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## **I. BACKGROUND**

In the context of finalizing the “Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and Other Benefits”,<sup>1</sup> 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 (OEWG) in reaching a final agreement

The OEWG listed the following areas requiring further technical consideration and study, drawing on lessons learnt from the pandemic (H1N1) 2009 and the ongoing outbreaks of influenza H5N1.<sup>2</sup> (see document A63/48, paragraph 7):

- 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;
  - (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.

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<sup>1</sup> As contained in document A62/5 Add.1.

<sup>2</sup> See document A63/48, Annex, paragraph 7.

## **PROCESS**

Work to develop terms of reference for the studies, based on the report of the OEWG (document A63/48) commenced immediately after the Sixty-third World Health Assembly in May 2010. The terms of reference were finalized and provided to Member States on 22 July 2010. Given the significant 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 agreed to provide 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 working on the project quickly; and its global team.

Based on the report of the OEWG and the terms of reference drawn therefrom, the WHO Secretariat and the McKinsey team started to develop the outline of the study in mid-August 2010. Defining the parameters of the study as well as the timetable for deliverables was first addressed and in the light of the extensive scope of the studies, a phased approach was agreed to allow preliminary findings to be shared in time for the December 2010 OEWG and the full study to be completed before the Sixty-fourth World Health Assembly.

A working outline of the study was provided to Member States on 20 October in all six official languages of the World Health Organization.<sup>1</sup> That document presented the outline of the study. This document provides the Preliminary Findings of the study, notably the current state for each technical area, several possible targets, options and costs, as well as possible funding scenarios. As stated in the working outline, in these preliminary findings, the focus of the access, affordability and effective deployment section is access to vaccines. Other commodities will be addressed in the final document which will be made available prior to the Sixty-fourth World Health Assembly.

The findings contained in this document are **preliminary** in nature. Further development work will be undertaken following the December 2010 meeting of the OEWG to complete certain sections and/or to further develop specific targets of interest to the OEWG.

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<sup>1</sup> See [http://apps.who.int/gb/pip/e/E\\_Pip\\_oewg2.html](http://apps.who.int/gb/pip/e/E_Pip_oewg2.html).

## **DATA AND SOURCES**

Given the very short time frame to develop the study, existing data were utilized where possible, and analysis was conducted on this data to generate the potential targets and options. New data were generated for pandemic vaccine capacity projections and identification of access barriers. Lessons learnt from the pandemic (H1N1) 2009 and the ongoing outbreaks of influenza H5N1 have been considered wherever appropriate. All costs provided are estimates based on publicly available data. Costs were estimates based on a range of sources, including publicly available information, manufacturer interviews, and other expert interviews.

## **II. METHOD OF WORK**

The starting point for these studies is the guidance and information contained in the following WHO documents: A62/5 Add.1; A63/48; and A/PIP/IGM/13, Annex 4.<sup>1</sup> A fact-based approach was used, based on data contained in WHO reports and other publicly available documents. All country-specific data has been aggregated. Consistent with the request made by the Health Assembly in resolution WHA63.1, and other relevant resolutions, the Director-General has undertaken consultations with stakeholders to ensure the appropriateness and feasibility of the proposed targets and options. All sources will be acknowledged in the final report.

Prior to the Sixty-fourth World Health Assembly, the full study and appendices will be completed, drawing on guidance obtained during the meeting of the open-ended working group to be held in December, and further stakeholder consultations as necessary.

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<sup>1</sup> The documents are all available at [http://apps.who.int/gb/pip/e/E\\_Pip\\_oewg2.html](http://apps.who.int/gb/pip/e/E_Pip_oewg2.html).

### **III. APPROACH TO THE TECHNICAL STUDIES**

Studies in each technical area will systematically address the following issues:

- *Current state*: description of current capacity and capacity gaps at country level in that technical area;
- *Targets*: description of potential targets to improve pandemic preparedness in the next five years. All targets must be scientifically sound, technically feasible, and quantified and measurable;
- *Strategic options to reach the targets*: a description of activities that could achieve each of the potential targets;
- *Costing*: an estimate of costs for each option identified.

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

### **IV. ASSUMPTIONS**

No two influenza pandemics are alike. Where appropriate, assumptions used to develop a potential target, option or model are clearly articulated.

## **V. LABORATORY & SURVEILLANCE CAPACITY BUILDING**

### **Goal**

- 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.<sup>1</sup>
- This supports the notification, reporting and verification requirements under the International Health Regulations (2005)(IHR).

### **Approach, assumptions, data sources and limitations**

#### **1. Approach**

Member States' current laboratory and surveillance capacities were assessed using three influenza-specific elements that build on the "Core capacity requirements for surveillance and response" set out in Annex 1 of the International Health Regulations (2005).

- 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 different channels, particularly health-care workers, animal health professionals, schools and employers, and the media.
- Laboratory analysis and surveillance – analysis of clinical specimens to characterize virus subtype, genetic sequence, and antigenic and other viral properties. This includes the shipping of virus samples from national to regional and global levels (e.g. to WHO H5 reference laboratories and WHO collaborating centres).

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<sup>1</sup> Document A62/5 Add.1 Pandemic influenza preparedness framework for the sharing of influenza vaccine and access to vaccines and other benefits, section 6.6.

**Figure 1. Laboratory and surveillance capacity elements and levels<sup>1</sup>**

Capacity levels		Low level → High level			
<b>1</b>	<b>Indicator-based surveillance<sup>1</sup></b>	Level 1: Ad hoc indicator-based surveillance	Level 2: At least one sentinel site for influenza-like illness surveillance	Level 3: Multiple sentinel sites with broad population coverage, at least one for severe acute respiratory illness	Level 4: Widespread national coverage for both influenza-like illness and severe acute respiratory illness
<b>2</b>	<b>Event-based surveillance<sup>1</sup></b>	Level 1: Ad hoc event-based surveillance	Level 2: Basic central reporting system is in place, and health worker sector has formal reporting	Level 3: School and employer sector, and animal health worker sector also have formal reporting	Level 4: All three sectors have formal reporting, and central media monitoring is in place
<b>3</b>	<b>Laboratory analysis and surveillance<sup>2</sup></b>	Level 1: No access to polymerase chain reaction testing	Level 2: Access to polymerase chain reaction testing but not to influenza-specific laboratories	Level 3: Access to influenza-specific laboratories with limited capacity	Level 4: Access to influenza laboratories that meet WHO National Influenza Centre terms of reference
<b>4</b>	<b>Virus sample shipping<sup>3</sup></b>	Level 1: No access to virus sample shipping available	Level 2: Virus sample shipping is possible with assistance from abroad	Level 3: Country has in-country capacity for shipping virus samples	

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

## 2. Assumptions

- Estimated costs in indicator- and event-based surveillance are the incremental costs over and above current surveillance spending. Estimates do not include the cost of strengthening non-influenza-specific capacities as required under the International Health Regulations (2005).
- In the event of a pandemic, annual operating costs for laboratories and surveillance sites will be substantially higher due to the increase in activity.<sup>2</sup> Estimated costs reflect this.

## 3. 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).

<sup>1</sup> For cost purposes, virus sample shipping has been maintained as a separate element in the table and throughout this section.

<sup>2</sup> For example, during the pandemic (H1N1) 2009, laboratories in many countries processed more than five times the normal volume of virus samples. In addition, laboratory and surveillance systems reported hiring additional staff and reassigning staff working in other disease areas, hence increasing influenza costs.



- 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.<sup>1</sup>
- **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<sup>2</sup> and other global costing projects.<sup>3</sup>
  - 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 Appendix X.

## **Current state**

### **1. Review of current state for each of the four elements (see Figure 1 above for capacity levels)**

- Indicator-based surveillance
  - Capacity is at a low level (i.e. capacity level 1 or 2)<sup>4</sup> in some 48% of countries. Surveillance systems at these levels currently do not meet minimal draft WHO definitions<sup>5</sup> for surveillance of influenza-like illness or severe acute respiratory illness,

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<sup>1</sup>The number of respondent countries were as follows from the regions: Africa (23), The Americas (17), Eastern Mediterranean (17), Europe (29), South-East Asia (10), and the Western Pacific (20).

<sup>2</sup>See <http://www.who.int/choice/en/> (accessed on 19 November 2010).

<sup>3</sup> See <http://www.who.int/bulletin/volumes/86/1/07-045096.pdf> (accessed on 19 November 2010).

<sup>4</sup> See Figure 1 for definitions of capacity levels.

<sup>5</sup> Forthcoming from the WHO technical working group on influenza surveillance.

or those contained in influenza surveillance guidance documents produced by the Regional Offices for the Americas, Europe, or the Western Pacific,<sup>1</sup> or in the guidelines issued by WHO during the pandemic (H1N1) 2009.<sup>2</sup>

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

### **1. Event-based surveillance**

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

### **2. Laboratory analysis and surveillance**

Capacity is low in 114 countries. These countries do not have access to an influenza laboratory with the ability to type/subtype influenza viruses, isolate viruses, and integrate laboratory data into influenza surveillance.

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

### **3. Virus sample shipping**

Twenty-one countries, representing 2% of the global population, currently do not have access to virus sample shipping 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, as well as countries with a population of less than one million, and in the Eastern Mediterranean Region.

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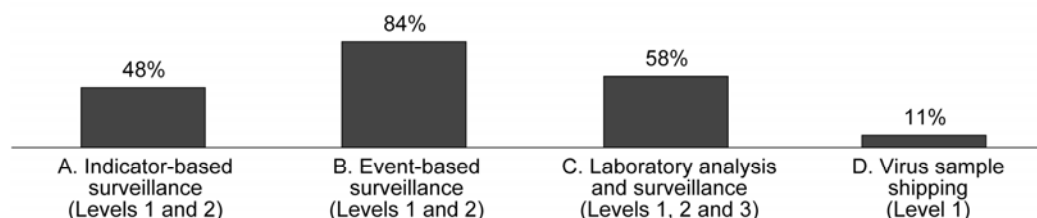
<sup>1</sup> e.g. *WHO Regional Office for Europe guidance for influenza surveillance in humans*, World Health Organization, 2009, available at: [http://www.euro.who.int/\\_data/assets/pdf\\_file/0020/90443/E92738.pdf](http://www.euro.who.int/_data/assets/pdf_file/0020/90443/E92738.pdf), (accessed on 7 November 2010).

<sup>2</sup>See <http://www.who.int/csr/resources/publications/swineflu/surveillance/en/index.html> (accessed on 19 November 2010).

**Figure 2. Current state: laboratory and surveillance capacity levels**

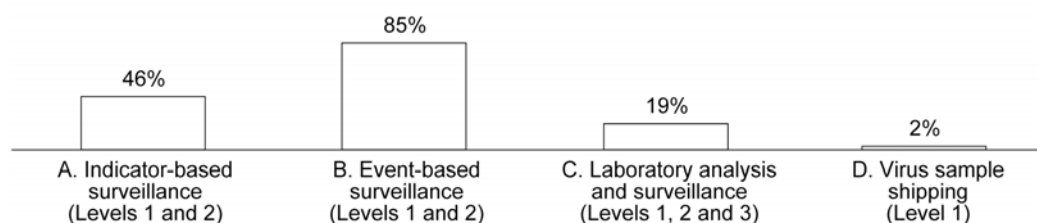
**Countries with low-level capacity (%)**

Percentage of countries (extrapolated from sample)



**Population of countries with low-level capacity**

Percentage of global population (extrapolated from sample)



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**Potential targets and strategic options**

Proposed potential targets aim to ensure that all Member States strengthen their influenza-specific capacity for epidemiological surveillance (indicator and event based), laboratory analysis and surveillance, and virus sample shipping, and that the capacity for global information sharing in each of these areas is strengthened.

There are two strategic options to achieve the potential targets:

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

**1. Potential targets and strategic options for each of the four capacities**

**Indicator-based surveillance**

**Target 1**

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

## **Target 2**

- 100% of countries at capacity level 1 or 2 reach capacity level 3 (develop surveillance including multiple influenza-like illness sentinel sites and at least one severe acute respiratory illness sentinel site, 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 influenza-like illness sentinel sites and at least one severe acute respiratory illness sentinel site, 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 in-country capacity building for all countries**

- Build and/or expand influenza-like illness sentinel surveillance system: through training for health workers; equipment; and salaries
  - Indicative costs per influenza-like illness sentinel site includes (on average)
    - One-time set-up costs of US\$ 6000 – \$ 6500
    - Annual recurring costs of \$ 6400 – \$ 6900<sup>1</sup>
- Build and/or expand severe acute respiratory illness sentinel surveillance system through training for health workers; equipment and salaries. Existing influenza-like illness sites may be upgraded to severe acute respiratory illness sites.
  - Indicative costs per severe acute respiratory illness site include (on average)
    - One-time set-up costs of \$ 1700 – \$ 2000, (in addition to the costs of setting up an influenza-like illness site)
    - Annual recurring costs of \$300 – \$500 (in addition to the annual costs of an influenza-like illness site)
- Build central data analysis capacity: equipment; training and salary for epidemiologists.
  - Indicative costs of building central data analysis capacity:
    - One-time set-up costs of \$10 000 – \$14 000 per country

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<sup>1</sup> Detailed assumptions and costs are provided in Appendix X.

- Annual recurring costs of \$35 000 – \$45 000 per country.
- Technical assistance
  - Costs range: \$6000 – \$40 000 depending on local costs and duration of technical assistance.

**Strategic option 2:** Support in-country capacity building for larger countries (i.e. those with a population of more than one million), and support access to external capacity (e.g. neighbouring states, regional networks) for smaller countries.

- For all countries, build and/or expand in influenza-like illness and severe acute respiratory illness sentinel surveillance networks as described in strategic option 1.
- For 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. Indicative costs for these countries include costs of influenza-like illness sites, severe acute respiratory illness sites, and technical assistance as detailed above.

### Costs

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

**Table 1. Indicator-based surveillance costs (US\$ million)**

		Set-up costs	Annual recurring costs in a non-pandemic year	Annual recurring costs during a pandemic
Target 1: all reach capacity level 3	Strategic option 1	\$4.4–\$6.6 M	\$9.8–\$14.7 M	\$30–\$74 M
	Strategic option 2	\$4.4–\$6.5 M	\$9.8–\$14.6 M	\$30–\$74 M
Target 2: all reach capacity level 3 and at least 20% at capacity level 4	Strategic option 1	\$4.6–\$6.8 M	\$9.9–\$14.9 M	\$30–\$74 M
	Strategic option 2	\$4.5–\$6.8 M	\$9.9–\$14.8 M	\$30–\$74 M
Target 3: all reach capacity level 3 and at least 40% at capacity level 4	Strategic option 1	\$6.8–\$10.3 M	\$12–\$17.9 M	\$30–\$74 M
	Strategic option 2	\$6.8–\$10.2 M	\$11.9–\$17.9 M	\$30–\$74 M

- The estimated set-up costs of building a full stand-alone influenza surveillance system (including both indicator-based and event-based surveillance) would be in the range of \$8000

to \$30 000 per one million population, with annual recurring costs for running and maintenance of \$5000 to \$20 000 per one million population.

