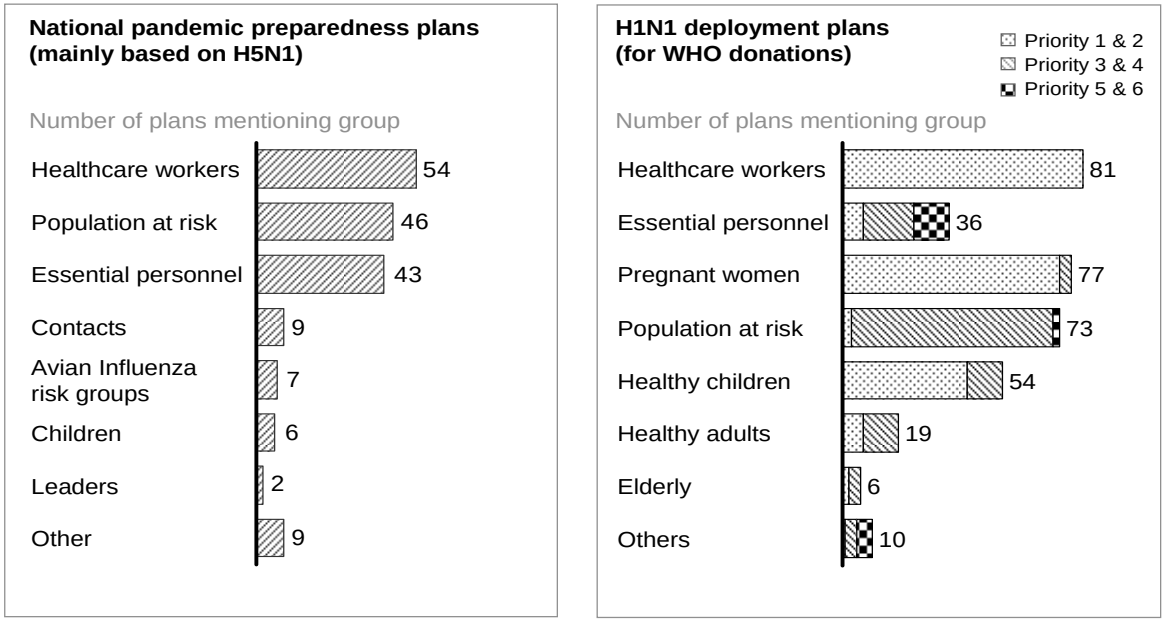
[4] Elderly are included in populations at risk in national pandemic preparedness plans.

[5] Strategic Advisory Group of Experts on Immunization (SAGE). *Report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic.* 7 July 2009.

[6] *Comparative analysis of national pandemic influenza preparedness plans.* Geneva, World Health Organization (unpublished draft, October 2010).

[7] Executive summaries of 82 H1N1 national deployment plans.

Figure A3.2. Prioritization of target groups in national pandemic preparedness plans and H1N1 deployment plans



2. On the basis of existing prioritizations, define three potential targets that include different sets of target groups.

3. Estimate the size of the target groups in countries without access to vaccine supply (from a population model that shows the population per target group in 176 countries).[1]

4. For each potential target:

- Calculate the size of the target populations included in the target considered.
- Multiply the population target by 2 to estimate the number of doses required (assumption is two doses per person).
- Estimate the percentage of the base case capacity that each target represents (drawing on the base case capacity defined in the capacity section for 6 months after release of the candidate vaccine virus to manufacturers, i.e. 1830 million doses by 2015).

All costs were rounded on the basis of the population targets (in terms of number of people).

The size of the target groups in countries without access to vaccine in 2015 is shown in Table A3.1. The percentage of the population in each target group evolves slightly between 2009 and 2015 as

[1] Based on a population model covering 176 countries developed by O. Wyman with data from WHO *World health statistics (2008)*, the International Labour Organization (ILO) Labour Statistics database (LABORSTA 2008), World Bank *World development indicators* (2006 Ed.), the United Nations Population Database (*World population prospects: 2006 revision*), the United Nations survey of crime trends (*Eighth United Nations survey on crime trends and the operations of criminal justice systems*, 31 March 2005) and the global prevalence of adult obesity (International Association for the Study of Obesity, December 2008) http://www.iotf.org/database/documents/GlobalPrevalenceofAdultObesityMarch08v4pdf.pdf). For countries for which data were not available for certain segments, estimates were created by extrapolating from countries with similar income levels for which the population sizes were known.

additional countries obtain access to local production in this time frame and due to demographic changes within countries.

