BUSINESS PLAN FOR THE GLOBAL PANDEMIC INFLUENZA ACTION PLAN TO INCREASE VACCINE SUPPLY

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TABLE OF CONTENTS

1. EXECUTIVE SUMMARY	4
2. INTRODUCTION	6
3. THE CHALLENGE	7
4. SOLUTIONS	11
5. ENABLERS	19
6. CONCLUSIONS	23
7. KEY RISKS	27
APPENDIX 1: METHODOLOGY AND ACKNOWLEDGEMENTS	28
APPENDIX 2: OVERVIEW OF KEY CALCULATIONS	29

1. EXECUTIVE SUMMARY

This business plan evaluates the short to medium-term (2007–2017) options available to pursue the *Global pandemic influenza action plan to increase vaccine supply* (GAP) goal of developing enough pandemic vaccine to immunize the world's population (6.7 billion people). While the GAP does not specify a time horizon within which vaccine should be made available to the market, this report assumes 6 months after the transfer of the vaccine prototype strain to industry.[1] Multiple sources indicate that intervention within this frame is likely to be critical to mitigating the effects of the first wave of a pandemic.

As the GAP makes clear, the world is not prepared to respond to a full-scale influenza pandemic:

- There remains a 3–4 month delay between the receipt of the reference strain and the production of the first pandemic immunization. This delay is not likely to shrink much in the next 5–10 years.
- In 2007, maximum pandemic capacity would be 2.7 billion monovalent, adjuvanted immunizations per year (two 5µg doses), rising to 6.2 billion annually in 2010
- Many new technologies are promising but not yet ready for mass production
- The supply and delivery chain is patchy, with significant gaps in fill/finish, syringe/dropper, and human resource availability

A combination of three solutions can greatly boost global supply of pandemic vaccine:

- Increase demand for seasonal vaccine (GAP objective 1)
- Increase and maintain production capacity beyond seasonal need after 2010 (GAP objective 2)
- Prepare for converting some IIV capacity to LAIV at the onset of a pandemic (GAP objective 2)

While these three solutions in combination could provide enough vaccine for 6.7 billion people within 9 months of the start of a pandemic, achieving the GAP goal of 6 months is not feasible with current technology.

New technologies offer the potential to dramatically shorten the time required to generate vaccine, but appear to be at least 10 years away from mass production. More research is needed to develop new production techniques and delivery mechanisms (GAP strategy 3).

While the focus of this report is on vaccine production, some of the critical enablers of pandemic preparedness are also considered. These include:

- Creating a robust supply and delivery chain (GAP objective 1)
- Developing stockpiles of H5N1 vaccines, ancillary supplies and antivirals (addition to the GAP)
- Resolving policy, regulatory and coordination issues (enablers to GAP objectives 2 and 3)

[1] The GAP states "short-term activities were defined as those for which returns would be expected in less than 5 years, medium-term activities would reach fruition in 5–10 years, and long-term activities would take more than 10 years to yield tangible results". WHO/IVB/06.13; WHO/CDS/EPR/GIP/2006.1; p. 6.

The total cost of a plan including the three identified solutions, and funding for research and enablers, would rise to $3.8–4.1 billion annually by 2012 and continue at that level through the end of the plan in 2017.

The initiatives to increase supply would account for $3.2–3.4 billion annually. The enablers would cost between $0.6 billion and $0.7 billion annually. Most of the total cost of the plan – $2.7–2.8 billion – would be spent by governments of high and middle income countries on seasonal vaccination programmes. **The incremental costs to global health donors would be $1.1–1.4 billion annually** (Table 11).

2. INTRODUCTION

The objective of the GAP is to increase the supply of pandemic vaccine. The GAP identified three major approaches to increase supply:

- Develop an immunization policy to increase demand for seasonal vaccines
- Increase influenza vaccine production capacity
- Promote research and development for new influenza vaccines

Initial GAP estimates indicated an investment in the range of $3–10 billion would be required to fund the activities in the GAP. The purpose of this business plan is to refine these activities and cost estimates.