### **Event-based surveillance**

#### **Target 1**

- 100% of countries currently at capacity level 1 reach capacity level 2 (basic central infrastructure and regular reporting of unusual influenza-related events from human health workers), and
- 50% of countries in each region reach capacity level 3 (develop regular reporting from all of the 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 the 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 of the three main sectors: animal health, human health, and schools and employers).
- At least 20% of countries in each region meet the capacity level 4 requirements (regular reporting from all of the three main sectors and have central media monitoring in place).

### **Strategic option 1: Support in-country capacity building for all countries**

- Build and/or support basic central reporting infrastructure for unusual events through, for example, establishment of a central telephone reporting hotline.
  - Estimated set-up and annual recurring costs for this activity are \$500 – \$700 each.
- Increase awareness of reportable unusual influenza events through distribution of educational materials to health worker, school, employer, and animal health networks.
  - Estimated set-up costs are: \$800 – \$1200 per network per country
  - Annual recurring costs for distributing influenza-specific material:
    - \$0.5 – \$1.0 per health worker per year;
    - \$800 – \$1200 per one million population for schools and employers;
    - \$300 – \$700 per one million population for animal health workers.
- Build central media monitoring infrastructure: salary and equipment for one media monitor.

- Estimated set-up costs range from \$6000-\$9000 per country;
- Annual costs range from \$10 000 to \$50 000 per country.
- Technical assistance
  - \$ 2000 – \$ 5000 depending on local costs and duration of technical assistance (this technical assistance would be additional to indicator-based surveillance).

**Strategic option 2:** Support in-country capacity building for larger countries (i.e. those with a population of more than one million), and support access to external capacity (e.g. neighbouring states, regional networks) for smaller countries

- 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 of \$ 2500 – \$ 3500, with annual recurring costs of \$ 7500 – \$ 25 000 per country. These costs are in addition to the costs of building and maintaining reporting networks (see strategic option 1).
- Technical assistance.
- \$ 2000 – \$ 5000 depending on local costs and duration of technical assistance (this technical assistance would be additional to indicator-based surveillance).

### Costs

- Costs are in addition to current surveillance spending. Estimates do not include the costs of building non-influenza-specific capacity under the International Health Regulations (2005).

**Table 2. Summary of event-based surveillance costs (US\$ million)**

		Set-up Costs	Annual recurring costs during a non-pandemic year	Annual recurring costs during pandemic
Target 1: all reach capacity level 2 and at least 50% reach capacity level 3	Strategic option 1	\$0.7–\$1 M	\$13.2–\$19.8 M	\$74–\$221 M
	Strategic option 2	\$0.6–\$1 M	\$13.2–\$19.8 M	\$74–\$221 M
Target 2: all reach capacity level 3	Strategic option 1	\$1.4–\$2.1 M	\$29–\$43.5 M	\$74–\$221 M
	Strategic option 2	\$1.4–\$2.1 M	\$29–\$43.5 M	\$74–\$221 M
Target 3: all reach capacity level 3 and at least 20% reach capacity level 4	Strategic option 1	\$2–\$3 M	\$29.4–\$44.1 M	\$74–\$221 M
	Strategic option 2	\$1.9–\$2.8 M	\$29.2–\$43.9 M	\$74–\$221 M

## **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 salary; training for technical and administrative staff
  - Indicative costs of training and salary support
  - Set-up costs: \$ 27 000 – \$ 76 000 per country
  - Annual recurrent costs: \$ 21 000 – \$ 57 000
- Support for equipment and maintenance
  - Set-up costs: \$ 110 000 – \$ 134 000
  - Annual recurrent costs: \$ 33 000 – \$ 40 000
- Support for operating expenses including utilities, telephone and Internet, transportation, and other overheads
  - Annual recurrent costs: \$ 24 000 – \$ 36 000
- Reagents and other material required for sample collection and analysis supplied by WHO Collaborating Centres
  - Estimated annual costs: \$ 81 000 – \$ 99 000



- Global coordination of virological surveillance activities and timely analysis of virological surveillance information (WHO Network)
- Estimated annual global costs: \$ 6 million – \$ 8 million

**Strategic option 2:** Build and/or support appropriate laboratory capacity and global level support for larger countries (e.g. those with a population of more than one million), and support access to external capacity (e.g. neighbouring states, regional networks) for smaller countries

- For larger countries, build and support appropriate laboratory capacity as in strategic option 1
- For smaller countries (e.g. those with a population of less than one million), support access to regional laboratory capacity, including:
  - Set-up costs: \$ 19 000 – \$ 34 000
  - Annual recurrent costs: \$ 17 000 – \$ 25 000
- Global coordination of virological surveillance activities and timely analysis of virological surveillance information (WHO Network)
- Estimated annual global costs: \$ 6 million – \$ 8 million

## Costs

**Table 3. Summary of laboratory analysis and surveillance costs (US\$ million)**

		Set-up costs	Annual recurring costs during a non-pandemic year	Annual recurring costs during pandemic
Target 1: all countries reach capacity level 3	Strategic option 1	\$7–\$10.5 M	\$10.4–\$15.6 M	\$56–\$169 M
	Strategic option 2	\$4.6–\$6.9 M	\$8.7–\$13.1 M	\$56–\$169 M
Target 2: all countries reach capacity level 4	Strategic option 1	\$9.5–\$14.3 M	\$17–\$25.5 M	\$56–\$169 M
	Strategic option 2	\$6.2–\$9.3 M	\$13.2–\$19.8 M	\$56–\$169 M
Target 3: all countries reach capacity level 4 ; at least 20% at capacity level 5; at least one Collaborating Centre per region	Strategic option 1	\$20.4–\$30.5 M	\$25.3–\$38 M	\$56–\$169 M
	Strategic option 2	\$17.1–\$25.6 M	\$21.6–\$32.3 M	\$56–\$169 M

## 2.4 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; for all countries without in-country dry ice, shipping material, and trained personnel (capacity level 2), provide dry ice equipment, shipping material and training for in-country personnel

- Estimated set-up costs: \$ 6400 – \$ 9600 per country
- Annual running costs: \$ 2600 – \$ 3900 per country
- International coordination of shipper training, materials, contract with courier for sample shipments. Includes global mobile shipping capacity (e.g. contract to have access to helicopter, chartering capacity, United Nations peace-keeping facilities etc). Annual costs: \$ 500 000

**Strategic option 2:** Expand WHO influenza specimen shipping project to all countries without adequate in-country shipping capacity

- Estimated annual costs per country: approximately \$ 6000 – \$ 9000 per country per year (based on WHO influenza specimen shipping project costs)
- Global level: internationally coordinated training, materials, courier routes. Annual costs: \$ 400 000 – \$600 000.

## Costs

**Table 4. Virus sample shipping costs (US\$ million)**

		Set-up costs	Annual recurring costs during a non-pandemic year	Annual recurring costs during pandemic
Target 1 all reach capacity level 2	Strategic option 2	NA	\$0.5–\$0.8 M	\$1.1–\$3.2 M
Target 2 all reach capacity level 3	Strategic option 1	\$0.8–\$1.1 M	\$0.7–\$1 M	\$1.1–\$3.2 M

## **VI. EXPANDING GLOBAL INFLUENZA VACCINE PRODUCTION CAPACITY**

### **Goal**

- Increase the global capacity to produce pandemic influenza vaccine to meet global needs during a pandemic.<sup>1</sup>

### **Definitions of Terms Used**

**Adjuvant:** Substance that, when mixed with an antigen and injected with it, enhance the immunogenicity of that antigen<sup>2</sup>. When an adjuvant is added to a vaccine, it reduces the amount of antigen needed for the vaccine to elicit an immune response. As such, use of adjuvants can increase the number of doses of vaccine that can be derived from a specific quantity of antigen.

**Antigen:** A substance that binds with a specific antibody<sup>3</sup>. For a vaccine, substance which induces an immune response.

**Antiviral:** In this document, short for antiviral drug. An agent (e.g., chemical preparation, drug), that acts directly against a virus, destroying it or impeding its ability to replicate<sup>4</sup>. An antiviral 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 for vaccine use 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/Trivalent vaccine:** A vaccine specific for a single (mono) or three (tri) antigens or organisms<sup>5</sup>. In the case of flu, the seasonal trivalent vaccine confers protection against three different strains or types of influenza virus. The monovalent pandemic vaccine, on the other hand, confers protection to the only influenza virus strain that causes the pandemic.

**Production yield:** The amount of virus and/or antigen that can be obtained per unit of production (egg or milliliters of cell culture). In this document, yield is expressed in percent to indicate the yield of pandemic vaccine production relative to seasonal vaccine produced in the same technology platform.

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

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<sup>1</sup> "Global pandemic influenza action plan to increase vaccine supply," WHO/IVB 06.13.

<sup>2</sup> Kuby Immunology, Richard A. Goldsby, Thomas J. Kindt and Barbara A. Osborne, W.H. Freeman & Company; 4th edition (January 15, 2000).

<sup>3</sup> Kuby Immunology, Richard A. Goldsby, Thomas J. Kindt and Barbara A. Osborne, W.H. Freeman & Company; 4th edition (2000).

<sup>4</sup> Dorland's Medical Dictionary, Elsevier, 31st edition (2007).

<sup>5</sup> Dorland's Medical Dictionary, Elsevier, 31st edition (2007).

**Time to 1st dose:** The time period elapsed between when the candidate vaccine virus becomes available to manufacturers and the release of first dose to market.

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

## **A. Approach, assumptions, data sources and limitations**

### **1. Approach**

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

- 1.1** Technology review: All influenza vaccine manufacturing technologies were reviewed, including those currently in use and those in development.
- 1.2** Current seasonal capacity: Data were collected for production capacity in all known seasonal influenza vaccine manufacturing facilities across technologies and aggregated to the total global level.
- 1.3** Seasonal to pandemic capacity conversion: Seasonal capacity was converted to potential pandemic capacity as the same physical infrastructure is used for production of both vaccine types. A range of conversion scenarios were developed based on a review of actual production and experiences with H5N1, H1N1, and seasonal vaccines using three conversion factors:
  - 1.3.1** Time to first dose: The time period from when the candidate vaccine virus for pandemic vaccine development is released to manufacturers and the point in which the first dose of vaccine can be produced. A shorter time to first dose will increase the number of doses produced over any fixed production timeframe.
  - 1.3.2** Pandemic dosage: The dosage levels required for pandemic vaccine relative to seasonal vaccine. Lower dosages will increase the number of doses produced.
  - 1.3.3** Relative production yield: The production yield of pandemic vaccine relative to seasonal vaccines. Higher relative yield will increase the number of doses produced.
- 1.4** Forecasted pandemic capacity: Future seasonal capacity was estimated for the period 2010–2015 based on all manufacturers' expansion plans (high, middle and low income country manufacturers). That future capacity was converted to potential pandemic capacity using the same conversion factors described in section 1.3.
- 1.5** Targets and gap: A range of capacity expansion targets was developed along 2 dimensions – the production capacity required and the timeframe allowed to produce all doses from the availability of candidate vaccine virus to manufacturers. These targets were then compared to expected capacity.

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<sup>1</sup> Dorland's Medical Dictionary, Elsevier, 31st edition (2007).

## 2. Assumptions

- Seasonal influenza vaccines are trivalent, i.e., contain components from three different strains of influenza virus.
- Pandemic vaccines are monovalent, i.e. contain components from a single strain of influenza virus, the pandemic strain.
- Complete immunization against pandemic influenza would be obtained after two doses of pandemic vaccine. The experience from H1N1 and H5N1 suggests that the required number of doses can be variable – for H5N1 vaccines, two doses seem to be required to confer protection against the infection<sup>1</sup>, while in the H1N1 case one dose was sufficient<sup>2</sup>. Given the unknown nature of pandemic viruses and vaccines derived from them, 2 doses are used as the safest planning assumption. All coverage estimates reported would be doubled (i.e. population coverage of 15% with 2 doses would be 30% with 1 dose) if only 1 dose is required.
- In the event of a pandemic, manufacturers can “push,” or increase, their production capacity by approximately 10%.<sup>3</sup>
- New influenza vaccine production technologies at development stages earlier than phase II clinical trials will not reach the market by 2015.
- New potency and sterility testing methods will become available by 2014, reducing the time to first dose by approximately 2 weeks.
- All seasonal capacity levels are based on a theoretical full year of production, accounting for 8 weeks of regular maintenance and 44 weeks of production.
- Pandemic vaccine capacity levels are based on a theoretical full year of production, accounting for 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

#### 2.1 Current and forecasted seasonal capacity estimates were based on:

- A survey of 28 manufacturers that currently produce seasonal vaccine, or will start producing by 2015 (14 in high-income countries and 14 in middle-income countries).
- Interviews with 17 manufacturers (10 in high-income countries and 7 in low and middle-income countries), accounting for approximately 90% of current capacity (26 manufacturers were contacted).

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<sup>1</sup> The Strategic Advisory Group of Experts. Working Group on H5N1 Influenza Vaccines. Report to SAGE, April 2009.

<sup>2</sup> Girard et al. (2010) “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 28:6811-6820.

<sup>3</sup> Oliver Wyman-IFPMA-WHO “Influenza vaccine supply and demand – Summary of findings”, March 2009.

- Interviews with health officials from high-income countries providing funding for the expansion of influenza vaccine production capacity.
- A survey of the status and plans of 11 middle-income country vaccine manufacturers that received capacity grants under the GAP programme.
- Consultations with experts on influenza vaccine manufacturing.

## **2.2 Seasonal to pandemic capacity conversion scenarios were based on:**

- A full literature review of influenza vaccine production experience<sup>1,2, 3,4, 5, 6, 7,8, 9</sup>
- Phone interviews with 17 manufacturers (10 in high-income countries and 7 in middle-income countries).
- Consultations with experts on influenza vaccine manufacturing.

## **2.3 Illustrative targets for pandemic capacity were defined based on:**

- The GAP<sup>10</sup>
- Results from pandemic outbreak modelling<sup>11, 12, 13</sup>

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<sup>1</sup> Hickling & D'Hondt IVR-WHO "A review of production technologies for influenza virus vaccines, and their suitability for deployment in developing countries for influenza pandemic preparedness", December 2006.

<sup>2</sup> PCAST "Report to the president on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza", August 2010.

<sup>3</sup> Collin & de Radigues (2009) "Vaccine production capacity for seasonal and pandemic (H1N1) 2009 influenza", Vaccine 27(38):5184-6.

<sup>4</sup> 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.

<sup>5</sup> Girard et al. (2010) "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 28:6811-682.

<sup>6</sup> J. Bernat-IFPMA "H1N1 Vaccine Production: The Industry Perspective", Geneva Health Forum 19 April 2010.

<sup>7</sup> Oliver Wyman-IFPMA-WHO "Influenza vaccine supply and demand – Summary of findings", March 2009.

<sup>8</sup> Uppsala Monitoring Center (www.who-umc.org) "A/H1N1 pandemic influenza vaccines", February 24th 2010.

<sup>9</sup> The Strategic Advisory Group of Experts. Working Group on H1N1 Influenza Vaccines. Report to SAGE, April 2009.

<sup>10</sup> "Global pandemic influenza action plan to increase vaccine supply," WHO/IVB 06.13

<sup>11</sup> Goldstein et al. (2009) "Reproductive numbers, epidemic spread and control in a community of households", Mathematical Biosciences 221:11-25.