Table A3.1. Size of population groups in countries without access to vaccine

Population group	2009		2015	
	No.	%	No.	%
Health-care workers	14	0.3	8	0.3
Essential personnel	462	11.1	269	11.0
Populations at risk	93	2.2	57	2.4
Pregnant women	106	2.6	7.3	3.0
Healthy children < 15 years	1314	31.6	843	34.6
People > 65 years	159	3.8	82	3.4
Healthy adults	2014	48.4	1105	45.3
Total	4162		2437	

3.1.4 Cost calculations for strategic options

The costs for the strategic options were estimated by the following approach:

1. The strategic options were designed on the basis of the volume of doses needed to achieve the 2015 targets. (It should be noted that the population with no access to a vaccine supply will decrease by more than 40% by 2015.)

2. The activities required to implement the strategic options were defined.

3. Activities were categorized by the type of costs they incur:

   - one-time costs incurred to put the strategic option in place,
   - annual costs incurred to maintain the mechanism in place and
   - costs incurred at the time of a pandemic to purchase and deploy vaccine to the populations of countries without access.

Each activity was broken down into types of cost and specific items. Assumptions were made for each cost item per dose to allow an estimate of the total costs for each potential target. Table A3.2 summarizes the type of cost, cost items, assumptions and sources for each activity. All costs are rounded to the nearest multiple of 5.

Table A3.2. Cost assumptions for strategic option 1 (Establish new pre-purchase agreements) and strategic option 2 (Expand existing pre-purchase agreements)

Activity	Type of cost	Cost item	Assumptions	Source
Negotiate pandemic vaccine pre-purchase agreements	Annual	Annual reservation fee to pre-contract capacity	Cost per dose per year: US$ 0.5	Public information on selected pre-purchase agreements Country interviews
Purchase and deploy vaccine	At time of a pandemic	Vaccine purchase	Price per dose: US$ 3[a]	WHO and Bill & Melinda Gates Foundation report on H5N1 stockpile,[b] interviews with selected manufacturers
		International transport of vaccine	Cost per dose: US$ 0.07	WHO H1N1 vaccine deployment team

Syringe purchase	Price per syringe: US$ 0.05	WHO H1N1 vaccine deployment team
Safety box purchase	Price per dose: US$ 0.009	WHO H1N1 vaccine deployment team
International transport of syringe and safety box	Cost per dose: US$ 0.052	WHO H1N1 vaccine deployment team
In-country deployment	Cost per dose: US$ 1	WHO H1N1 vaccine deployment team

[a] Assuming use of tiered pricing for lower-income countries (which should be confirmed), and an average price per dose for higher-income countries of ~US$ 8–10. Determination of the exact price per dose would require a more detailed analysis with manufacturers and stakeholders.

[b] WHO and Bill & Melinda Gates Foundation. *Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology.* 2009.

Table A3.3 shows the breakdown per target of the cost items in Table A3.2.

Table A3.3. Cost breakdown per cost item for strategic option 1 (Establish new pre-purchase agreements) and strategic option 2 (Expand existing pre-purchase agreements)

Activity	Type of cost	Cost item	Target 1 (US$ million)	Target 2 (US$ million)	Target 3 (US$ million)
Negotiate pandemic vaccine pre-purchase agreements.	Annual	Annual reservation fee to pre-contract capacity	8	138	334
		Total	8	138	334
		Rounded total	10	140	335
Purchase and deploy vaccine.	At time of a pandemic	Vaccine purchase	48	828	2004
		International transport of vaccines	1	19	47
		Syringe purchase	0.8	14	33
		Safety box purchase	0.1	3	6
		International transport of syringes and safety boxes	0.8	14	35
		In-country deployment	16	276	668
		Total	67	1154	2793
		Rounded total	70	1155	2795

3.1.5 Feasibility of potential access targets

For each potential target for access, it is possible to estimate the percentage of the base case capacity that each target represents (drawing on the base case capacity defined in the capacity section for 6 months after release of the candidate vaccine virus to manufacturers, i.e. 1830 million doses by 2015). The percentage of base case capacity represented for each target is as follows:

- Target 1: Covering health-care workers would require 4% of base case capacity in 2009 and 1% in 2015.
- Target 2: Covering essential personnel and pregnant women would require 60% of base case capacity in 2009 and 15% in 2015.
- Target 3: Covering essential personnel and populations at risk would require 159% of base case capacity in 2009 and 36% in 2015.

The feasibility of reaching targets 2 and 3 is low given the amount of existing capacity that would have to be used. In addition, it is estimated that current pre-purchase agreements will fully engage the majority of production capacity for the first 7–8 months after release of the candidate vaccine virus to manufacturers. Reaching these targets would require governments with existing pre-purchase agreements or local vaccine production capacity to reconsider their pandemic requirements so that a portion of future capacity could be re-allocated to countries without access.