Although monovalent pandemic vaccines were not available during previous pandemics, mathematical models predict that pandemic vaccination would reduce the severity of the pandemic and augment the efficacy of antiviral drugs.[2] The effect of vaccination depends greatly on the time between the outbreak and the beginning of mass vaccination. Use of H5N1 stockpiles has been advocated as a stopgap measure during this period. It is probable that any such stockpile would not offer complete protection against the pandemic strain due to constant antigenic drift and the possible emergence of an entirely different pandemic strain.[3] The capability to produce enough specific pandemic vaccine to cover the global population is therefore a crucial element of the overall response to pandemic influenza.

Global pandemic influenza preparedness is patchy, with a clear shortfall in middle- and low-income countries. This threatens the effectiveness of the global response to a pandemic.

The solutions presented in this business plan were developed through extensive literature reviews as well as interviews with over thirty experts and stakeholders spanning science, industry and policy. We are extremely grateful for their generous provision of time and insight.

[2] Ferguson et al., Nature, 2006

[3] Consensus from interviews with epidemiologists and virologists

3. THE CHALLENGE

The GAP defines an overarching objective of producing enough vaccine to immunize the world's population (6.7 billion people). While the GAP does not specify a time horizon within which vaccine should be made available to the market, this report assumes 6 months after the transfer of the vaccine prototype strain to industry. Given the likely 3 month lag between transfer of the strain and initial production, meeting the GAP goal would require producing 2–3 billion doses of pandemic vaccine per month to generate 6.7 billion courses within 6 months.

Currently, most influenza vaccines are produced using egg-based techniques, predominantly in the form of inactivated influenza vaccines (IIV). Centres of manufacturing are concentrated in the EU and North America. In addition, egg-based production technology is a specialised form of production limited in use to the manufacture of vaccines against influenza, yellow fever and (to a small extent) rabies. While the technology has been available for more than 40 years, significant knowledge and technical skills, and the completion of rigorous protocols are necessary before new production facilities can go on-line.

Global pandemic production capacity depends on existing seasonal capacity. In turn, the demand for seasonal vaccine dictates the global production capacity for pandemic vaccine. The rising uptake of seasonal vaccines through national immunization programmes has stimulated a significant increase in planned global production capacity. Seasonal capacity is forecast to rise from the 340 million trivalent doses produced in 2007 to 815 million doses in 2010.[4]

The question then becomes how this seasonal capacity might translate into pandemic capacity. Seasonal preparations typically contain 15µg of antigen from each of three different strains, blended into a trivalent vaccine containing 45µg of viral antigen. At the time of the outbreak of a pandemic, manufacturers would switch to the production of a monovalent vaccine with antigen from a single strain responsible for the pandemic. Based on this, one could expect global production capacity to increase threefold in a pandemic. However, any estimate of global pandemic vaccine supply is affected by four key considerations, largely derived from industry's experience in developing vaccines directed against the H5N1 strain:

1. Differences in the strain can markedly affect the production yield, e.g., H5N1 viruses yield less HA in chicken embryos.

2. Two doses of pandemic vaccine, given 3 weeks apart, may be required to generate ad equate immunity, based on the available technology.

3. A much higher quantity of antigen (compared to the typical 15µg of antigen required for each strain in seasonal vaccine) may be required to generate what is thought to be a protective immune response.[5]

[4] The 2007 seasonal production estimate of 340 million trivalent IIV doses consists of 300 million from IFPMA members (IFPMA survey 2007) and 40 million from non-IFPMA producers (WHO estimate). The 2010 seasonal planned capacity estimate of 815 million doses consists of 690 million trivalent IIV doses (Bear Stearns; analyst reports; interviews) and an additional 125 million LAIV doses (analyst reports; interviews).

[5] The first vaccines directed against H5N1 required 180µg of antigen divided over two doses to generate an acceptable immune response. Over the last few years, progress in the field of adjuvants has gradually led to a reduction in antigen content to as low as 7.6µg over two doses. In the event that the pandemic is caused by an atypical strain, it remains possible that the adjuvant technology available will not allow for such a stringent reduction in antigen content, limiting the doses of pandemic vaccine available.

4. Knowing that plants tend to run below their maximum capacity, it is uncertain to what extent and how quickly productivity in existing plants can be geared up to meet pandemic requirements.