<sup>12</sup> Yang et al. (2009) "The Transmissibility and Control of Pandemic Influenza A (H1N1) Virus", Science 326(5953):729-733

<sup>13</sup> Germann et al. (2006) "Mitigation strategies for pandemic influenza in the United States", PNAS 103(15):5935-5940

- Actual coverage levels achieved for H1N<sup>1</sup>
- Herd immunity literature review<sup>2</sup>

### **3. Limitations**

The main limitation of this study is the forecasted nature of capacity through 2015. This forecast is based on a survey of manufacturers in which they communicated their expansion plans. Changes in seasonal demand and in pandemic preparedness efforts by governments and international organizations could lead to reduction of existing capacity or modification of expansion plans. Detailed modelling of seasonal demand and assessment of its impact on manufacturer expansion plans was not conducted.

## **B. Current State**

### **1. Technology**

#### **1.1 Overview of current and future technologies**

1.1.1 Current technologies: Currently there are three market-approved technologies used for commercial production of influenza vaccines.

1.1.1.1 Egg-derived inactivated influenza vaccine (also referred to as “egg-IIV”): This technology was first introduced in the 1940s. The vaccine is produced by growing influenza virus in hen eggs, then purifying and inactivating it with a chemical agent. Three types of inactivated vaccines 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 egg-IIV vaccines, all in advanced stages of development, i.e., Phase II/III, in middle-income countries (see Figure 1).

1.1.1.2 Cell-based inactivated influenza vaccine (also referred to as “tissue-culture-derived inactivated influenza vaccine” or “cell-IIV”): Inactivated vaccine produced in cell culture rather than traditional hen eggs<sup>3</sup>. Three high-income manufacturers and one middle-income manufacturer currently market cell-IIV vaccines. One manufacturer has a vaccine at early stages of development, i.e. pre-clinical or Phase I clinical stage (see Figure 1).

1.1.1.3 Egg-derived live attenuated influenza vaccine (egg-LAIV) (also referred to as “cold-adapted influenza vaccine” (CAIV)). Egg-based vaccine

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<sup>1</sup> “Avec 60 % de sa population vaccinée, la Suède figure loin devant la plupart des pays”, *Le monde*, January 6, 2010

<sup>2</sup> Glezen (2006) “Herd protection against influenza”, *Journal of Clinical Virology* 37:237-243; Asllani & Ettkin (2010) “A generic simulation model to manage a vaccination program”, *Journal of Medical Systems*, Online First™, 28 January 2010, DOI: 10.1007/s10916-009-9423-1

<sup>3</sup> Novartis Vaccines press release, November 5th 2009

containing live virus that is weakened so as not to cause influenza, but induce an immune response<sup>1</sup>. This technology has been used since 1954<sup>2</sup>. Egg-LAIV vaccines are produced by 3 manufacturers, 1 in a high-income, 2 middle-income countries. One manufacturer has egg-LAIV products in Phase 2/3 development stage (see Figure 1)

- 1.1.1.4 Adjuvants Technology: Inactivated influenza vaccines sometimes contain adjuvants, which can range from traditional adjuvants (alum) to newer potent adjuvants (e.g., oil in water emulsions). Adjuvants can have a meaningful impact on dosage levels required for pandemic production (see Section 1.3) and potential cross protection across strains.
- 1.1.2 Future technologies: Manufacturers and biotechnology companies are developing a number of new technologies<sup>3</sup> (see below). These technologies target a range of potential improvements, including increased protection, and more efficient production. Most products from these new technologies are in pre-clinical or Phase I stages of development (see Figure 1).
  - 1.1.2.1 Cell-based live attenuated influenza vaccine (cell-LAIV): Vaccine containing live virus, grown in mammalian cells. The virus is weakened so as not to cause the flu, but produce an immune response. One known product in Phase 2/3 and 3 in early stages of development.
  - 1.1.2.2 Recombinant HA and viral-like particle (VLP) influenza vaccine: vaccine containing viral proteins, mainly HA antigen, synthesized under the direction of molecularly cloned viral genes and expressed in different types of cell-based systems. While recombinant protein vaccines consist only of the purified antigen, VLP vaccines include the antigen in a particle that resembles an actual influenza virus. 13 companies have products in development, including 2 in Phase 2/3. One of those products is expected by the manufacturer to be licensed over the next year and the other one by 2015. There are several types of products under development in this category of vaccines:
    - 1.1.2.2.1 Mammalian cell: The recombinant protein is expressed in purified mammalian cells. Two products are in early development phases.
    - 1.1.2.2.2 Insect cells: Recombinant proteins expressed or VLPs generated in purified insect cells. Four products in development, with two in early development phases, 1 in Phase 2 and the other one in Phase 3 and undergoing regulatory approval.

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<sup>1</sup> MedImmune press release, June 1st 2009

<sup>2</sup> [http://www.who.int/vaccine\\_research/diseases/influenza/Roudenko.pdf](http://www.who.int/vaccine_research/diseases/influenza/Roudenko.pdf).

<sup>3</sup> The number of products under development listed here do not include efforts undertaken by academic institutions.



- 1.1.2.2.3 Plant-based: Recombinant proteins expressed or VLPs generated in plants<sup>1</sup>. Two known products are in pre-clinical or Phase 1 development stage.
- 1.1.2.2.4 Other platforms: Recombinant proteins expressed or VLPs generated in other protein expression systems, e.g., bacterial, fungal, or yeast cells. 5 products are in pre-clinical or Phase 1 stage of development using these other platforms.
- 1.1.2.3 “Universal” influenza vaccine: Recombinant vaccine providing protection against present and future strains of influenza virus by targeting the parts of the influenza virus that do not mutate<sup>2</sup> (e.g., stable elements of the HA protein). Seven known products are in early stages of development.
- 1.1.2.4 Viral-vectored influenza vaccine: Vaccine developed by genetically engineering different non-pathogenic viruses, e.g., adenovirus, poxviruses to contain antigens from influenza viruses and present them to the immune system to induce an immune response. Seven known products in early development stages.
- 1.1.2.5 DNA influenza vaccine: DNA 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 vaccine components which provide potential cross strain protection.<sup>3,4</sup> Three known products in pre-clinical or Phase 1 development stages.

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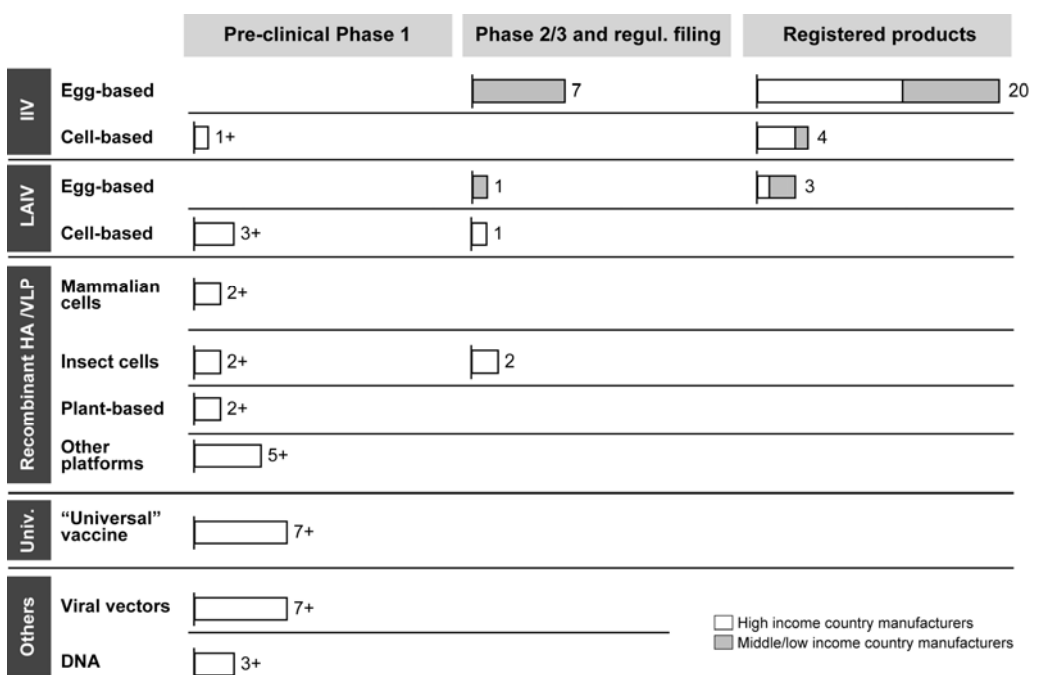
<sup>1</sup> PCAST report August 2010 “Report to the President on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza”.

<sup>2</sup> PCAST report August 2010 “Report to the President on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza”.

<sup>3</sup> Website of biotechnology company Viral Vical website(<http://www.vical.com>).

<sup>4</sup> Viral web site.

**Figure 1. Number of manufacturers present in each technology and stage of development**



WHO 10.38

## 1.2 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.

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

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

As described in detail in the 2007 WHO document on intellectual property<sup>1</sup> 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:

### **1. 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.

### **2. 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.

### **3. 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<sup>2</sup>. 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.

### **4. 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<sup>TM</sup>, 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.

### **5. 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

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<sup>1</sup>[http://www.who.int/vaccine\\_research/diseases/influenza/Mapping\\_Intellectual\\_Property\\_Pandemic\\_Influenza\\_Vaccines.pdf](http://www.who.int/vaccine_research/diseases/influenza/Mapping_Intellectual_Property_Pandemic_Influenza_Vaccines.pdf)

<sup>2</sup> [http://www.who.int/vaccine\\_research/diseases/influenza/Flu\\_vacc\\_manuf\\_tech\\_report.pdf](http://www.who.int/vaccine_research/diseases/influenza/Flu_vacc_manuf_tech_report.pdf)

does not require needles and syringes, facilitating immunization. originally developed over 30 years ago, these vaccines are gaining increasing acceptance in the USA, 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 to already 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 with the above methodologies:**

- 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)<sup>1</sup>. 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<sup>2</sup>.

### **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

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<sup>1</sup> 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.

<sup>2</sup> [http://www.who.int/csr/disease/influenza/avian\\_flu\\_landscape.pdf](http://www.who.int/csr/disease/influenza/avian_flu_landscape.pdf).

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<sup>1</sup> 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.

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

#### 1.3.1 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 (Figure 2).

1.3.1.1 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 (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 Section 1.3.2 below).

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

1.3.1.3 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 (Exhibit 2). 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.

1.3.1.4 Recombinant technology could reduce time-to-first dose to 7 weeks. The trivalent seasonal vaccine closest to licensure utilizes 135 micrograms of

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<sup>1</sup> [http://www.who.int/immunization/sage/Influenza\\_Vaccine\\_Access\\_Strategies\\_OCT2007.pdf](http://www.who.int/immunization/sage/Influenza_Vaccine_Access_Strategies_OCT2007.pdf).

antigen in total for the three strains, or 45 micrograms per strain<sup>1</sup>. 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.

**Figure 2. Overview of variables impacting conversion factors for each technology**

	<b>Time to 1<sup>st</sup> dose</b>	<b>Seasonal dosage per strain<sup>1</sup></b>	<b>Pandemic dosage</b>	<b>Production yield</b>
<b>Egg-IIV</b>	12–14 weeks	15 mcg	3.8–90 mcg	30%–100%
<b>Cell-IIV</b>	12–14 weeks	15 mcg	3.8–90 mcg	30%–100%
<b>Egg-LAIV</b>	10 weeks	~10 <sup>6.5–7.5</sup> PFU <sup>2</sup>	~10 <sup>7.5–8</sup> PFU <sup>2</sup>	~100%
<b>Insect cell-based recombinant</b>	7 weeks	45 mcg	45–90 mcg	~100%

<sup>1</sup> As most seasonal vaccines are trivalent, the total seasonal dosage is 3 times the dosage per strain.

<sup>2</sup> Plaque Forming Units, a measure of the number of viruses.

WHO 10.39

### 1.3.2 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; see Section 2), 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.<sup>2,3</sup> The dosage level varied with the adjuvant used: the majority of

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<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> J. Bernat-IFPMA "H1N1 Vaccine Production: The Industry Perspective", Geneva Health Forum 19 April 2010.

unadjuvanted vaccines required 15 micrograms of antigen and vaccines using potent adjuvant technologies (oil in water emulsions) required 3.8 to 7.5 micrograms<sup>1</sup>.

- The H5N1 case on the other hand, showed better production yields, reaching 100% for some of the vaccine viruses. However, much larger amounts of antigen were required 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<sup>2</sup>. Nearly all H5N1 vaccines required use of 2 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%)<sup>3</sup>. 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 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<sup>4</sup>. 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%).

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<sup>1</sup> Uppsala Monitoring Center (www.who-umc.org) "A/H1N1 pandemic influenza vaccines", February 24th 2010. Girard et al. (2010) "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 28:6811-6820.

<sup>2</sup> The Strategic Advisory Group of Experts. Working Group on H5N1 Influenza Vaccines. Report to SAGE, April 2009.

<sup>3</sup> 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.

<sup>4</sup> Oliver Wyman-IFPMA-WHO "Influenza vaccine supply and demand – Summary of findings", March 2009.

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; this time is anticipated to decrease to 12 weeks by 2015 due to expected improvements in vaccine testing methods.

## **2. Current and forecasted pandemic capacity**

### **2.1 Estimates for 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<sup>1</sup>:

- (a) *Low* case conversion scenario: 850 million doses,
- (b) *Base case* conversion scenario: 2,260 million doses, and
- (c) *High* case conversion scenario: 8,980 million doses.

These estimates of pandemic vaccine production capacity account for the potential output of all manufacturers 38 weeks (one production year) after the candidate vaccine virus becomes available to industry<sup>2</sup>. See figure 3 for the full impact of different assumptions on pandemic vaccine dosage and production yields. The difference among scenarios is substantial. Since production yields will remain unknown, technologies (e.g. potent adjuvants that can reduce pandemic dosage) may have the largest impact on capacity.

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<sup>1</sup> The seasonal to pandemic capacity conversion factors for the *low*, *base case*, and *high* scenarios are 1.1, 2.9, and 11.1 respectively (see Appendix); the timeline of production is 38 weeks for the first pandemic year.

<sup>2</sup> 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 3: Pandemic vaccine manufacturing capacity scenarios<sup>1</sup>**

**2009 Pandemic capacity**

Million doses  
12 mo. after candidate vaccine virus release  
(i.e., 38 weeks of actual production)

Yield of production <sup>1</sup>	100%	2.500	3.680	8.980 High
	60%	1.560	2.260 Base case	5.440
	30%	850 Low	1.200	2.790
		15µg	10µg	4µg
		Pandemic antigen <sup>2</sup>		

<sup>2</sup> Yield variable for IIV; constant for other technologies.