3.2 Antiviral medicines

Table A3.4. Summary of information on available antiviral medicines

	Neuraminidase inhibitor		Adamantanes	
	Oseltamivir	Zanamivir	Amantadine	Rimantadine
Lowest reported price (US$ per treatment course)	6.5[a]	17.8	1.6	4
Proprietary manufacturer	Roche	GlaxoSmithKline	Generic	Generic
Other manufacturers including sub-licensees	≥ 15	≥ 2	Not applicable	Not applicable
No. of manufacturers in low- or lower-middle-income countries	At least three	At least two	Current production capacity is uncertain and may be limited.	
Maximum global production capacity[b] (per annum)	At least 450 million treatment courses	At least 200 million treatment courses	Current availability is uncertain and may be limited, as none of the current strains are susceptible to this class of medicine.	
Commonest formulation	Capsule	Powder for inhalation	Tablet	Tablet
WHO prequalification	Yes (Roche, Cipla, Stride)	Yes (GlaxoSmithKline)	No	No
WHO Model Essential Medicines List	Yes[c]	No	No	No
Limitations on use (clinical)	Formulations difficult for infants and severely ill people	Not for children < 5 years Inhalation only	Some adverse events	Some adverse events Not recommended in pregnancy
Limitations on use (public health)			Resistance can arise rapidly. All currently circulating strains are resistant to this class. Not effective against type B	
Likely to be useful in a pandemic	High. No clear reports of resistance to neuraminidase inhibitors in animal viruses		Uncertain. Resistance of circulating animal viruses, including avian H5N1 viruses, to adamantanes is well documented.	

Information for table derived from a range of public sources.

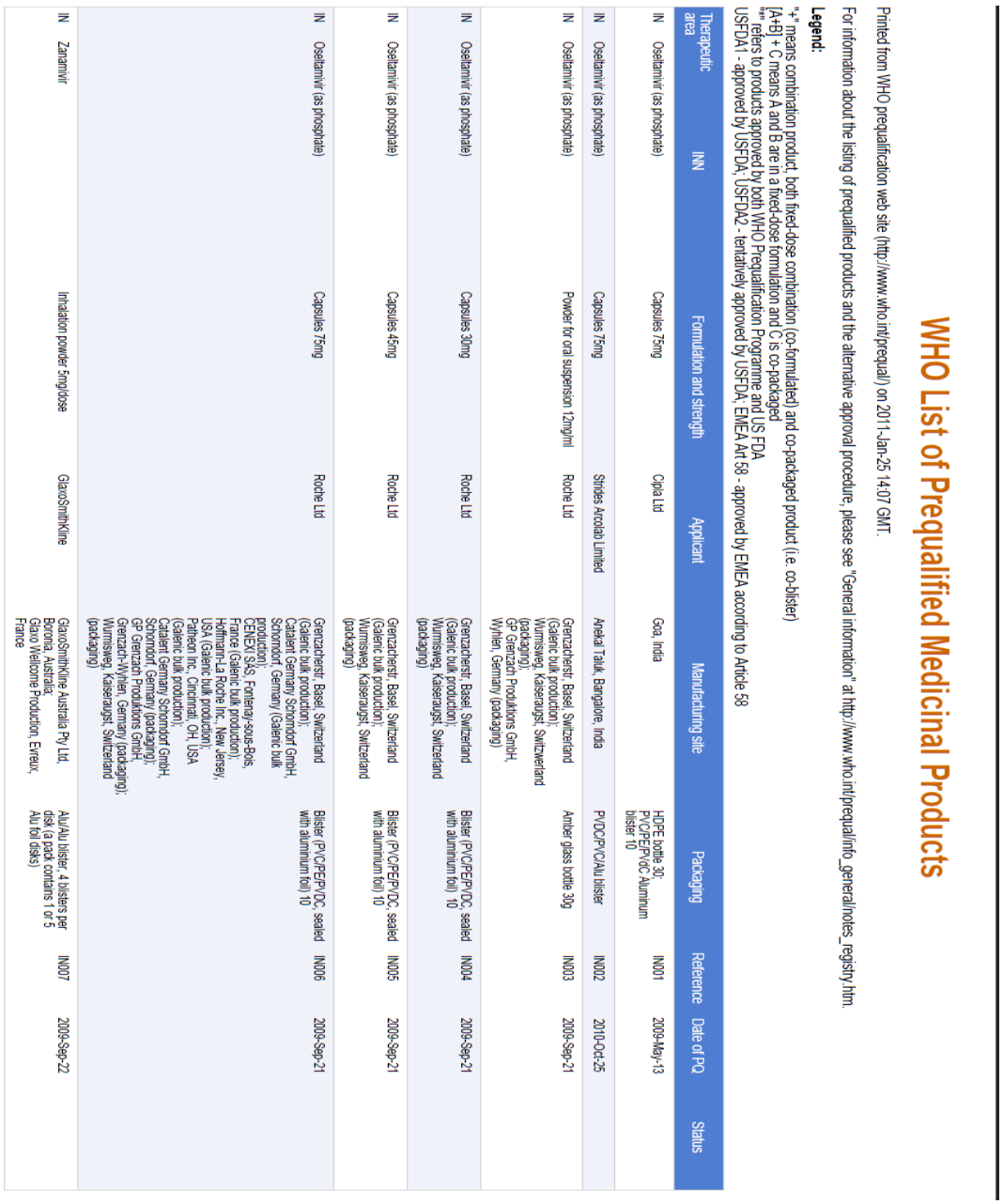
[a] Based on tiered pricing, for lowest-income countries.