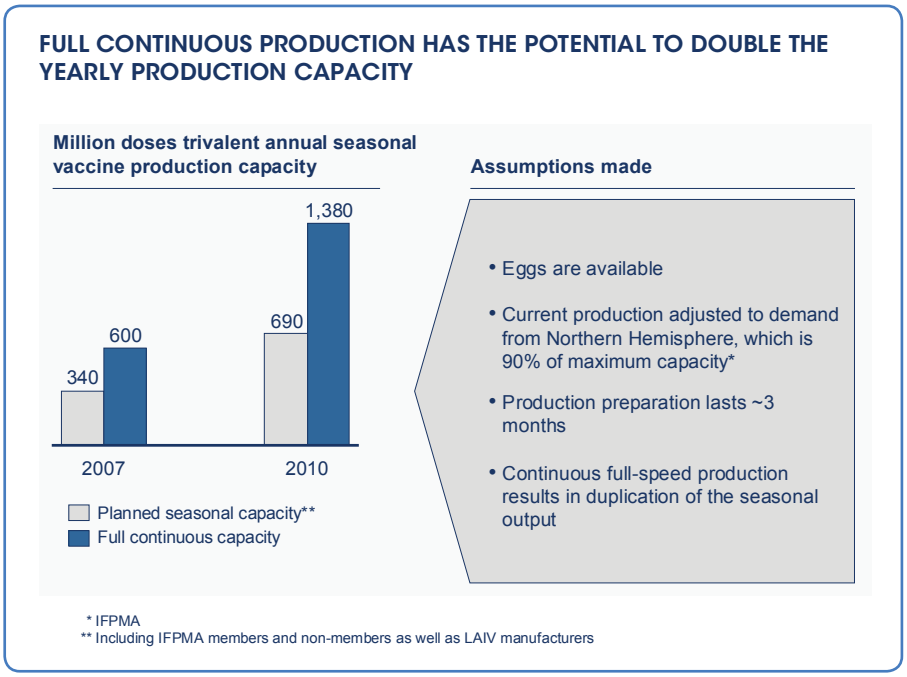
Based on evidence and discussions with a wide range of experts, this report makes two important assumptions for IIV:

1. 5µg of antigen per dose would be sufficient when used with an effective adjuvant.
2. Two pandemic vaccine doses will be required to generate host immunity.

Seasonal IIV capacity can thus theoretically be expanded by a factor of 4.5 during a pandemic.[6]

The next element to consider is how much theoretical seasonal capacity would exist if plants were to run at full production continuously. Industry estimates that it could currently produce between two and three times the amount of seasonal capacity if plants were to run continuously.[7] This report takes a conservative figure and assumes that maximum production capacity would be double seasonal capacity. This implies that maximum 2007 capacity would be about 600 million trivalent IIV doses, rising to 1.4 billion in 2010 (Figure 1).[8]

Figure 1: Theoretical annual capacity



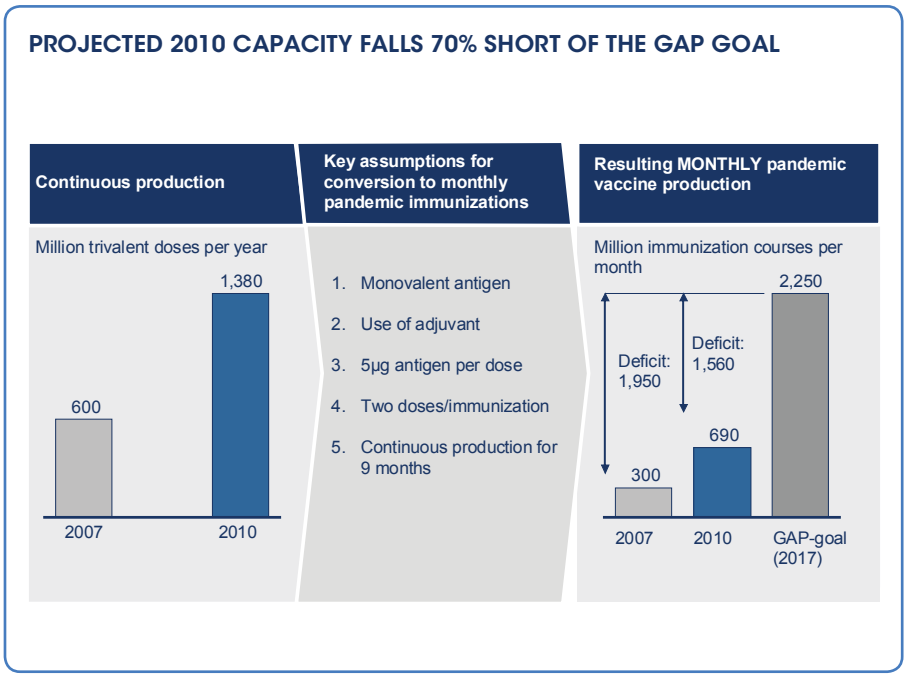
[6] Step 1: Three monovalent vaccine doses for each trivalent 45µg seasonal vaccine (multiply by 3)
Step 2: Pandemic dose of 5µg made possible by adjuvants (multiply by 3)
Step 3: Two doses required per pandemic immunization (divide by 2)
Total: Multiply by 4.5 to get from trivalent seasonal to monovalent pandemic immunizations
LAIV capacity is not considered for these calculations because at the time of writing this report, no pandemic LAIV is licenced.