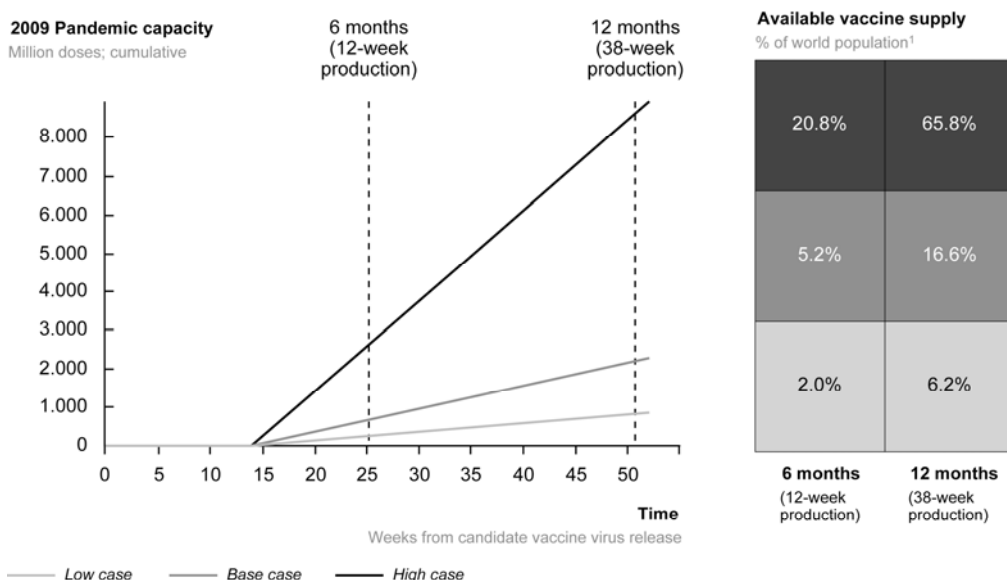
<sup>3</sup> HA content in micrograms for IIV; constant for other technologies.

WHO 10.40

Regardless of the conversion scenario, current pandemic capacity would be insufficient to achieve broad population coverage. Depending on the conversion scenario, twelve months after availability of the candidate vaccine virus to manufacturers, there would be sufficient pandemic vaccine to immunize between 6.2% and 65.8% of the world's population with 2 doses (Exhibit 4). Six months after the release of the candidate vaccine virus, only 2% to 20.8% of the world population could be immunized with the number of doses produced.

<sup>1</sup> Although pandemic antigen indicated is based on IIV technologies, the actual conversion factors used take into account the differences among technologies and the proportion of each technology in global seasonal production capacity.

#### **Exhibit 4: Pandemic vaccine production capacity in 2009 and available supply to cover the world's population**



<sup>1</sup> Percent of the population that could be immunized with two doses of vaccine, as per GAP target, given estimated vaccine supply; world population of 6.8 billion in 2009

WHO 10.41

### **2.2 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<sup>1</sup> (Figure 5) with 82% IIV, and 18% other technologies (LAIV and recombinant). This growth in capacity is due to the upgrade of existing manufacturing facilities or the building of new plants. Completion of these plans would result in 560 to 900 million doses. of excess seasonal capacity as compared to seasonal demand.<sup>2,3</sup> Manufacturers indicated that such an excess may result in expansion plans not materializing or existing capacity being shut down.

<sup>1</sup> Interviews with developed and developing country manufacturers.

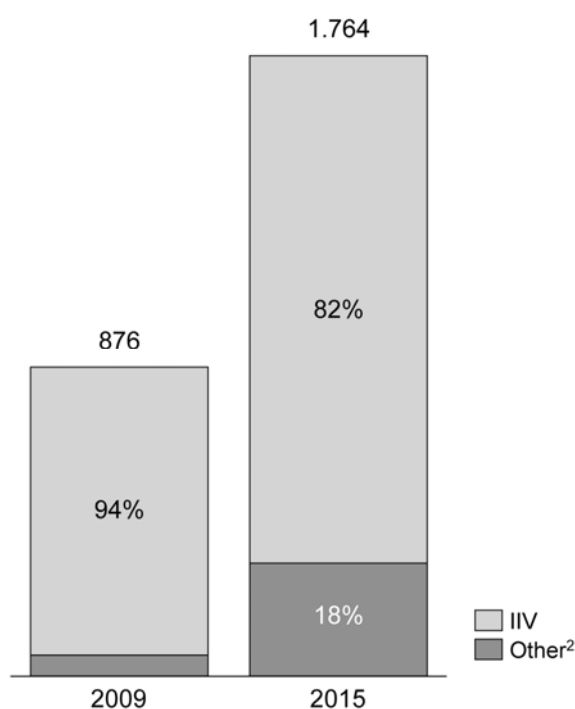
<sup>2</sup> Accounting for the fact that most seasonal demand originates in the Northern hemisphere and that a maximum of 35 weeks of production are used to manufacture the vaccine for that hemisphere.

<sup>3</sup> Oliver Wyman-IFPMA-WHO "Influenza vaccine supply and demand – Summary of findings", March 2009.

**Figure 5: Forecast of global seasonal vaccine manufacturing capacity**

**Seasonal capacity**

Million doses per year  
(i.e., 44 weeks of actual production<sup>1</sup>)



<sup>1</sup> Approximately 8 weeks per year are needed for maintenance.

<sup>2</sup> Includes LAIV and recombinant.

WHO 10.42

Accounting for the increase in seasonal vaccine production capacity, the resulting increase in pandemic capacity would be substantial. By 2015 the pandemic capacity, a year after the release of the candidate vaccine virus for manufacturing, could reach:

- (a) *Low* case conversion scenario: 2,620 million doses
- (b) Base case conversion scenario: 5,240 million doses; and
- (c) *High* case conversion scenario: 17,680 million doses (see Figure 6).

**Figure 6: Forecast of pandemic production capacity**

**2015 Pandemic capacity**

Million doses<sup>1</sup>

12 mo. after candidate vaccine virus release

(i.e., 40 weeks of actual production)

Yield of production <sup>2</sup>	100%	5.680	7.860	17.680 High
	60%	3.930	5.240 Base case	11.130
	30%	2.620 Low	3.380	6.220
		15µg	10µg	4µg
Pandemic antigen <sup>3</sup>				

1 Includes expected surge recombinant capacity not producing seasonal vaccine.

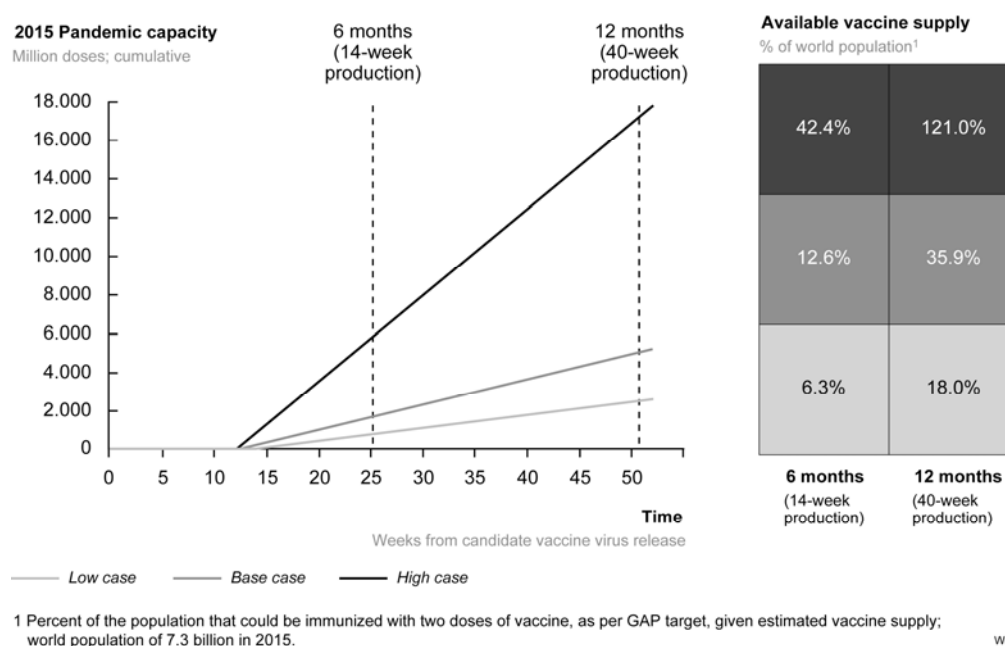
2 Yield variable for IIV; constant for other technologies.

3 HA content in micrograms for IIV; constant for other technologies.

WHO 10.43

Despite the potential increase in capacity by 2015, the production capacity would still fall short of producing enough doses to immunize the global population within 6 months of the release of the candidate vaccine virus. Indeed, available supply would be enough to cover 6.3% to 42.4% the estimated world's population. (see Figure 7).

**Figure 7: Potential pandemic vaccine production capacity in 2015 and available supply to cover the world's population**



## C. Illustrative Targets

### Target 1

Cover 70% of the global population<sup>1</sup> with 2 doses of pandemic vaccine within 6 months of the release of the candidate vaccine virus to manufacturers; this represents a total of approximately 10 billion doses available within 6 months.

### Target 2

Cover 100% of the population with two doses of pandemic vaccine within 6 months of the release of candidate vaccine virus; this represents a total of approximately 14 billion doses available within 6 months. This corresponds to the target in the Global Pandemic Influenza Action Plan to Increase Vaccine Supply (GAP).<sup>2</sup>

### Rationale for target coverage range of 70%–100%

Evidence from H5N1 and H1N1 suggests that the long-term target range for consideration is 70% to 100% of the global population with two doses of vaccine:

- Most national pandemic preparedness plans reviewed set vaccination targets at 100% of the population

<sup>1</sup> UN population statistics, 2006 revision.

<sup>2</sup> “Global pandemic influenza action plan to increase vaccine supply”, WHO/IVB/06.13.

- Modeling literature suggests that coverage of 70% to 80% of the population could reduce pandemic spread<sup>1,2,3</sup>
- Expert advisory groups from two countries that aim to vaccinate 100% of their population recognized that, in the event of a pandemic, vaccine demand may be significantly below 100%: the Canadian Pandemic Influenza Committee considered prudent to plan for 75% coverage<sup>4</sup> and the US President's Council of Advisors in Science and Technology assumed 80% in a recent report<sup>5</sup>
- Evidence on herd immunity, or the protection against a disease in one group by vaccinating another group, against influenza<sup>6</sup> suggesting coverage as low as 60% may reduce infection<sup>7</sup>

### **Rationale for 6 months time frame target**

The GAP 6-month timeframe remains the most realistic planning assumption: the primary technology (IIV) requires 3 months to first dose, so a shorter time frame is not likely by 2015.

A longer target for the time between the release of the candidate vaccine virus to manufacturers and availability of first dose (over 6 months) might result in vaccine becoming available too late to intervene before the second pandemic peak. Indeed, in the case of the 2009 pandemic, the second, most severe pandemic wave started in September 2009, approximately 3 months after the release of the candidate vaccine virus to industry<sup>8</sup>.

### **D. Illustrative Strategic Options**

Even at the lowest proposed population coverage target (70% total population), a sizeable gap remains relative to planned capacity by 2015 (Figure 8).

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<sup>1</sup> Goldstein et al. (2009) "Reproductive numbers, epidemic spread and control in a community of households", *Mathematical Biosciences* 221:11-25.

<sup>2</sup> Yang et al. (2009) "The Transmissibility and Control of Pandemic Influenza A (H1N1) Virus", *Science* 326(5953):729-733.

<sup>3</sup> Germann et al. (2006) "Mitigation strategies for pandemic influenza in the United States", *PNAS* 103(15):5935-5940.

<sup>4</sup> "Canadian Pandemic Influenza Plan", February 2004.

<sup>5</sup> PCAST "Report to the president on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza", August 2010.

<sup>6</sup> Glezen (2006) "Herd protection against influenza", *Journal of Clinical Virology* 37:237-243.

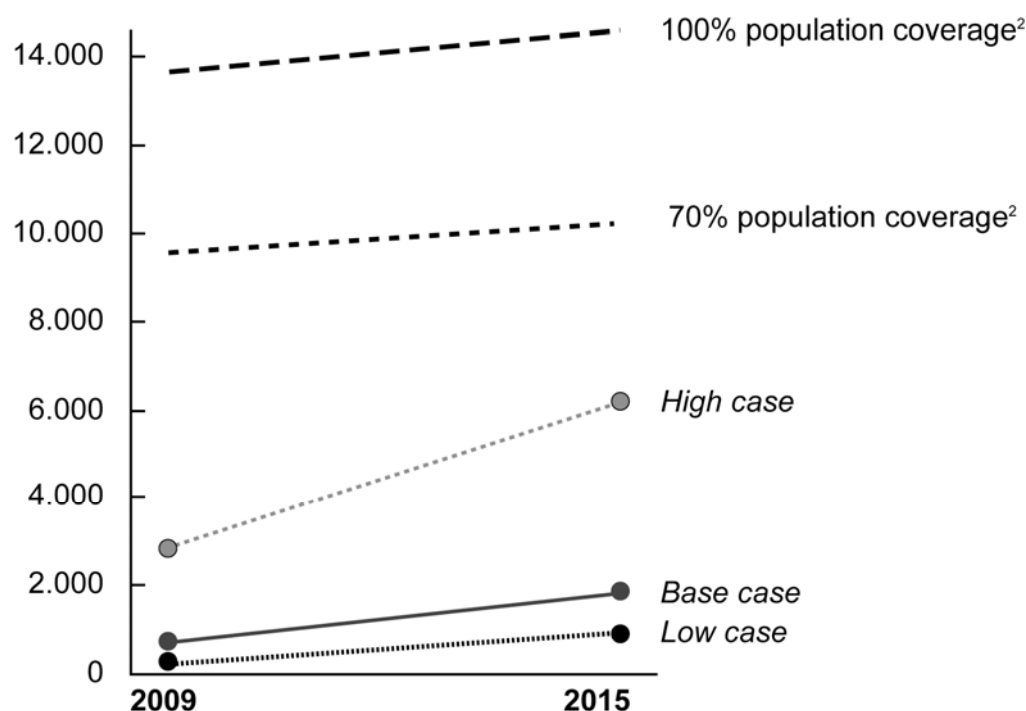
<sup>7</sup> Asllani & Ettkin (2010) "A generic simulation model to manage a vaccination program", *Journal of Medical Systems, Online First*<sup>TM</sup>, 28 January 2010, DOI: 10.1007/s10916-009-9423-1.

<sup>8</sup> PCAST report August 2010 "Report to the President on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza".

**Figure 8: Gap between the different scenarios of pandemic vaccine manufacturing capacity and the 70–100% coverage target with 2 doses**

**Pandemic capacity**

Million doses; in target timeframe  
(i.e., 12–14 weeks of actual production<sup>1</sup>)



<sup>1</sup> 12 weeks of production in 2009, 14 weeks in 2015.

<sup>2</sup> Coverage with 2 doses of vaccine.

WHO 10.45

To fill the gap between pandemic influenza vaccine manufacturing capacity and population coverage targets, a range of complementary strategic options may be considered:

**Strategic option 1: Increase seasonal demand<sup>1</sup>**

- **Description:** Provide support to increase seasonal demand in order to improve the business case for maintaining and building capacity, a solution proposed in the GAP. Without seasonal demand, facilities to produce pandemic vaccine remain idle during the inter-pandemic period. Average seasonal vaccination rates throughout the world are low today: 20% in high-income, 5% in middle-income, and less than 1% in low-income countries.

<sup>1</sup> “Global pandemic influenza action plan to increase vaccine supply,” WHO/IVB 06.13, 4.1.