[b] Manufacturers report that it could take up to 12 months to scale up to this level from seasonal baselines.

[c] For treatment of pandemic (H1N1) 2009 in accordance with WHO guidelines.

WHO prequalified influenza antiviral medicines

Seven products from four manufacturers have been prequalified (six with oseltamivir and two with zanamivir[1]).



WHO List of Prequalified Medicinal Products

Printed from WHO prequalification web site (http://www.who.int/prequal/) on 2011-Jan-25 14:07 GMT.

For information about the listing of prequalified products and the alternative approval procedure, please see "General information" at http://www.who.int/prequal/info_general/notes_registry.htm.

Legend:

"+" means combination product, both fixed-dose combination (co-formulated) and co-packaged product (i.e. co-blister)
[A+B] + C means A and B are in a fixed-dose formulation and C is co-packaged
"*" refers to products approved by both WHO Prequalification Programme and US FDA
USFDA1 - approved by USFDA; USFDA2 - tentatively approved by USFDA; EMEA Art 58 - approved by EMEA according to Article 58

Therapeutic area	INN	Formulation and strength	Applicant	Manufacturing site	Packaging	Reference	Date of PQ	Status
IN	Oseltamivir (as phosphate)	Capsules 75mg	Cipla Ltd	Goa, India	HDPE bottle 30; PVC/PE/PVdC Aluminum blister 10	IN001	2009-May-13	
IN	Oseltamivir (as phosphate)	Capsules 75mg	Strides Arcolab Limited	Anekal Taluk, Bangalore, India	PVDC/PVC/Alu blister	IN002	2010-Oct-25	
IN	Oseltamivir (as phosphate)	Powder for oral suspension 12mg/ml	Roche Ltd	Grenzacherstr, Basel, Switzerland (Galenic bulk production); Wurmisweg, Kaiseraugst, Switzwerland (packaging); GP Grenzach Produktions GmbH, Wyhlen, Germany (packaging)	Amber glass bottle 30g	IN003	2009-Sep-21	
IN	Oseltamivir (as phosphate)	Capsules 30mg	Roche Ltd	Grenzacherstr, Basel, Switzerland (Galenic bulk production); Wurmisweg, Kaiseraugst, Switzerland (packaging)	Blister (PVC/PE/PVDC, sealed with aluminium foil) 10	IN004	2009-Sep-21	
IN	Oseltamivir (as phosphate)	Capsules 45mg	Roche Ltd	Grenzacherstr, Basel, Switzerland (Galenic bulk production); Wurmisweg, Kaiseraugst, Switzerland (packaging)	Blister (PVC/PE/PVDC, sealed with aluminium foil) 10	IN005	2009-Sep-21	
IN	Oseltamivir (as phosphate)	Capsules 75mg	Roche Ltd	Grenzacherstr, Basel, Switzerland (Galenic bulk production); Catalent Germany Schorndorf GmbH, Schorndorf, Germany (Galenic bulk production); CENEXI SAS, Fontenay-sous-Bois, France (Galenic bulk production); Hoffmann-La Roche Inc., New Jersey, USA (Galenic bulk production); Patheon Inc., Cincinnati, OH, USA (Galenic bulk production); Catalent Germany Schorndorf GmbH, Schorndorf, Germany (packaging); GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany (packaging); Wurmisweg, Kaiseraugst, Switzerland (packaging)	Blister (PVC/PE/PVDC, sealed with aluminium foil) 10	IN006	2009-Sep-21	
IN	Zanamivir	Inhalation powder 5mg/dose	GlaxoSmithKline	GlaxoSmithKline Australia Pty Ltd, Boronia, Australia; Glaxo Wellcome Production, Evreux, France	Alu/Alu blister, 4 blisters per disk (a pack contains 1 or 5 Alu foil disks)	IN007	2009-Sep-22	

[1] Relenza Rotacaps was prequalified in November 2009 but is no longer listed, as its temporary market authorization by the European Medicines Agency has lapsed. See http://apps.who.int/prequal/info_press/pq_news_21September2010_withdrawIN008.htm (accessed 17 January 2011).