[7] Industry interviews. Currently, 90 per cent of seasonal production serves the northern hemisphere countries. The result is that plants are idle or operate below capacity for several months of the year. By running continuously, experts estimate maximum annual production could be double or triple seasonal capacity.

[8] Maximum 2007 capacity of 600 million calculated as 565 million trivalent IIV doses (IFPMA survey 2007) and an additional 40 million trivalent IIV doses from non-IFPMA manufacturers (WHO estimate). This is slightly under two times seasonal capacity of 340 million trivalent IIV doses. Maximum 2010 capacity of 1.4 billion (rounded to nearest 100 million) doses calculated as two times seasonal IIV capacity (690 million IIV *2 = 1,380 million IIV).

Given that at least 3 months are required to identify the seed strain and prepare for bulk manufacturing, there are essentially 9 months left over for production. So maximum monthly production capacity in 2007 is somewhere in the range of 67 million trivalent doses per month. Multiplied by 4.5, this would yield 300 million courses of pandemic vaccine per month.[9] With the increase in capacity envisioned by 2010, this monthly figure could rise to 690 million pandemic courses per month.[10] Given the need for 2.25 billion courses per month to cover the global population within 6 months, a significant capacity gap remains. (Figure 2)

Figure 2: Monthly pandemic immunization capacity



Based on current production technology, the global supply of pandemic vaccine falls short of need. Given the uneven spread of vaccine production across the globe and the substantial preparation time to make the vaccine available, the lack of vaccine will affect in particular the WHO African, Eastern Mediterranean, South-East Asia and the Western Pacific regions.

Current capacity could generate 900 million immunization courses within 6 months of the industry receiving the strain. This could rise to 2.1 billion immunizations within 6 months in 2010.[11] Both fall short of the 6.7 billion target. In 2010, it will take 12.7 months to produce sufficient pandemic vaccine for all (Figure 3).[12]

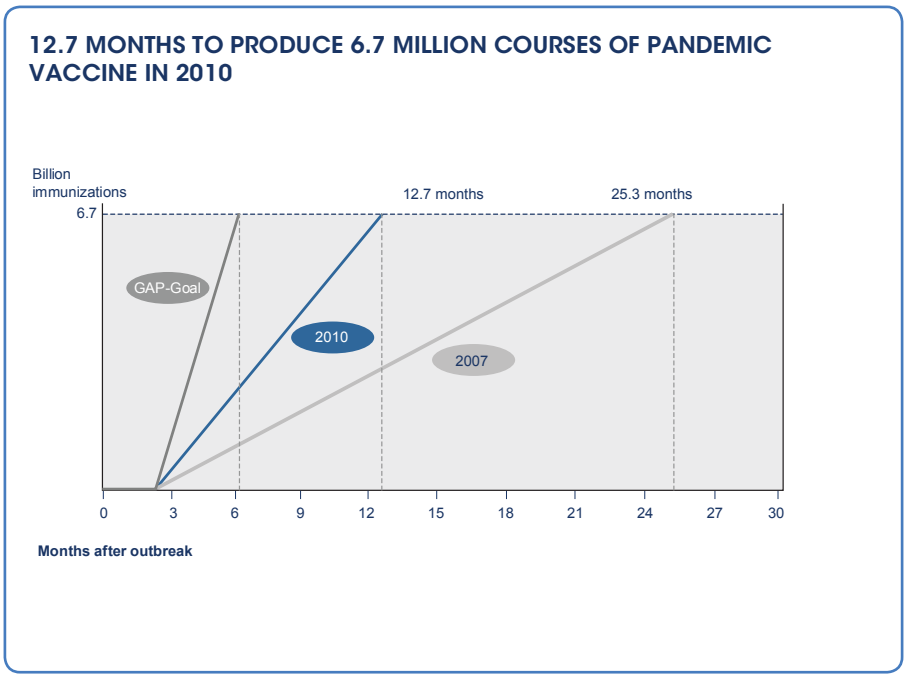
[9] 2007 maximum monthly trivalent IIV production = 600 million trivalent IIV doses/9 = 67 million trivalent IIV doses per month. 2007 monthly monovalent pandemic course production = 67 million trivalent IIV doses * 4.5 = 300 million monovalent courses (immunizations) per month. (1 course = 2 five microgram doses)