- **Activities:**

1. Conduct burden of seasonal flu disease studies for low- and middle-income countries
2. Encourage seasonal influenza to be prioritised by key organizations (e.g., GAVI)
3. Mobilize the public to follow seasonal recommendations, including marketing and promotion campaigns
4. Implement national seasonal vaccination campaigns, including funding of vaccine

- **Potential Impact:** ~0–630 million pandemic doses of new capacity within 6 months (enabling 0–4% of population coverage<sup>1</sup>)

- This option, on its own, is not feasible to sustain capacity needed to fill the gap. Generating enough seasonal demand to not even completely fill the gap would require vaccinating the whole world every influenza season.
- A more realistic seasonal coverage expansion goal might be to increase seasonal vaccination levels from the average level within each income bracket to the highest level achieved for any country within each income bracket. Reaching the following levels would result in 655 million additional doses of seasonal demand:

- 48% for high-income countries
  - 24% for upper middle-income countries
  - 9% for lower middle-income countries
  - 4% for low-income countries<sup>2</sup>

- This increase in demand would help to reduce the level of excess capacity expected by 2015 (estimated at 560–900 million doses without additional demand generation efforts). 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 satisfy 655 million doses of new seasonal demand, the resulting pandemic capacity would be 630 million doses of pandemic vaccine within 6 months of the candidate vaccine virus release in the *base case* scenario. 450 million of those doses would be supported by increase of seasonal demand in low and middle income countries.

- **Feasibility:** This option has a low to moderate level of feasibility as it would require a significant increase in coverage levels to reach higher coverage targets, e.g.

- Recommending universal coverage in high-income countries
  - Driving demand in low and middle income countries, where disease priority is low

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<sup>1</sup> Coverage of population in 2015 with 2 doses of vaccine.

<sup>2</sup> As data on low income country seasonal coverage is sparse, and current estimations put the average below 1%, for the purpose of this study, a middle point between current average and lower-middle income countries was assumed.



- **Costs:**<sup>1</sup>

- **One time:** ~280 USD million including costs to conduct burden of disease studies as well as to launch marketing and promotion of seasonal vaccination in low and middle income countries. These costs, in a per pandemic dose basis<sup>2</sup>, are equivalent to 0.6 USD per dose.
- **Operating Expenses:** ~3.7 USD billion, to implement national seasonal campaigns in low and middle income countries, including seasonal vaccine cost and the cost of administering the vaccine needed. These costs, in a per pandemic dose basis,<sup>2</sup> are equivalent to US\$8.3 per dose.

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

- **Description:** Establish sustainable local/regional manufacturing capacity in countries currently without production capacity. This option would be a natural extension of the WHO initiative to facilitate acquisition by developing country vaccine manufacturers of influenza vaccine production technology.<sup>3,4</sup> Candidate new producers could also be supported for the construction of facilities with capacity that exceeds potential demand and subsidized. This new capacity could preferably be considered with egg-IIV, egg-LAIV, and recombinant technologies due to their cost effectiveness, and plan for the possibility to use IIV-LAIV conversion (Strategic Option 4) or adjuvants (Strategic Option 5) in the event of a pandemic.
- **Activities:**

1. Sustain support to complete current projects of the GAP grant program
2. Extend GAP grant program by soliciting expressions of interest from countries based on ability to sustain local capacity
3. Establish partnership with local manufacturer, select appropriate technology and transfer technology needed to manufacture the vaccine
4. Build production facilities
5. License and/or WHO pre-qualify product

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<sup>1</sup> All costs included in this on the options below do not include the cost of purchase and deployment of vaccine in the event of a pandemic.

<sup>2</sup> 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.

<sup>3</sup> “Global pandemic influenza action plan to increase vaccine supply,” WHO/IVB 06.13, 4.2.1.

<sup>4</sup> “Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits” A62/5 Add.1 6.13.1.

- **Impact:** Assuming production can be established in 2–7 additional countries (beyond the current GAP grantees), additional capacity would be ~40–160 million seasonal doses or ~40–150 million pandemic doses within 6 months (enabling <1–1% of population coverage<sup>1</sup>)
  - A population size of 40 million people was identified as the minimum size needed to sustain local production. A population of 40 million people would have the potential for 10 million doses of seasonal demand assuming ~25% vaccination rates (the highest level achieved for any middle income country<sup>2</sup>). This would enable minimal efficient scale for an influenza vaccine manufacturing facility at approximately 10M doses.
  - 12 low- and middle-income countries without existing GAP grants have population sizes above 40 million. Seven of those countries have existing seasonal demand over 200 thousand doses suggesting the potential for a seasonal market. Among those seven countries, two have established vaccine manufacturing capabilities (evidenced by the existence of a DCVMN<sup>3</sup> member in the country).
  - This suggests the potential for 2–7 additional facilities, ranging from 10–30 million doses of capacity each (depending on the population size). Building facilities in countries with DCVMN member would result in two facilities with a total of 40 million doses of seasonal capacity, while building in all seven countries would result in a combined 160 million seasonal doses of capacity
- **Feasibility:** Current GAP grantees are on target to reach their capacity goals suggesting this option is viable. However, pursuing this option in addition to existing grants has medium feasibility due to the current low seasonal demand levels in these new countries and the relatively limited experience with vaccine manufacturing. Pursuit of Strategic Option 1 may improve the feasibility of this option by increasing seasonal demand and improving the business case for ongoing use of these facilities.
- **Costs:**
  - **One time:** ~125–490 USD million to complete ongoing GAP grant program projects and extend program to establish two to seven facilities, assuming egg-IIV technology costs. These costs include the construction costs of the 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. These costs, in a per pandemic dose basis, are equivalent to 3.2 USD per dose.
  - **Operating Expenses:** No annual costs assuming that manufacturers sustainably operate these facilities in the inter-pandemic period

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<sup>1</sup> Coverage of population in 2015 with 2 doses of vaccine.

<sup>2</sup> IFPMA Influenza Vaccine Supply International Task Force, "Provision of seasonal influenza vaccines in 157 countries (2004-2009)".

<sup>3</sup> Developing Country Vaccine Manufacturer Network (<http://www.dcvmn.com/>).

### **Strategic option 3: Subsidize idle capacity above seasonal demand levels**

- **Description:** Establish mechanisms to support maintaining capacity above seasonal demand levels with readiness to produce influenza vaccine in the event of a pandemic. Subsidization could be pursued for two sources of capacity:
  - Existing or planned capacity to prevent its down-sizing 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 moderate to high:
  - Avoiding downsizing of existing capacity would keep online 560–900 million doses of seasonal capacity that might otherwise be eliminated. However, it is unclear whether subsidies are needed to maintain this capacity as existing pre-purchase agreements for 1.2–1.4 billion pandemic doses may already be enough to ensure this capacity remains.
- **Feasibility:** The main challenges with this option are financial. It would require ongoing support, including operationally maintaining these facilities to be able to produce at the point of a pandemic.
- **Costs:**
  - **Operating expenses:**
    - ~280–450 USD million to subsidize potential excess capacity of 560–900 million doses. These costs, in a per pandemic dose basis<sup>1</sup>, are equivalent to 0.4 USD per dose. As mentioned above, existing prepurchase agreements may already be covering these costs.

### **Strategic option 4: Stimulate IIV to LAIV convertible capacity**

- **Description:** Support IIV producers to establish the capabilities to be able to convert their production to LAIV technology in the event of a pandemic, increasing the effective capacity by 10–20 times. IIV facilities built in the context of Strategic Option 2 could be considered as prime candidates for this conversion.
- **Activities:**
  1. Conduct initial pilots with manufacturers using both technologies to assess feasibility of IIV to LAIV conversion
  2. Establish commercial scale capability to switch between technologies

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<sup>1</sup> 560 to 900 million doses of seasonal capacity are approximately equivalent to 0.7 to 1.1 billion pandemic doses within 6 months.

3. License pandemic LAIV vaccine

4. Produce ongoing commercial batches each year (at least 1 per year) to maintain capability

- **Impact:** Converting all IIV manufacturers in low and middle income countries would increase pandemic capacity by 1.9 billion doses within 6 months of the release of the candidate vaccine virus (enabling 13% of population coverage<sup>1</sup>). For the purpose of this estimation,  $10^{7.5}$  PFU per dose and  $10^8$  PFU per ml. of yield were assumed. The impact of this option could be higher if lower dosages or higher yields were obtained.
  - Converting the two manufacturers with current capabilities in both technologies (~40 million seasonal doses of capacity) could produce ~0.4 billion pandemic doses within six months
  - Assuming high-income producers 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 6 months
- **Feasibility:** This option has medium feasibility – despite its clear theoretical advantages, it is still unproven at commercial scale. One manufacturer, however, is preparing its facility for this option to be possible. Conversion requires manufacturers to establish capacities in both technologies, as well as licensing products under both production processes and the costs associated with the pre-clinical and clinical programs, and regulatory filings. And, establishing LAIV capacity may require additional equipment, e.g. ultrafiltration and diafiltration or freeze drying and space may not exist in all facilities for this expansion.
- **Costs:**
  - **One time:** ~130–230 USD million to pilot the conversion in the two manufacturers with both technologies, add the necessary equipment to the other 12 manufacturers and support the pre-clinical, clinical and regulatory approval costs. These costs, in a per pandemic dose basis, are equivalent to approximately 0.1 USD per dose<sup>2</sup>.
  - **Operating expenses:** ~0.6–0.8 USD million to purchase small-scale commercial test batches from all the convertible facilities, and personnel costs to inspect those test production runs. The costs in a per dose basis are negligible.

**Strategic option 5: Expand the use of potent adjuvant technology**

- **Description:** Expand the use of adjuvanted vaccines in the event of a pandemic and support the necessary mechanisms to allow producers to access potent adjuvant (oil in water) technology<sup>3</sup>. The use of adjuvanted seasonal vaccines would be discouraged in this option as the replacement of current seasonal IIV formulation (45 micrograms of active ingredients)

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<sup>1</sup> Coverage of population in 2015 with 2 doses of vaccine.

<sup>2</sup> 7 to 10 cents per dose based on 1.9 billion pandemic doses.

<sup>3</sup> “Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits” A62/5 Add.1 6.13.2.

with lower antigen content adjuvanted IIV (11 to 23 micrograms of active ingredients) would result in significant decrease of surge capacity during a pandemic.

- **Activities:**

1. Encourage high- and middle-income countries to adopt adjuvanted vaccines in the event of a pandemic, enabling full use of existing capacity among manufacturers with current adjuvanted products

- 1(a). Facilitate acceptance of adjuvanted products by National Regulatory Authorities

- 1(b). Facilitate acceptance of adjuvanted products by the general public

2. Transfer technology to manufacturers without potent adjuvant technology<sup>1</sup>

3. Extend grants to license adjuvanted pandemic vaccine

4. Produce ongoing commercial batches of adjuvant each year (at least 1 per year) to maintain capability

- **Impact:** Enabling all IIV manufacturers to produce pandemic vaccine with six months of the release of the candidate vaccine virus (enabling 30% of population coverage<sup>2</sup>)

- Full use of potent adjuvant technology by manufacturers with current adjuvanted product (assumes demand exists) could produce an additional ~2.2 billion pandemic doses on top of the base case within 6 months by 2015

- Use of potent adjuvant technology by manufacturers without current adjuvanted products could add another ~2.1 billion pandemic doses within 6 months

- **Feasibility:** This option has a medium to high feasibility considering some high-income countries have been reluctant to use adjuvanted vaccine if there is no immunogenicity need. However, the technology can be transferred to most IIV split manufacturers. The use of potent adjuvant technology with IIV whole virion vaccines still needs clinical testing.

- **Costs:**

- **One time:** ~230–420 USD million including technology transfer costs for all manufacturers acquiring the technology (equipment placed in an existing building, set up and trainings), pre-clinical and clinical program to build regulatory dossier, and licensing process. These costs, on a per pandemic dose basis<sup>3</sup>, are equivalent to 0.1–0.2 USD per dose.

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<sup>1</sup> “Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits” A62/5 Add.1 6.13.2.

<sup>2</sup> Coverage of population in 2015 with 2 doses of vaccine.

<sup>3</sup> Based on the 2.1 billion pandemic doses that could be added by manufacturers currently without the technology.

- **Operating expenses:** ~0.6–1 USD million per year in total to produce 1 commercial batch of adjuvant in all the manufacturers acquiring the technology. The costs on a per dose bases are negligible.

#### **Strategic option 6: Convert other biologic capacity to pandemic vaccine production at onset of pandemic**

- **Description:** Support other biologic manufacturers to prepare for a conversion of their facilities to pandemic influenza vaccine production in case of a pandemic. This capacity could be converted from other vaccines, other proprietary biologics, and biologics contract manufacturers. The production of influenza vaccine in cell-based and recombinant systems expands the potential for sharing capacity with other biological manufacturers. Modifications would need to be made to existing facilities and influenza vaccine technology would need to be transferred and the vaccines licensed from those facilities in advance of the pandemic.
- **Activities:**
  1. Identify manufacturers with compatible technology to pilot the conversion process
  2. Transfer technology and establish commercial scale capability to switch from one technology to the other
  3. License pandemic vaccine in convertible facilities
  4. Produce ongoing commercials batches each year (at least 1 per year)
- **Impact:** A significant amount of cell-based capacity exists globally today to produce other biologic products, estimated at 3 million litres. Assuming the use of recombinant technology, 5% of that capacity would need to be converted in order to produce one billion doses of pandemic vaccine within six months.
- **Feasibility:** This option has low feasibility due to the potential technical and intellectual property challenges.
  - Current recombinant influenza vaccines close to registration are produced in insect cells. It is estimated that only a small portion of the current cell-based capacity is insect cell-based, which could be more feasibly used. The changeover from mammalian to insect cell culture, however, in the same facility would need to be proven at commercial scale and may be less feasible.
  - Intellectual property and licensing issues may restrict the number of producers available to test and develop the conversion process.
  - The production of cell-IIV vaccine in mammalian cell culture facilities is another possibility, but the level of bio-safety containment needed for vaccine production is not in place in the majority of cell culture facilities. Additionally, cell-based IIV vaccine production requires ultracentrifugation equipment that may not be in place in most biological manufacturing facilities.

- **Estimated Costs:**

- **One time:** US\$ 38–94 million to pilot the conversion in 2 manufacturers, adding the necessary equipments and supporting the pre-clinical, clinical and regulatory approval costs. These costs, on a per pandemic dose basis, are equivalent to 0.04–0.09 USD per dose. These costs do not include licensing fees incurred to transfer the technology to the convertible facilities. Costs depend on the number of facilities assumed. If more facilities are needed to produce one billion pandemic doses, one-time costs would increase.
- **Operating expenses:** ~4–9 USD million to buy the production of a commercial vaccine batch, produced in 10,000 litre bioreactors every year from 2–3 facilities able to produce a combined 1 billion pandemic doses within 6 months. Operating expenses depend on the number of facilities assumed. If more facilities are needed to produce one billion pandemic doses, these costs would increase. These costs, in a per pandemic dose basis, are equivalent to 0.01 USD per dose or less. This is the cost to make these facilities ready for conversion and does not reflect the cost of the vaccine itself.

#### **Strategic option 7: Accelerate the development of new technologies**

- **Description:** Accelerate the development of new production technologies with faster time to 1st dose, more rapidly scalable capacity, and broader cross-protection across virus strains. Given the technology landscape, the most viable options would be recombinant platforms of production other than those already reaching the market. The long-term ideal solution would be the production of a universal flu vaccine that would provide protection against a wide range of influenza virus strains and subtypes.<sup>1,2</sup>
- **Activities:** Extend grants to support research and development of full pre-clinical and clinical programs for new influenza vaccine manufacturing technology
- **Impact:** While the potential impact of new technologies is high, this impact would be long term considering the average development time for a new biological product is over 10 years. Although there is large support by governments and private investors for accelerating new technologies, an internationally funded program might have the impact of ensuring the intellectual property associated with these developments can be accessed by developing world manufacturers.
- **Feasibility:** Feasibility for one recombinant technology (production in insect cells) is high in 5 years time. Feasibility for other technologies in early pre-clinical phase is low given the research and development uncertainty.