3.3 Diagnostic reagents and test kits

3.3.1 Laboratory assays for the detection of influenza virus in clinical specimens

The assays may be for detection of the virus itself, viral structural components (proteins and nucleic acids) or specific antibodies against viral antigens. The methods used routinely are listed in Table A3.5.

Table A3.5. Methods used routinely for the detection of influenza virus in clinical specimens

Element detected	Method	Requirements and use
Virus	Virus culture	Cell culture systems
		Biosafety containment settings
	Electron microscopy	Electron microscope
Virus isolate	Haemagglutination inhibition assay	Kits (mainly non-commercial) with specific reference sera, sample treatment reagents and standards
		Identification and subtyping of virus
Virus nucleic acids	Polymerase chain reaction	Kits (commercial and non-commercial) with specific nucleic acid amplification primers, standards and reagents
Virus proteins	Immunofluorescence	Kits (commercial and non-commercial) with specific antisera, reagents and standards
		Detection of virus-infected cells
	Enzyme immunoassays (including rapid point-of-care testing)	Kits (commercial and non-commercial) with specific antisera, indicator systems, reagents and standards
Virus-specific antibodies	Haemagglutination inhibition assay Single radial haemolysis assay	Kits (mainly non-commercial) with specific reference sera, sample treatment reagents and standards
	Microneutralization test	Cell culture systems
		Biosafety containment settings

3.3.2 Non-commercially available diagnostic kits (laboratory-based)

The WHO Influenza Reagent Kit is available for identifying influenza virus isolates in the haemagglutination inhibition or immunofluorescence assay. The haemagglutination inhibition reagent collection consists of reference influenza antigens and antisera for identifying (pandemic) influenza A(H1N1) 2009, seasonal A(H1N1), A(H3N2) and B isolates from eggs or cell culture. These reagents are neither intended, nor evaluated, for use in test procedures other than haemagglutination inhibition testing for identification of field virus strains. The antigens can also be used for serological diagnosis.

The kits are supplied by WHO Collaborating Centres to National Influenza Centres annually. They are not proprietary products. The kits contain:

- influenza A and B control antigen,
- influenza reference sheep antiserum,
- influenza negative control sheep serum and
- receptor-destroying enzyme.

More details of the kit can be found at http://www.influenzacentre.org/reports/pamphlet_2010.pdf.

Molecular diagnostic assays for detecting and characterizing virus in clinical specimens and virus isolates are available from (one of the) Collaborating Centres, which supplies molecular products and standards to National Influenza Centres for rapid, sensitive detection of genetic material from human influenza virus in clinical specimens or virus isolates (by reverse transcription polymerase chain reaction assays). These products (primers and probes) are based on genetic material from the virus. Some (H5 and seasonal but not pandemic (H1N1) 2009) are proprietary products and are subject to associated material transfer agreements. The panels also contain control viruses and reagents to validate the assay.

More details can be found at: https://www.influenzareagentresource.org/Catalog/tabid/1587/Default.aspx.

ANNEX 4

Financing mechanisms: case studies

4.1 UNITAID[1]

Basic facts and mission

UNITAID is an international facility for the purchase of drugs against HIV/AIDS, malaria and tuberculosis. Its mission is to contribute to improving access to treatment for HIV/AIDS, malaria and tuberculosis, primarily for people in low-income countries, by leveraging price reductions for high-quality diagnostics and medicines and accelerating the pace at which these are made available.

It raised US$ 730 million in funds in 2006–2008[2] and US$ 170 million from the airline solidarity levy in 2009, France contributing US$ 160 million of that amount.[3]

Operations

UNITAID raises additional funds for global health through airfare taxes and voluntary contributions. It channels funds through implementing partner agencies and sets specific objectives to fill gaps in the provision of needed health commodities. It negotiates price reductions on essential drugs and diagnostics through bulk purchase and offers a predictable market for the creation of new drugs and diagnostics.

Governance

The main decision-making body is the 11-member Executive Board, which represents the founding countries, recipient countries, nongovernmental organizations and WHO (WHO has observer status with limited rights). A small secretariat based at WHO in Geneva implements board recommendations and executes strategy. WHO also serves as UNITAID's trustee.

History and key steps

Two reports published in 2004 described the advantages of using tax-based models for fund-raising for development projects. France then championed a solidarity tax on airline tickets. UNITAID was launched in 2006 by the governments of Brazil, Chile, France, Norway and the United Kingdom. Six of 29 member countries implemented a levy in 2009.