[10] 2010 maximum monthly trivalent IIV production = 1380 million trivalent IIV doses/9 = 153 million trivalent IIV doses per month. 2010 monthly monovalent pandemic course production = 153 million trivalent IIV doses * 4.5 = 690 million monovalent courses (immunizations) per month.

[11] 2007 courses within 6 months = 300 million courses per month * 3 months available procution = 900 million courses. 2010 courses within 6 months = 690 million courses per month * 3 months available production = 2.07 billion courses. Both calculations assume 3 month lag between strain identification and production of first course.

[12] Time required to vaccinate = (6.7 billion/690 million immunizations per month) + 3 months prior to production of first course = 12.7 months. In 2012, this would rise to 6.9 billion/690 + 3 months = 13 months.

Figure 3: Pandemic production deficit



Furthermore, if we consider current capacity and assume that manufacturing countries will first supply their own population followed by their region, a significant global imbalance in the timing of supply becomes apparent. With 2010 capacity, Europe and the Americas could potentially be covered within 6 or 7 months while the other four regions could only be fully supplied by 13 months (Figure 4).

Table 1: Monthly distribution of pandemic vaccine supply by region in 2010[13]

Region	African Region	Eastern Mediterranean Region	European Region	Region of the Americas	South-East Asia Region	Western Pacific Region	GLOBAL
Population (millions)	790	600	890	930	1,760	1,800	6,770
IIV capacity (million doses)	0	0	310	285	0	95	690
Time (months)	**Number of vaccination courses available**						
3	0	0	0	0	0	0	0
4	0	0	310	285	0	95	690
5	0	0	620	570	0	190	1,380
6	8	6	**890**	855	17	294	2,070
7	109	83		**930**	243	504	2,760
8	225	171			502	732	3,450
9	341	259			760	959	4,140
10	457	347			1,019	1,186	4,830
11	573	436			1,278	1,413	5,520
12	690	524			1,536	1,641	6,210
13	**790**	**600**			**1,760**	**1,800**	**6,770**

[13] Analysis assumes that producers first serve the entire need of their regions before supplying others

4. SOLUTIONS

Five potential solutions to increase pandemic capacity emerged from the research for this business plan:

1. **Increase demand for seasonal vaccines (GAP objective 1)**
2. **Increase production capacity beyond seasonal need (GAP objective 2)**
3. **Convert some IIV capacity to LAIV during a pandemic (GAP objective 2)**
4. **Switch animal to human production during a pandemic (GAP objective 2)**
5. **Research and develop new vaccine technologies (GAP objective 3)**

The role of H5N1 stockpiles is considered in the following chapter on enablers of overall preparedness.

Each potential solution was assessed against six criteria (Figure 4):

Figure 4: Solution Assessment Criteria

EACH POTENTIAL SOLUTION WAS ASSESSED AGAINST SIX CRITERIA

Criteria	Details
A Technical feasibility	• Can be implemented by 2012 and last through 2017
B Capacity	• Amount of pandemic capacity created
C Delivery time	• Time to first vaccination • Time to vaccinate total population
D Ease of implementation	• Ability to overcome non-technical (e.g., policy and regulatory) hurdles • Ability to bring together necessary partners • Ability of countries to deliver solution
E Risk	• Probability of success • Political implications of failure
F Cost	• Up-front investment required • Annual funding need

Increase demand for seasonal vaccines (GAP objective 1)

The GAP identified increasing seasonal vaccination rates as an important means to create greater seasonal capacity. In response to increasing demand, manufacturers are already planning to increase seasonal capacity from about 340 million to up to 815 million trivalent seasonal doses by 2010. The majority of this capacity still relies on the proven egg-based technique, whereas a small but increasing percentage will come from cell-based technology.[14] Projected 2010 capacity is substantially higher than forecasted demand, which could lead to market oversupply. This oversupply might force the industry to reduce capacity through phasing out older production facilities.