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<sup>1</sup> “Global pandemic influenza action plan to increase vaccine supply,” WHO/IVB 06.13, 4.3.2.

<sup>2</sup> Business Plan for the Global Pandemic Influenza Action Plan to increase vaccine supply, February 2008.

- **Costs:**

- **One-time:** The estimated costs of supporting a development plan are in the order of ~50–200 USD million. The total cost of this option would depend on the number of funded development programs. Considerably more resources would be needed to bring such product to market. In addition, the value added of this funding is unclear because governments and the private sector are already funding these types of research and development efforts.



## **VII. ACCESS, AFFORDABILITY AND EFFECTIVE DEPLOYMENT**

### **Goal**

- Develop mechanisms to ensure real-time access, based on public health need, to affordable pandemic vaccines by Member States without such access.<sup>1</sup>

### **Approach, limitations, assumptions, and data sources**

#### **1. Approach and limitations**

- Lessons learnt from the pandemic (H1N1) 2009 and ongoing outbreaks of H5N1 have informed consideration of issues related to access, affordability and effective deployment of pandemic vaccines by Member States without such access.
- Several obstacles faced by Member States to gain access to vaccine were identified and reviewed. Obstacles to availability of supply were analysed in further detail, as these are considered to be the most critical.
- Obstacles associated with WHO allocation of donated vaccine and in-country logistics (i.e., transfer of vaccines from point of entry to vaccination sites) were not analysed.
- This study does not address the establishment of an international stockpile of H5N1 vaccine or other influenza vaccines. Options to establish an international stockpile of H5N1 vaccine were developed in response to the request made to the Director-General, inter alia, in resolution WHA 60.28,<sup>2</sup> and shared with Member States in February 2009.<sup>3</sup> Further to the recommendations of the Strategic Group of Experts on immunization (SAGE) the stockpile was to contain 150 million doses, assuming a donation of the initial 150 million doses.<sup>4</sup> The establishment of the stockpile (including materials and transport, storage, management and replenishment) was estimated in nominal cost to range from US\$ 70 million to US\$ 880 million.<sup>5</sup> An update of the recommendations made by SAGE in 2007 is planned in the light of the lessons learnt from pandemic (H1N1) 2009.<sup>6</sup> If the pandemic is caused by a strain of virus close to current H5N1 viruses, an H5N1 vaccine stockpile could provide real time access to some pandemic vaccine. It would, however, have no value or impact 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

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<sup>1</sup> Document A62/5 Add.1 Pandemic influenza preparedness framework for the sharing of influenza vaccine and access to vaccines and other benefits, section 6.6.

<sup>2</sup> Resolution WHA60.28, subparagraph 2(2).

<sup>3</sup> 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](http://www.who.int/csr/disease/influenza/H5N1_Stockpile_Design_Feb2009.pdf) (accessed 26 November 2010).

<sup>4</sup> See <http://www.who.int/wer/2008/wer8301.pdf>.

<sup>5</sup> 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](http://www.who.int/csr/disease/influenza/H5N1_Stockpile_Design_Feb2009.pdf), page 25/47 (accessed 26 November 2010).

<sup>6</sup> See <http://www.who.int/wer/2008/wer8301.pdf>.

Preparedness: sharing of influenza viruses and access to vaccines and other benefits”,<sup>1</sup> as well as in “Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology”<sup>2</sup>

## **2. Assumptions**

- Countries with the following characteristics were assumed to have access to supply: countries with domestic production capacity, countries with pre-purchase agreements in place (e.g. contracts between countries and manufacturers ensuring the supply of a specific volume of vaccine to the country 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
- Pre-purchase agreements would be satisfied before releasing supply to other countries
- All calculations are based on the use of two doses of vaccine per person
- The cost estimates for strategic options are based on the 2015 targets.

## **3. Data sources**

- One hundred and nineteen national pandemic preparedness plans and 82 national H1N1 deployment plans were reviewed to identify trends in populations targeted for vaccine coverage
- Recommendations of the Strategic Advisory Group of Experts on immunization (SAGE)
- Interviews with high-income and developing country vaccine manufacturers and countries with pre-purchase agreements
- Extensive press search to identify the size of vaccine pre-purchase agreements, doses received under these agreements, and timing of receipt
- Population data sources which define the size of target population groups (e.g. number of health-care workers by country)<sup>3</sup>

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<sup>1</sup> See document A/PIP/IGM/13, Annex 4 pages 37-38 and 44-47.

<sup>2</sup> *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](http://www.who.int/csr/disease/influenza/H5N1_Stockpile_Design_Feb2009.pdf), page 25/47 (accessed 26 November 2010).

<sup>3</sup> Based on a population model covering 176 countries developed by Oliver Wyman with data from WHO World Health Statistics (2008), International Labour Organization Occupation (ILO) Data (Labour Statistics database LABORSTA 2008), World Bank World Development Indicators (World Development Indicators 2006 edition), United Nations Population Database (World Population Prospects: The 2006 Revision), United Nations Survey of Crime Trends (The Eighth United Nations Survey on Crime Trends and the Operations of Criminal Justice Systems, March 31st 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 where data were not available for specific segments, estimates were created by extrapolating from countries with similar income levels where population sizes were known.

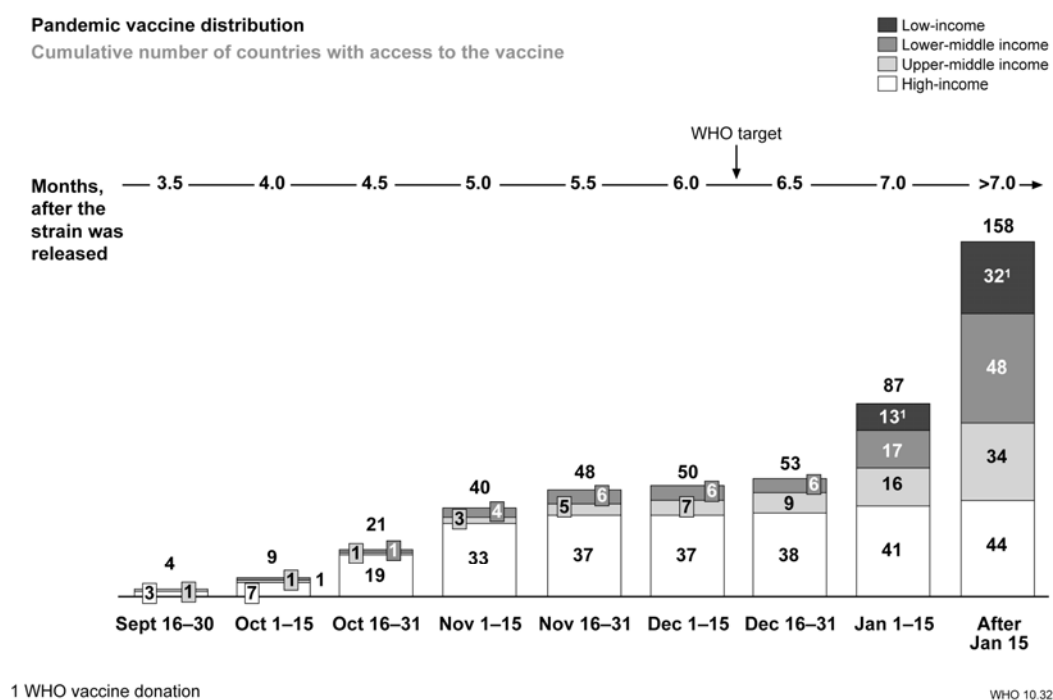
- “Options for the design and financing of an H5N1 vaccine stockpile: key findings and study methodology”

## Current state

### 1. Summary of timeline and volume of H1N1 vaccines deployed by WHO

- High-income countries received doses within 3.5 months of manufacturers’ receipt of candidate vaccine virus.<sup>1</sup> A similar timeline was achieved by middle-income countries with local production capacity.<sup>1</sup>
- Low-income countries received the first doses of H1N1 vaccine approximately seven months after influenza vaccine manufacturers had received the candidate vaccine virus (See Figure 1).<sup>2</sup> Based on available public information, most doses provided to low-income countries came from donations made through WHO.<sup>3</sup>

Figure 1. Timeline of country access to H1N1 pandemic vaccine



<sup>1</sup> World Health Organization, Pandemic (H1N1) 2009 media monitoring/communications surveillance, 11 December 2009.

<sup>2</sup> WHO H1N1 Pandemic vaccine deployment update – 24 August 2010.

<sup>3</sup> Urgent support for developing countries’ response to the H1N1 influenza pandemic, 30 June 2010, WHO, United Nations Office for the Coordination of Humanitarian Affairs, and United Nations System Influenza Coordination; Press search.

## **1. Obstacles to access**

### **2.1 Lack of available supply**

If a pandemic were to occur at the time of writing, pre-purchase agreements would fully commit the majority of vaccine supply available in the first six months after release of the candidate vaccine virus<sup>1</sup>. 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 (see Figure 2). Mainly contracted after the H5N1 outbreaks, the 19 pre-purchase agreements identified allowed countries to provide 50% to 100% of their populations with two doses of vaccine<sup>2</sup>. This represents commitments for 1200 million – 1400 million doses of pandemic vaccines. Assuming that these agreements were served first, they would fully engage all production capacity in the first seven to eight months after the candidate vaccine virus was made available to the manufacturers (in a base case capacity scenario). Countries without access would therefore not receive any vaccine within the six-month target time frame<sup>3</sup>.

An additional eight countries do not have pre-purchase agreements, but do have local vaccine production capacity (including four middle-income countries). Local demand in pandemic times would most likely absorb much of this local production capacity. This situation – pre-purchase agreements and local vaccine production capacity – would enable 27 countries to have direct access to vaccine.

One hundred and forty-two of the 146 low- and middle-income countries analysed did not have pre-purchase agreements or local manufacturing facilities and were categorized as having limited or no access to pandemic vaccine (Figure 2). This represents approximately 4200 million people<sup>4</sup>. By 2015, eight new middle-income country manufacturers are expected to begin producing vaccine, mostly as a result of the Global Action Plan programme. The effect will be to reduce the population without access to approximately 2400 million people.<sup>5</sup>

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<sup>1</sup> Based on 1.2 to 1.4 billion doses of pre-purchase agreement volumes (see footnote 8), and a total base case pandemic capacity of approximately 260 million doses per month (note that time to first dose is 14 weeks).

<sup>2</sup> Two of the 19 pre-purchase agreements provide two doses to 30% to 40% of the countries' population.

<sup>3</sup> *Global pandemic influenza action plan to increase vaccine supply*, see document WHO/IVB/06.13.

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

<sup>5</sup> Impact of 11 grants given to developing countries manufacturers as part of the Global Action Plan which will allow to increase capacity by over 200 million trivalent doses per year by 2015. Source: World Health Organization, *Development of sustainable influenza vaccine production capacity in developing countries*.

**Figure 2. Countries with limited or no access to pandemic influenza vaccine**

**Number of countries, 2009**

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

■ Identified as countries without access to supply

<sup>1</sup> Including 10 countries that have local production.

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

WHO 10.33

## 2.2 Lack of national deployment plan or funds to operationalize plan

Based on the 119 national pandemic preparedness plans reviewed, 91% of Member States included the use of vaccine during a pandemic. However:

- Only 61% of plans prioritized population target groups for vaccination
- Only 40% of plans defined in-country logistic vaccine distribution guidelines
- Only 25% of plans had in-country vaccine storage guidelines<sup>1</sup>
- Only 42% of plans outlined the financial resources needed during a pandemic<sup>1</sup>
- Only 8% of Member States conducted pandemic simulation exercises to test their plans prior to pandemic (H1N1) 2009.<sup>1</sup>

<sup>1</sup> WHO report *Comparative analysis of national pandemic influenza preparedness plans*, in draft as at October 2010.

### **2.3 Limited in-country regulatory and contracting capacity**

Obstacles associated with limited capacity of National Regulatory Authorities (NRAs) include:

- Limited legal capacity rapidly to assess acceptability of the terms in the legal donation agreements, such as exceptional liability and indemnification clauses
- Limited NRA capacity including delays in authorizing use and importation of the pandemic vaccine through either provisional approvals for emergencies, or through normal regulatory processes
- Limited or absence of harmonization of regulatory approvals that would allow countries to recognize authorizations granted by other national regulatory authorities
- Limited or absence of harmonization regarding technical manufacturing data required for approvals
- Requirements to approve pandemic vaccine on a batch or lot level basis.

### **2.4 Limited logistics infrastructure**

The following logistics obstacles were experienced during the pandemic (H1N1) 2009, which caused delays in deployment. The situation would have been further exacerbated in the case of an extreme pandemic with greater demand for logistics capabilities.

- Limited cold-packing capacity at manufacturers' sites
- Lack of cold-storage infrastructures (e.g. in Europe, only one airport (Paris, Charles De Gaulle airport) had sufficient cold storage capacity to host large vaccine shipments)
- Limited space available on commercial aircraft
- Lack of airport infrastructure and sufficient land transport resources in recipient countries to unload and dispatch the required vaccine volumes.

**Affordability** (to be addressed in a full study to be made available before the Sixty-fourth World Health Assembly)

**Effective deployment** (to be addressed in the full study to be made available before the Sixty-fourth World Health Assembly)

## **Illustrative targets**

### **1. Targets have been established according to how much (quantity) and when (time frame) affordable pandemic vaccines will be available to countries without access.**

#### **1.1 Quantity targets**

##### **Target 1: Health-care workers**

Countries have access to sufficient pandemic vaccine to cover their health-care workers. This represents roughly 0.3% of country populations (Figure 3).<sup>1</sup>

- 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.<sup>2</sup>
- By 2015, the advent of new developing country manufacturers 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 the 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. This represents approximately 5.5% of country populations.<sup>1</sup>

- 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.<sup>3</sup>
- By 2015, the advent of new developing country manufacturers 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.

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<sup>1</sup> Based on a population model covering 176 countries developed by Oliver Wyman with data from WHO *World Health Statistics (2008)*, International Labour Organization Occupation (ILO) Data (Labour Statistics database LABORSTA 2008), World Bank World Development Indicators (World Development Indicators 2006 edition), United Nations Population Database (World Population Prospects: The 2006 Revision), United Nations Survey of Crime Trends (The Eighth United Nations Survey on Crime Trends and the Operations of Criminal Justice Systems, March 31st 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>, accessed 26 November 2010. For countries where data were not available for specific segments, estimates were created by extrapolating from countries with similar income levels where population sizes were known.

<sup>2</sup> Base case capacity assuming vaccination of target population within 6 months and ~12 weeks lead time until release of first dose.

<sup>3</sup> Base case capacity assuming vaccination of target population within 6 months and ~12 weeks lead time until release of first dose.