[1] UNITAID web site (http://www.unitaid.eu/en/).

[2] UNITAID *Annual report 2008* (http://www.unitaid.eu/images/news/annual_report_2008_en.pdf).

[3] UNITAID *Annual report 2009* (http://www.unitaid.eu/images/NewWeb/documents/AR09/unitaid2009ar_web%20spreads.pdf).

4.2 United States Vaccine Injury Compensation Program

Basic facts and mission

The United States Vaccine Injury Compensation Program is a Federal compensation system for permanent injuries and deaths resulting from vaccination to prevent infectious childhood diseases. It is intended to provide an alternative to the tort system for dealing with claims of vaccine-related injury. It is also intended to contribute to improving immunization rates, stabilizing the supply and price of vaccines, encouraging new and improved vaccines and reducing the burden and uncertainty of litigation

It is funded by a US$ 0.75 per dose tax on all vaccines sold in the United States. A total of US$ 235 million was raised in 2009.[1]

Operations

The funds are managed through the Vaccine Trust Fund. Individuals who are injured by a vaccine that is covered by the Fund can file a claim against United States Department of Health and Human Services in the Court of Federal Claims, seeking compensation from the Vaccine Trust Fund.

Governance[2]

The Vaccine Injury Compensation Program is located in the Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Vaccine Injury Compensation. Three Federal Government offices play a role in the Vaccine Injury Compensation Program: the Department of Health and Human Services, the Department of Justice and the Court of Federal Claims

History and key steps

The National Childhood Vaccine Injury Act of 1986 (Public Law 99-660) created the National Vaccine Injury Compensation Program on 1 October 1988.

4.3 Network of Medical Councils of the South-East Asia Region[3]

Basic facts and mission

The Network's mission is to share information among member medical councils of the South-East Asia Region to facilitate proactive coordination, cooperation and collaboration among member councils. Its objectives are to establish close collaboration and mutual exchange of information among medical councils and assist member councils in developing and establishing strategies for improving standards. A membership fee is charged, which is reviewed from time to time by the networking committee.

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[1] *Budget of the United States Government: Appendix fiscal year 2011* (detailed budget estimates by agency for the Department of Health and Human Services). http://www.gpoaccess.gov/usbudget/fy11/pdf/appendix/hhs.pdf.

[2] Health Resources and Services Administration web site (http://www.hrsa.gov/vaccinecompensation/).

[3] Medical Councils of the South-East Asia Region web site (www.mcsear.org).

Operations

The WHO Regional Office for South-East Asia and the WHO country office provide technical and financial assistance.

Governance

The Network presently consists of the medical councils and regulatory bodies of 11 Member States of the Region.

History and key steps

The WHO Regional Office for South-East Asia established the Network of Medical Councils of the South-East Asia Region in February 2007.

4.4 Thai Health Promotion Foundation[1]

Basic facts and mission

The Thai Health Promotion Foundation is a foundation in Thailand that promotes healthy lifestyles and tobacco and alcohol control. Its mission is to empower civic movements promoting the well-being of Thai citizens. ThaiHealth emphasizes healthy public policies, issue-based programmes and holistic approaches

Annual funds are raised from a 2% excise tax on tobacco and alcohol. The Foundation raises ~US$ 35 million per year for health promotion.

Operations

ThaiHealth provides grants for projects to develop social movements and the health system in order to increase the well-being of Thai people.

Governance

The Foundation is governed by two boards, the Governing Board, chaired by the Prime Minister, and the Evaluation Board, which evaluates the performance of ThaiHealth. The two boards have equal standing. They are appointed by the Executive Cabinet. It is the only Government organization to report directly to the Cabinet and Parliament on its performance

History and key steps

The idea was initially introduced in 1996, when the chief executive officers of successful health promotion foundations, including the Health Promotion Foundation of Australia, promoted the concept of a ThaiHealth foundation to the Minister of Finance. The Thai Government established committees to develop the concept and mandate of the fund in 1996–2000. The Foundation was established by an act of Congress in 2001.

[1] Thai Health Promotion Foundation web site (http://en.thaihealth.or.th/).

4.5 Debt2Health[1]

Basic facts and mission

Debt2Health is a Global Fund-facilitated debt-swap agreement to increase funding for health programmes. Creditors forego repayment of a portion of their claim on the condition that the beneficiary country invests the amount in domestic health through Global Fund-approved programmes. Thus far, Australia and Germany have participated in the initiative, resulting in investments in Indonesia and Pakistan.

Operations

The Global Fund facilitates a three-party agreement between crediting countries and recipient countries and then disburses funds on the same principles as traditional grants.