[14] Detailed information on the capacity-split between egg- and cell-based production is considered competitively sensitive and is therefore not given.

How much seasonal demand can reasonably be expected over the next 10 years? For reference, seasonal capacity would need to rise to 2.25 billion trivalent IIV doses in order to generate 6.7 pandemic immunizations within 6 months of a pandemic.[15] In developed countries, a compelling case exists for seasonal vaccination. Guidelines in most OECD-nations recommend the vaccination of all young children (from 6 months to 5 years of age) and adults above the age of 65, as well as those suffering from specific chronic diseases (e.g., diabetes, asthma, chronic obstructive pulmonary disease, immuno-suppression including AIDS). This translates into 16–21 per cent of the population (1.1–1.4 billion people globally). In practice, seasonal flu vaccination rates vary widely between countries. While the average seasonal vaccination rate in high-income countries is 25 per cent, the highest-uptake countries (Canada, Republic of Korea, Japan, the United States) achieve between 30 per cent and 35 per cent. In middle-income countries, the average is 4 per cent with the Russian Federation, Hungary and Chile achieving 13–15 per cent. In low-income countries, the highest rates are 3–5 per cent, whereas the average of countries applying seasonal vaccination stands at 2–3 per cent and is substantially lower if all low-income countries are taken into account.

If each country achieved the highest rate of seasonal influenza vaccination in its peer group (30 per cent for high income, 15 per cent for middle income and 2.5 per cent for low income), demand would rise to 650 million annual trivalent doses by 2012. This is well below estimated production capacity of 815 million doses in 2010.

Taking into account vaccine, administration and social mobilisation costs, the annual estimated incremental cost of increasing annual demand to 650 million trivalent doses would be close to $3 billion a year by 2012 (Table 3 in appendix). Over 85 per cent of this cost would be borne by high and middle income countries through their expanded seasonal vaccination efforts. So while the costs seem high, they need to be considered in light of the benefits. Seasonal vaccination has been shown to be cost-effective by reducing healthcare spend and lost workdays.[16] The yearly immunization programmes have also undoubtedly developed the infrastructure and skills that would support mass vaccination during a pandemic.

Further studies are required to validate the cost-benefit of seasonal influenza vaccination, particularly in middle income and developing countries. The relative funding of healthcare priorities is an issue, especially given that influenza vaccine is far more expensive than other vaccines such as DTP ($0.08 a dose) and the need for a yearly update. Even if the funds were available to subsidize the costs of vaccine and administration, many experts feel that preferential promotion of influenza vaccination could potentially divert resources from more pressing public health priorities. As a result, increasing seasonal vaccination will only fill a small portion of the capacity required to achieve the goals of the GAP.

Increase production capacity beyond seasonal need (GAP objective 2)

Building surplus capacity, some of which would remain idle between pandemics, is a plausible option. In fact, it is possible that industry's current production plans would result in 200 million surplus trivalent doses a year by 2010.

[15] 2250 million pandemic courses per month required. This implies a yearly capacity of 2250 million * 9 = 20250 million monovalent courses per year. This could be generated by 20250 million/4.5 = 4500 million trivalent IIV doses. To generate 4500 million trivalent IIV doses at maximum continuous capacity, 4500 million/2 = 2250 million doses of seasonal trivalent IIV capacity would be required. This assumes that the ratio of maximum continuous to seasonal capacity remains at 2. As more demand shifts to the Southern Hemisphere, that ratio might be expected to fall. This would cause a rise in the number of seasonal production trivalent IIV doses required to vaccinate 6.7 billion people within 6 months of a pandemic.