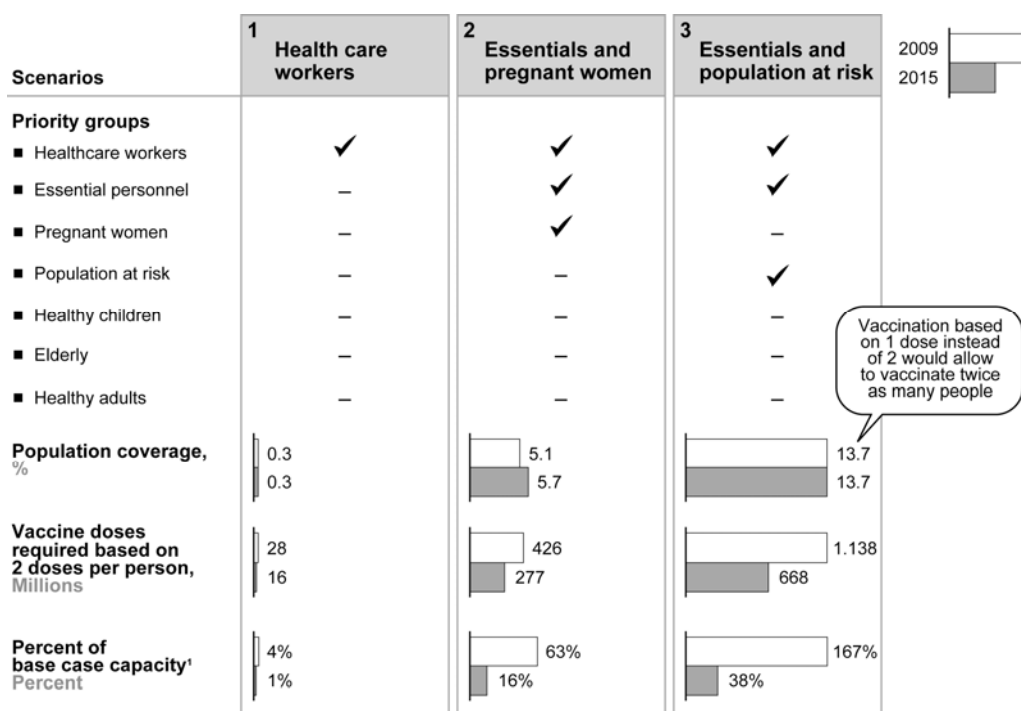
### Target 3: Essential personnel and populations at risk

Countries have access to sufficient pandemic vaccine to cover the groups prioritized in their pandemic preparedness plans: health-care workers, essential personnel, and populations at risk. This represents roughly 13.7% of country populations.<sup>1</sup>

In 2009, this represented 569 million people, or a total of 1138 million doses, for countries without access, and consumes 159% of base case production capacity.<sup>2</sup>

- By 2015, the advent of new developing country manufacturers 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.

**Figure 4. Overview of potential target for access**



<sup>1</sup> Base case assuming vaccination of target population within 6 months and ~12 weeks lead time until 1st dose.

WHO 10.34

<sup>1</sup> Based on a population model covering 176 countries developed by Oliver Wyman with data from WHO World Health Statistics (2008), International Labour Organization Occupation (ILO) Data (Labour Statistics database LABORSTA 2008), World Bank World Development Indicators (World Development Indicators 2006 edition), United Nations Population Database (World Population Prospects: The 2006 Revision), United Nations Survey of Crime Trends (The Eighth United Nations Survey on Crime Trends and the Operations of Criminal Justice Systems, March 31st 2005), and the Global Prevalence of Adult Obesity (International Association for the Study of Obesity. December 2008).

<sup>2</sup> Base case capacity assuming vaccination of target population within 6 months and ~12 weeks lead time until release of first dose.



## **Rationale for quantity targets – definition of population groups**

- SAGE recommendations: SAGE recommended that health care workers be the first priority for vaccination against the pandemic (H1N1) 2009 virus. SAGE recommended that other groups should include pregnant women; populations at risk; healthy children; elderly; and healthy adults, though their order of priority is for individual countries to decide.<sup>1</sup>
- Prioritization as defined by countries:
  - National pandemic preparedness plans (drafted principally to address H5N1 pandemic scenarios) identified health-care workers, populations at risk, and essential personnel for priority vaccination (see Appendix for additional details)
  - H1N1 national deployment plans in all countries eligible for WHO vaccine donations assigned highest priority to health-care workers, followed in most cases by pregnant women, populations at risk and healthy children (see Appendix for additional details).

## **1.2 Time-frame targets**

### **Target 1 “Real time access”**

Countries without direct access through domestic production or pre-purchase agreements have a guarantee to receive pandemic vaccine at the same time as countries with access, through a mechanism which reserves a certain percentage of real-time production output. For example, during the pandemic (H1N1) 2009, two manufacturers committed 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 of time”**

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

## **Strategic options**

Strategic options pursued to increase capacity (Section D) will also have an effect on improving access in the long term, both by increasing the absolute volume of vaccine doses available and by increasing the number of countries with local manufacturing capacity. Until capacity targets are achieved, the following strategic options would enable increased access to pandemic vaccine by countries without such access.

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<sup>1</sup> Strategic Advisory Group of Experts on Immunization (SAGE) “Report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic”, 7 July 2009.

### **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. This pooled pre-purchase agreement could be established by an international agency on behalf of countries without access. The agreement terms could be similar to those in the existing pre-purchase agreements. Key terms would include: price per dose (based on a tiered pricing scheme so that lower-income countries are paying less than higher-income countries) guarantee of payment; quantity; and timing of availability.<sup>1,2</sup>

#### **Activities to implement this option:**

- **Establish pooled pre-purchase agreement.** Agreements would need to be established between governments of recipient countries which currently lack access (or an international agency on their behalf) and vaccine manufacturers
- **Purchase and deploy** pre-contracted vaccine to countries without access to supply at the time of a pandemic.

#### **Feasibility:**

It is estimated that current pre-purchase agreements will fully engage the majority of production capacity for the first seven to eight months following availability 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 to enable a portion of future capacity to be re-allocated for countries without access. The feasibility of reaching Quantity Target levels 2 and 3 is low given the amount of existing capacity that would need to be utilized.

### **Strategic option 2: expand existing pre-purchase agreements**

Expand volumes of existing pre-purchase agreements held by countries to include provision of vaccine for countries without access. Similarly to option 1 above, these expansions to pre-purchased volume agreements could be pooled and held by an international agency on behalf of countries without access.

#### **Activities to implement this option:**

- **Establish agreements to expand existing pre-purchase agreements between countries with current agreements and vaccine manufacturers.** The revised pre-purchase agreements would need clearly to 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 the countries without access to supply.

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<sup>1</sup> See WHO immunization financing briefcase: key concepts: tiered pricing.  
[http://www.who.int/immunization\\_financing/options/en/briefcase\\_pricingtiers.pdf](http://www.who.int/immunization_financing/options/en/briefcase_pricingtiers.pdf) (Accessed 24 November 2010).

<sup>2</sup> Asian Development Bank. *Immunization financing in developing countries and international vaccine market*, 2001. Accessed on-line at [http://www.adb.org/Documents/Books/Immunization\\_Financing/default.asp](http://www.adb.org/Documents/Books/Immunization_Financing/default.asp) on 24 November 2010).

### **Feasibility:**

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

### **Estimated additional pre-purchase requirements:**

Based on the size of existing pre-purchase agreements held by high-income countries (see paragraph 2.1 above), this option would require expanding existing pre-purchase agreements by the following aggregate amounts by 2015 in order to ensure access to countries without such access:

- Quantity target 1: 1 additional pre-purchased dose for each 74 doses currently pre-purchased
- Quantity target 2: 1 additional pre-purchased dose for each 4.3 doses currently pre-purchased
- Quantity target 3: 1 additional pre-purchased dose for each 1.7 doses currently pre-purchased.

### **Impact:**

If sufficient vaccine production capacity becomes available, both strategic options 1 and 2 could enable real-time access to meet the quantity targets set out above for 2015 (of between 16 million and 668 million doses).

### **Estimated costs**

Costs are similar for strategic options 1 and 2.

- Costs will vary depending on the pre-purchase agreement terms. Existing agreements are structured in many ways. Costs below are estimated based on the following terms: (a) no up-front payment; (b) an ongoing fee to reserve capacity, and (c) a one-time payment to purchase and deploy vaccine at the time of the pandemic. For purposes of the estimated costs below, US\$ 3 has been used as the purchase price per dose of pandemic vaccine.
- **Annual costs to reserve capacity:<sup>1</sup>**
  - **Quantity target 1:** US\$ 10 million
  - **Quantity target 2:** US\$ 140 million
  - **Quantity target 3:** US\$ 335 million.

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<sup>1</sup> Estimate based on an annual reservation fee of US\$ 0.5 per dose to reserve capacity. Source: public information on the pre-purchase agreements made by the United Kingdom.

- **One-time cost to purchase and deploy vaccine:<sup>1</sup>**
  - **Quantity target 1:** US\$ 70 million
  - **Quantity target 2:** US\$ 1155 million
  - **Quantity target 3:** US\$ 2795 million.

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<sup>1</sup> The cost to purchase and deploy the vaccine at the time of the pandemic is estimated at US\$ 4.2 per dose to purchase vaccine, and US\$ 1.2 per dose for the 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), op.cit. and manufacturers' interviews; WHO H1N1 deployment data; and press searches. Further details on assumptions are outlined in the Appendix.

## **VIII. SUSTAINABLE FINANCING, SOLIDARITY MECHANISMS AND OTHER APPROACHES**

### **Goal**

- Establish sustainable financing mechanisms for pandemic influenza preparedness and response.<sup>1</sup>

### **Approach, assumptions, data sources and limitations**

#### **1. Approach**

- The cost of options set out in the technical sections above was used as the basis for potential financial needs over the next five years.
- Examples were gathered of relevant financing mechanisms employed to raise funds for health (e.g. by UNITAID, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the GAVI Alliance). Based on these models, potential funding mechanisms for pandemic influenza preparedness were identified. Where possible, illustrative quantified estimates for these were calculated. The estimates are illustrative, and would require additional analysis to assess the amounts that might be raised.

#### **2. Assumptions**

- 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 are made concerning the feasibility, setup costs, or operating costs of potential financing models for pandemic influenza preparedness. Further detailed analysis underlying various options will be required based on Member State preferences.

#### **3. Data sources and limitations**

- Data sources for all cost estimates include reports from WHO, other reports in the public domain, and expert interviews.

### **Current state**

#### **1. Financing for pandemic influenza preparedness, including response to pandemic (H1N1) 2009**

- Current financing for pandemic influenza preparedness includes funding provided to support seasonal influenza preparedness and vaccines, as well as preparedness for future pandemic events. Funding is provided at country, regional, and global levels and covers various types of costs. This includes, for example, both Member States' funding of their national laboratory and surveillance systems, procurement of vaccines, and the regular

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<sup>1</sup> See document A62/5 Add.1, Appendix, paragraph 6.14 on sustainable and innovative financing mechanisms.

financial support provided by Member States for laboratories within the WHO Network in their countries (National Influenza Centres, WHO collaborating centers for influenza, essential regulatory laboratories and H5 research laboratories) and to support research and development of seasonal influenza vaccines and influenza medicines.

- Current funding for activities is provided, *inter alia*, by Member States, multilateral organizations, development banks, philanthropic organizations, private sector institutions, nongovernmental organizations, and private citizens.
- There are currently no sustainable financing mechanisms in place to fund a number of elements of the pandemic influenza preparedness benefit sharing system,<sup>1</sup> which aims to increase global pandemic preparedness and response capacities, particularly in developing countries. Unpredictable by their nature, ad hoc contributions are unsustainable. They therefore do not support long-term activities that could strengthen national and global capacities 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, antivirals, 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.<sup>2</sup> By June 2010, at least US\$ 536 million had been mobilized.<sup>3</sup>

### **Projected resource requirements for pandemic preparedness**

- The following tables are a summary of the estimated costs of the different strategic options identified in the previous sections. Readers are reminded to review the actual sections to understand the full picture for each option (including impact, feasibility, and other considerations). Based on decisions taken by Member States, it is possible that multiple funding sources and mechanisms will be required.

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<sup>1</sup> See document A62/5 Add.1, Appendix, section 6.

<sup>2</sup> Urgent Support for Developing Countries' Responses to the H1N1 Influenza Pandemic, October 1 2009, WHO, OCHA, UNSIC.

<sup>3</sup> Urgent Support for Developing Countries' Responses to the H1N1 Influenza Pandemic, June 30 2010, WHO, OCHA, UNSIC.

## 1. Laboratory and surveillance capacity building<sup>1</sup>

### 1(a). Indicator based surveillance

Target	Strategic Option	One-time cost (US\$ million)	Operating expenses (US\$ million)	Surge cost at time of pandemic <sup>2</sup>
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% at 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% at capacity level 4	1	~ 7–10	~ 12–18	~ 30–74
	2	~ 7–10	~ 12–18	~ 30–74

### 1(b) Event-based surveillance

Target	Strategic option	One-time cost (US\$ million)	Operating expenses (US\$ million)	Surge cost at time of pandemic
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

<sup>1</sup> Costs estimated in laboratory and surveillance section are rounded to the nearest US\$1 million; these estimates are preliminary and would need to be validated through further study.

<sup>2</sup> For laboratory and surveillance capacity building “surge cost at time of pandemic” signifies annual operating expenses in a pandemic year. These are substantially higher than costs set out in the column “operating expenses,” which are operating expenses in a non-pandemic year.

### 1(c). Laboratory analysis and surveillance

Target	Strategic option	One-time cost (US\$ million)	Operating expenses (US\$ million)	Surge cost at time of pandemic
1. All countries reach capacity level 3	1. Build and/or support lab capacity to achieve recognition as a NIC	~ 7–11	~ 10–16	~ 56–169
	2. Build and/or support lab capacity for larger countries, support to 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% at capacity level 5; at least one collaborating centre per region	1	~ 20–30	~ 25–38	~ 56–169
	2	~ 17–26	~ 22–32	~ 56–169

### 1(d) Virus sample shipping

Target	Strategic option	One-time cost (US\$ million)	Operating expenses (US\$ million)	Surge cost at time of pandemic
1. All reach capacity level 2	2. Expand WHO influenza specimen shipping project to all countries without adequate in-country shipping capacity	NA	~ <1	~ 1–3
2. All reach capacity level 3	1. Support in-country capacity building for all countries	~ 1	~ 1	~ 1–3



## 2. Expanding global influenza vaccine production capacity<sup>1</sup>

Strategic option	One-time cost (US\$ million)	Operating expenses (US\$ million)	Surge cost at time of pandemic (US\$ million) <sup>2</sup>
1. Increase seasonal demand	~ 280	~ 3 720	N/A
2. Build and/or expand capacity in countries that have government support and/or business case to sustain production	~125–490	0	N/A
3. Subsidize idle capacity above seasonal demand levels	~ 330–770 (new capacity)	~280–450 (existing capacity) ~ 370–1470 (new capacity)	N/A
4. Stimulate IIV to LAIV convertible capacity	~ 130–230	~ <1	N/A
5. Expand the use of potent adjuvant technology	~ 230–420	~ <1	N/A
6. Convert other biologic capacity to pandemic vaccine production at onset of pandemic	~ 38–94	~ 4–9	N/A
7. Accelerate the development of new technologies	~ 50–200/ development programme	0	N/A

## 3. Access, affordability & effective deployment

Target	Strategic option	One-time cost (US\$ million) <sup>3</sup>	Operating expenses (US\$ million)	Surge cost at time of pandemic (US\$ million)
1. Healthcare workers	1. Create new pre-purchase agreements	N/A	~ 10	~ 70
	2. Expand existing pre-purchase agreements			
2. Essentials and pregnant women	1	N/A	~ 140	~ 1 155
	2			
3. Essentials and population at risk	1	N/A	~ 335	~ 2 795

<sup>1</sup>Costs estimated in “Expanding global influenza vaccine production capacity” and “Access, affordability & effective deployment” sections are rounded to the nearest \$5M; these estimates are preliminary and would need to be validated with further study.