Governance

The Global Fund manages the process; no additional governance structure is required. Debt-swap agreements are managed through legal framework agreements between the recipient country, the Global Fund and the donor government that is cancelling the debt.

History and key steps

The Global AIDS Alliance and Advocacy International conducted a feasibility study of the debt-for-health swap concept for the Global Fund in 2005. The Debt2Health initiative was approved by the board of the Global Fund in April 2007. Germany agreed to pilot-test the concept as the first creditor and cancelled debts in Indonesia (2007) and Pakistan (2008). In July 2010, Australia signed a third agreement, with Indonesia for AUS$ 75 million.

4.6 World Bank Investment Partnership for Polio

Basic facts and mission[2]

The Partnership combines World Bank and private donor funds to create a unique system of incentives to encourage aggressive, effective efforts to eliminate poliomyelitis. The total amount of funding for the Partnership for the period 2003–2009 was US$ 316 million.

Operations[3]

The loans are funded through the International Development Association, the World Bank's soft-loan arm for the poorest countries. The International Development Association provides long-term, zero-interest loans that are highly concessional. The Partnership buys down a country's loans upon

[1] Global Fund web site (http://www.theglobalfund.org/en/innovativefinancing/debt2health/?lang=en).

[2] *Global Polio Eradication Initiative annual report 2009.* http://www.polioeradication.org/content/publications/AnnualReport2009_ENG.pdf.

[3] United Nations Foundation web site (http://www.unfoundation.org/press-center/press-releases/2003/financial-innovation-will-buy-polio-vaccine.html).

successful completion of that country's polio eradication programme. The generous loan terms mean each grant dollar unlocks US$ 2.50–3.00 for affected countries to fight poliomyelitis.

Governance[1]

The World Bank, the Bill & Melinda Gates Foundation, Rotary International and the United Nations Foundation together comprise the Investment Partnership for Polio. The Partnership was established with a trust fund of US$ 25 million from the Gates Foundation and US$ 25 million from Rotary International and the United Nations Foundation.

History and key steps[1]

The Partnership was launched in April 2003. In 2003, World Bank approved a US$ 28 million no-interest loan for the purchase of oral polio vaccine in Nigeria.

4.7 International Financing Facility for Immunization[2]

Basic facts and mission

The International Financing Facility for Immunization is a mechanism for raising funds for vaccination by issuing donor-backed bonds on the capital markets. Its mission is to accelerate the availability and predictability of funds for vaccination. It is designed to pilot-test the international financing facility concept and has proposed to raise US$ 50 billion to fund the Millennium Development Goals through 2015 and to provide US$ 4 billion to vaccination programmes through GAVI.

The donors include France, Italy, Norway, South Africa, Spain, Sweden and the United Kingdom.

Operations

Donors make legally binding payment agreements to the International Financing Facility for Immunization (via the GAVI Fund Affiliate). The Foundation then issues AAA/Aaa/AAA- rated bonds in the international capital markets. The treasury manager manages the bond proceeds until they are needed for vaccination programmes.

When they are needed, funds flow to the GAVI Fund Affiliate and are disbursed for GAVI-approved programmes. The Foundation repays bondholders with funds provided by donors, as outlined in payment agreements.

Governance

The Foundation consists of two operating entities: the International Financing Facility for Immunization, a United Kingdom charity and company, and the GAVI Fund Affiliate. It is managed by two boards and has no employees.

[1] United Nations Foundation web site (http://www.unfoundation.org/press-center/press-releases/2003/financial-innovation-will-buy-polio-vaccine.html).

[2] International Financing Facility for Immunization web site (http://www.iff-immunisation.org).

The Foundation's board and the GAVI Fund Affiliate board manage two operating entities of the Foundation. The GAVI Alliance secretariat fills all administrative functions and supports the two boards. The World Bank is the financial adviser and treasury manager.

History and key steps

Gordon Brown (then United Kingdom's finance minister) proposed the international financing facility mechanism to raise additional money to meet the Millennium Development Goals. In 2004, the United Kingdom and the GAVI Alliance agreed to pilot-test the programme on the basis of research that indicated a need for predictable, "front-loaded" funding for vaccination. Working groups that included representatives of key stakeholders (e.g. WHO, UNICEF, GAVI, World Bank, United Kingdom) developed the model and secured donors, and, in 2006, the International Financing Facility for Immunization was launched, with an inaugural bond issuance.

4.8 Caribbean Catastrophe Risk Insurance Facility[1]

Basic facts and mission

The Caribbean Catastrophe Risk Insurance Facility is a regional catastrophe fund for Caribbean governments, designed to limit the financial impact of devastating hurricanes and earthquakes by quickly providing financial liquidity when a policy is triggered. The Facility was developed to mitigate the short-term cash flow problems from which developing economies suffer after major natural disasters. It combines the benefits of pooled country reserves with the financial capacity of the international financial markets.