<sup>2</sup> Costs included in this section include costs to establish vaccine manufacturing capacity, but do not include costs of purchase and deployment of vaccine in the event of a pandemic.

<sup>3</sup> Assumes pre-purchase agreement terms are similar to existing pre-purchase agreements, key terms include no upfront payment.

## **Potential funding sources and mechanisms**

1. National governments provide a substantial share of the current pandemic influenza financing that benefits their own countries directly. This is likely to continue to be the main financing mechanism for improvements to national public health systems, which includes pandemic influenza preparedness.
2. National sources of health finance are largely derived from general taxation revenues and national health/social insurance schemes.
3. In addition, countries use various mechanisms to generate further national funds for health, some of which might be applied to PIP. For example, mandatory levies on specific products and tax-based systems are two mechanisms which countries rely upon to support health:
  - 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.
4. The WHO World Health Report on Health Financing (2010) cites several other examples<sup>1</sup>, including:
  - 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 for many years.
5. Additional pandemic influenza financing derives from international sources. The call for global solidarity at the outset of pandemic (H1N1) 2009 generated 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 funding sources, specifically focusing on mechanisms that would be predictable and sustainable.<sup>2</sup>
6. **Overview of funding mechanisms:** A number of funding mechanisms are currently in use in global health, some of which (through adaptation, replication, or direct integration) may be relevant to pandemic influenza preparedness. Types of funding mechanisms to consider include:
  - **Mechanisms used to raise funds/resources.** These include levies on products or services, subscriptions and assessments, endowment funds, debt relief, loans, and cash donations. In some defined limited cases, in-kind donations may further supplement cash donations.

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<sup>1</sup> World Health Report, page 29.

<sup>2</sup> These mechanisms will 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 to which donors and national governments give pandemic influenza risk.

- **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.

**7. Application to pandemic influenza preparedness financing.** Examples of mechanisms relevant to pandemic influenza preparedness are described below and include an illustrative application for pandemic influenza preparedness. All funding amounts are illustrative. Further analysis would be needed to assess the amounts that might be raised in practice. None of the mechanisms described are 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. Funds may be raised from products or services 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. The fund serves to compensate people for vaccine-related injury or for death claims for covered vaccines. This programme is funded through a US\$ 0.75 per dose levy on certain vaccines sold in the United States. A total of US\$ 235 million was raised in 2009.<sup>1</sup> The total assets of the fund as at 30 September 2010 were US\$ 3200 million.<sup>2</sup>

- **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 development budget voluntary contributions. Those countries relying on the airline ticket levy use a formula for their levy based on economy or business class. The levy is from €1 for an economy class fare to €40 for a business class fare.<sup>3</sup> In 2009, countries using the solidarity levy generated US\$ 170 million for UNITAID (Chile, France, Madagascar, Mauritius, Niger and the Republic of Korea); with France contributing US\$ 160 million of that amount.<sup>4</sup> The total UNITAID revenue in 2009 was over US\$ 300 million.

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<sup>1</sup> 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>.

<sup>2</sup> Unaudited balance sheet; <ftp://ftp.publicdebt.treas.gov/dfi/tfmb/dfivi0910.pdf>.

<sup>3</sup> <http://www.brookings.edu/~media/Files/Projects/globalhealth/healthsnapshots/airline.pdf>.

<sup>4</sup> UNITAID Annual Report 2009 ([http://www.unitaid.eu/images/NewWeb/documents/AR09/unitaid2009ar\\_web%20spreads.pdf](http://www.unitaid.eu/images/NewWeb/documents/AR09/unitaid2009ar_web%20spreads.pdf)).

• **Example 3**

Although not a mandatory levy, voluntary levies have been used with other consumer or industry activity such as air travel, mobile phone use, etc. 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 the national level. A similar model might be applied to seasonal influenza vaccines to raise money at the global level. As with UNITAID, Member states could choose whether or not to participate. The model may be applied to seasonal influenza vaccines sales using a fixed levy per dose (the table below shows US\$ 0.01, 0.05, and 0.10 per dose), or alternatively using a percentage of the price per dose. The levy could also 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 2**

Number of seasonal vaccine doses per year (million)	Levy per dose (US\$)	Funds available after one year (U\$ million)	Funds available after three years (U\$ million)	Funds available after five years (U\$ million)
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 or researchers). These include, but are not limited to: candidate vaccine viruses, reference reagents, vaccine potency reagents, high growth reassortant influenza viruses, and influenza reference viruses. A possible fund-raising mechanism is to apply

either a yearly subscription fee or a per-product user fee on the various products developed by the WHO Network.

The illustrative table below shows possible subscription rates which could be charged to various users – subscription rates could vary by type of user, for example by some measure of income.

**Table 3**

<b>Income classification</b>	<b>Number of institutions</b>	<b>Annual subscription (US\$ million)</b>	<b>Funds available after one year (US\$ million)</b>	<b>Funds available after three years (US\$ million)</b>	<b>Funds available after five years (US\$ million)</b>
Low income	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 income	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. The illustrative table below shows possible subscription rates for Member States, which could also vary by income level.

**Table 4**

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

- **Global health initiatives.** A number of global health initiatives have been created to address major global health problems and to increase voluntary cash support provided by governments, industry, or other donors. Examples include the Global Fund to Fight AIDS, Tuberculosis and Malaria and the GAVI Alliance. Mechanisms to replenish voluntary contributions are unsustainable by their very nature. Many of these global health initiatives have been able to generate funds over the last 10 years.

- **Examples**

- As at October 2010, the GAVI Alliance had US\$ 10 600 million in donor commitments, with US\$ 4500 million in cash receipts from 1999–2009.<sup>2</sup>
- The Global Fund to Fight AIDS, Tuberculosis and Malaria has received US\$ 18 200 million in cash donations from a pledged total of US\$ 28 600 million for the period 2001–2015.<sup>3</sup>

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<sup>1</sup> World Bank OECD data as at September 2010.

<sup>2</sup> See: the GAVI Alliance website <http://www.gavialliance.org>.

<sup>3</sup> See: the Global Fund to Fight AIDS, Tuberculosis and Malaria website [http://www.theglobalfund.org/documents/pledges\\_contributions.xls](http://www.theglobalfund.org/documents/pledges_contributions.xls).

- **Applying a similar model to pandemic influenza preparedness**

Similar approaches to those used by the organizations above could be used to generate funds for specific pandemic influenza preparedness projects. The illustrative table below shows how much could be raised assuming influenza specific donations amount to 1%, 5% and 10% of average annual donations to the GAVI Alliance and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

**Table 5**

	Average annual donations (US\$ million)	Potential donations that might similarly be raised for influenza (%)	Funds available after one year (US\$ million)	Funds available after three years (US\$ million)	Funds available after five years (US\$ million)
GAVI Alliance	410	1	4	12	21
		5	21	62	103
		10	41	123	205
Global Fund to Fight AIDS, Tuberculosis and Malaria	1200	1	12	36	60
		5	60	180	300
		10	120	360	600

- **In-kind donations** are voluntary contributions of products and services provided by governments, industry, or other donors. They are typically used in emergency settings, although the experience of neglected tropical diseases demonstrates that long-term agreements with companies donating can be secured.<sup>1</sup> Examples of in-kind contributions include antiviral drugs and vaccine donations 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 for vaccine donations. In-kind product donations need to be accompanied by financial support for any required 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 deployment costs.<sup>2</sup> A number of

<sup>1</sup> Merck has contributed Ivermectin for onchocerciasis control for over 30 years.

<sup>2</sup> Urgent Support for Developing Countries' Responses to the H1N1 Influenza Pandemic, June 2010, WHO, OCHA, UNSIC.

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. Based on clear criteria, vaccines, medicines, personal protection equipment kits, and diagnostic kits, could be donated. Specific attention is required to ensure longer-term sustainability, as well as rules for emergencies such as pandemic situations.

- **Debt relief** is the partial or total forgiveness of loans directly by the lender or indirectly via a third party. As part of the arrangement, the funds allocated for use by the country to repay the debt can be redirected to support a public good (e.g., health services). Examples include the Global Fund to Fight AIDS, Tuberculosis and Malaria Debt2Health initiative, the World Bank Investment Partnership for Polio, and the Heavily Indebted Poor Countries debt relief programme. Debt-for-health swaps can take upwards of 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 forgo 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 an individual country which 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 forgo 50% of that amount, and US\$ 50 million would be either used by the country to pay for pandemic influenza preparedness projects, or contributed to a pooled fund at the global level which would be used for pandemic influenza preparedness.

The illustrative table below shows how much funding could be made available for influenza programmes assuming 25%, 50% and 75% discounts during loan cancellation.



**Table 6**

<b>Loan level (US\$ million)</b>	<b>Discount from loan cancellation (%)</b>	<b>Funds available after one year (US\$ million)</b>	<b>Funds available after three years (US\$ million)</b>	<b>Funds available after five years (US\$ million)</b>
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

• **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 specific loan upon successful completion of that country's 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/UN Foundation.<sup>1</sup> The International Development Association's generous loan terms mean that each donor dollar is converted to US\$ 2.50–US\$ 3.00 for affected countries to fight poliomyelitis. The total amount of funding for the partnership was US\$ 316.37 million for the period 2003–2009. The total amount of funding for the partnership was US\$ 316.37 million for the period 2003–2009.<sup>2</sup>

• **Applying a similar model to pandemic influenza preparedness**

A similar mechanism might be applied to raising pandemic influenza preparedness funding. The illustrative table below shows how much funding might be unlocked for influenza programmes assuming influenza specific donations amount to 1%, 5% and 10% of the Investment Partnership for Polio average annual funding.

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<sup>1</sup> United Nations Foundation website (<http://www.unfoundation.org/press-center/press-releases/2003/financial-innovation-will-buy-polio-vaccine.html>)

<sup>2</sup> Global Polio Eradication Initiative Annual Report 2009  
([http://www.polioeradication.org/content/publications/AnnualReport2009\\_ENG.pdf](http://www.polioeradication.org/content/publications/AnnualReport2009_ENG.pdf))

**Table 7**

Average annual partnership funding (US\$ million)	Estimated funds unlocked	Potential donations that might similarly be unlocked for influenza (%)	Funds available after one year (US\$ million)	Funds available after three years (US\$ million)	Funds available after five years (US\$ million)
45	124	1	1	4	6
		5	6	19	31
		10	12	37	62

**7.1 Mechanisms to better match the timing of needs and 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 mechanisms.

- **Bonds.** Bonds are financial instruments that allow their buyers and sellers to change the timing of their cash flows. 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 (IFF and IFFIm), 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 immunization. The bonds are guaranteed by participating Member States. Effectively, the private sector raises the cash for immediate use, with the public sector repaying in the future. To date IFFIm has sold over US\$ 2000 million of these bonds to investors, which will be paid back with interest by IFFIm's donors over the next three to five 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 also 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 to pay for major up-front capacity building (e.g., for upgrading the 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 be highly dependent 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 can issue catastrophe bonds, a bond that functions as an insurance mechanism against catastrophic costs. The sellers of these bonds (e.g., national governments) pay investors interest, as on a normal bond, and the proceeds from the sale of the bond are held in a special purpose vehicle. In the event of a pre-defined 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 get their principal back). 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 at the point 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 ready access to vaccine in the case of a pandemic could decrease the risk of global spread and, therefore global financial losses. More analysis would be needed to assess the financial impact of such a mechanism in the event of a pandemic.

**Insurance;** insurance allows its users to finance future costs that are uncertain but potentially very 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 totaling \$21 million in 2010, and receive financing when an insured disaster strikes, while the World Bank and Caribbean Development Bank bear some financial risk for pay-outs. For example, Haiti's annual premium was US\$ 385 500, and it received US\$ 7.7 million within two weeks of the January 2010 earthquake.<sup>1</sup>

**Applying a similar model to pandemic influenza preparedness**

This mechanism can be an effective way to pay for surge expenses at the time of a pandemic, such as purchase of vaccines, medicines, and other commodities. The agreed

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<sup>1</sup> CCRIF Annual report  
[http://www.ccrif.org/sites/default/files/publications/CCRIF Annual ReportSeptember272010\\_0.pdf](http://www.ccrif.org/sites/default/files/publications/CCRIF%20Annual%20ReportSeptember272010_0.pdf)

definition of the event has a substantial influence on the price of insurance payment terms. If this is seen as a viable option, extensive work must be done to determine this definition and the payment terms.

## **Example 2**

**The World Bank Catastrophe Risk Deferred Drawdown Option (CAT DDO)** 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% front-end fee and committed repayment terms. In 2008 Costa Rica became the first country to utilize this facility, establishing a US\$ 65 million revolving credit line (with a front-end 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 through 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 pandemic such a facility would require access to enough money to cover the credit lines extended. As with the CCRIF, an agreed definition of the event will have an impact on the price of insurance. If this is seen as a viable option, further work would need to be done to define the terms and determine the price range.

**Revolving funds.** Such funds use income to finance continuing operations. Initial capital may be generated by any number of national or international sources. Ongoing 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 to contribute to better multicountry planning.

## **Example 1**

Created in 1979 by WHO/PAHO, the PAHO Revolving Fund for the purchase of vaccines, syringes and other related supplies requires interested country participants to provide PAHO with their forecasted 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 reimbursement of 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 and/or replicated to enable bulk purchases of vaccines at pre-negotiated prices either in advance of the pandemic or at the point of a pandemic. Various funding sources (e.g. national governments, international mechanisms outlined in section 5.1), could be used to establish the fund. Some degree of reimbursement and a service fee could be charged to ensure sustainability.

## **8. Implementing potential financing mechanisms**

There are a number of principles to consider 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 currently in use for global health. In assessing the feasibility any potential financing mechanisms, it is important to consider the relative priority and urgency placed by donors and national governments on pandemic influenza risk.

- **Balance of funding sources**

Given the magnitude of funds required and the various funding flow requirements (e.g. one-time, operating, and surge funding) required 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 likely be required.

- **Necessity of political negotiations and agreements**

The majority of these mechanisms require multilateral agreements, both to generate funds and to manage and disburse them. The timeline for these negotiations must be considered in the overall timeline for setting up a functioning mechanism.

- **Building new mechanisms vs. using existing ones**

Concerning all possible mechanisms, specific decisions will be required whether to establish pandemic influenza preparedness-specific mechanisms, or to partner with existing mechanisms to take advantage of organizations, infrastructure, and systems already in place.

- **Mechanisms to hold, manage and disburse funds**

While not discussed in these studies, the management model required for any international pool of funds will need to be further developed. Considering that multiple mechanisms may need to be pursued in parallel, due consideration will need to be given to the need for a centrally coordinated mechanism to effectively manage, disburse, and monitor funds/contracts.

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