The Facility was set up with funding from the Japanese Government and was capitalized by contributions to a multi-donor trust fund from the Government of Canada, the European Union, the World Bank, the governments of France and the United Kingdom, the Caribbean Development Bank and the governments of Bermuda and Ireland, as well as from membership fees paid by participating governments.

The payouts to date have been: ~US$ 1 million to Dominica and St Lucia in 2007; ~US$ 6.3 million to the Turks and Caicos Islands in 2008; and US$ 7.75 million to Haiti in 2010 (about 20 times the premium of US$ 385 500).

Operations

The Facility functions similarly to a mutual insurance company, controlled by its participating governments. The premiums are determined by the amount of coverage, the attachment and the exhaustion points of that coverage and the risk profile of a country. Each country pays in exact proportion to the amount of risk it is transferring, so that there is no cross-subsidization.

Governance

The Caribbean Catastrophe Risk Insurance Facility operates as a public–private partnership and is set up as a non-profit "mutual" insurance entity in the Cayman Islands.

[1] Caribbean Catastrophe Risk Insurance Facility web site (http://www.ccrif.org).

History and key steps

The idea of such a facility was prompted by Hurricane Ivan in 2004, which caused billions of dollars of losses across the Caribbean. The Heads of Government of the Caribbean Community approached the World Bank for assistance in designing and implementing a cost–effective risk transfer programme for member governments, which was initially capitalized by the participating countries themselves, with support from donors.

4.9 World Bank MultiCat catastrophe bond issuance platform[1]

Basic facts and mission

MultiCat is a platform developed by the World Bank to facilitate the issuance of "catastrophe bonds" by national governments. Catastrophe bonds are an insurance mechanism whereby the bond seller pays the bond buyer interest on principal up to the time of a predefined catastrophe, at which point the seller provides the principal in a lump sum.

The MultiCat programme allows participants to buy insurance coverage for earthquakes, floods, hurricanes and other wind storms. It establishes a common documentation, legal and operational framework for future catastrophe bond issuances.

Operations

The programme is administered by the World Bank, with private banks and insurers brokering the bond purchase deals and pricing. A special-purpose vehicle is established to write a parametric insurance contract (i.e. insurance that makes payment when a triggering event occurs) with each government and issues the bond. The World Bank then places the bond with institutional investors through investment banks.

The special-purpose vehicle invests the proceeds in AAA-rated assets, which form the source of payouts if a covered event occurs. Each bond issued under the platform carries the MultiCat brand name and has a common legal structure and documentation.

Governance

MultiCat is under the World Bank's governance mechanisms, and details of contracts are agreed by national governments and bond purchasers.

History and key steps

To date, one country, Mexico, has taken advantage of this platform, issuing US$ 290 million in MultiCat bonds. Other parties (e.g. national governments) are developing documentation to issue similar bonds, although no others have yet been issued.

[1] http://treasury.worldbank.org/bdm/pdf/Handouts_Finance/Financial_Solution_MultiCat.pdf.

4.10 World Bank Catastrophe Risk Deferred Drawdown Option

Basic facts and mission

The Catastrophe Risk Deferred Drawdown Option is a financial product offered to middle-income country governments by the International Bank for Reconstruction and Development, part of the World Bank group. Its purpose is to make financing available immediately after a natural disaster, like an earthquake or hurricane, to fill the gap while other sources of funding, such as emergency relief aid, are being mobilized. Countries can access funds from the facility if they declare a state of emergency as a result of a natural disaster, pandemic or other incident resulting in a declared state of emergency. Countries that sign up for the Option must have an adequate hazard risk management programme in place that is monitored by the World Bank.

The credit lines can be as large as 0.25% of GDP, up to US$ 500 million. The cost of securing a credit line is 0.5% of the value of the loan (the initial fee, set at 0.25%, was increased on 5 August 2009), which is higher than the standard rate of the International Bank for Reconstruction and Development.

Operations

Credit lines under the Catastrophe Risk Deferred Drawdown Option are extended by the International Bank for Reconstruction and Development and are revolving lines of credit. Contracts are valid for 3 years and can be renewed. The loan terms are similar to those of standard International Bank for Reconstruction and Development loans, including a 2–3-year grace period, interest rates that are below standard market rates and a repayment period of 15–25 years.

Governance

The Catastrophe Risk Deferred Drawdown Option is under the World Banks' International Bank for Reconstruction and Development governance structure.

History and key steps

To date, Colombia, Costa Rica and Guatemala have taken advantage of the Option's credit facilities, taking out credit lines of US$ 150 million, US$ 65 million and US$ 85 million, respectively.

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