[16] Cochrane Review, 2007

Maintaining excess capacity would entail either producing excess vaccine and disposing of unused doses or keeping surplus production lines idle. In the latter case, the necessary workforce and raw materials would need to be readily available at the time of a pandemic. Capacity would need to be flexible. This would probably require rotating production lines and ensuring that sufficient eggs, equipment and human resources could be mobilised on short notice during a pandemic. Maintaining surplus production lines could prove logistically and technically challenging, since over time, industry would tend to streamline the scale of the workforce and raw materials around existing demand. To circumvent this, long-term commitments and regular and test-batch production would be needed to ensure that industry maintains appropriate resources to meet a sudden spike in demand.

This solution on its own will not be sufficient, as over 1.5 billion doses of trivalent seasonal capacity would have to remain idle to achieve the required 2.25 billion seasonal doses. This would mean that idle capacity would be larger than current capacity and would require new facilities to be built and kept idle from day 1. This option seems highly unfeasible, as getting an idle plant into activity in a pandemic would need time and substantial resources. However, there is a strong rationale for considering means to encourage industry to maintain existing capacity in a functional state. The rationale is that existing facilities already have the labour and know-how required to produce vaccines, so it ought to be logistically easier to maintain the capacity to produce. **The cost of maintaining 200 million trivalent doses of seasonal capacity idle would be about $100 million per year in 2012.**[17]

Convert some IIV capacity to LAIV during a pandemic (GAP objective 2)

The bulk of seasonal influenza vaccine production is in the form of inactivated influenza vaccine (IIV). While live attenuated influenza vaccine (LAIV) production has been used extensively in Russia for decades, it has only recently become available in the EU or North America. Russian experience suggests that LAIV production generates 50–100 times higher antigen yields and lower downstream processing requirements than IIV-methods. In efficient plants, this translates into 3–6 times more pandemic immunizations per egg than with IIV. The reason for this is that the capacity for one dose of trivalent seasonal IIV can be used to produce 50–100 doses of trivalent seasonal LAIV. Assuming that two doses of monovalent pandemic LAIV are required for a full immunization course, the capacity for one dose of trivalent seasonal IIV would translate into 75–150 courses of pandemic LAIV immunization.[18] In practice, it appears that the titre of LAIV in pandemic vaccine will need to be increased relative to seasonal by a factor of 5. As a result, a more prudent estimate would be that 1 dose of trivalent IIV could yield between 15–30 courses of pandemic LAIV. This is 3–6 times more than yield of 4.5 courses of pandemic IIV immunizations from seasonal IIV. This expansion ability therefore provides a rapid technique to scale up production to meet pandemic needs.[19]

[17] Breakdown of production costs based on industry data: Industry data suggests fixed costs of $0.75 per unit of capacity for egg-based trivalent IIV. According to estimates, $0.50, two-thirds of total fixed costs, are labour-related. Half of these costs are taken into account in the cost for overcapacity, since the other half is assumed to be absorbed by normal workforce through working longer shifts of, e.g., 12 instead of 8 hours during a pandemic.

[18] One dose of trivalent seasonal IIV = 50 – 100 doses of trivalent seasonal LAIV; One dose of trivalent seasonal IIV = 150 – 300 doses of monovalent LAIV. 150 – 300 doses of monovalent LAIV = 75 – 150 LAIV immunization courses (2 courses per individual). LAIV cannot be adjuvanted.

[19] The Serum Institute of India (Pune) in India and the Government Pharmaceutical Organization (GPO) in Thailand are considering the option of seasonal IIV production that can be converted to LAIV-production during a pandemic to materialise upon the scalability achieved by such a switch.

Each large vaccine plant in the EU and North America typically delivers 50–100 million doses of seasonal vaccine annually. A single 100 million seasonal dose IIV plant could provide an additional 1.5–3 billion pandemic immunization courses if converted to LAIV production. To match the goal of full global vaccination within 6 months would require 400 million doses of trivalent IIV capacity to be made convertible to LAIV.[20] Table 2 illustrates the impact of LAIV conversion on the time to achieve full global coverage (Tables 5 to 7 in the appendix illustrate the impact of LAIV conversion per WHO region).

Table 2: Impact of LAIV conversion on time to achieve global coverage in 2012

Time to achieve full coverage (months)	Total IIV capacity (million)	Non-convertible (million)	LAIV-convertible (million)
6	690	290	400
9	690	550	140
12	690	660	30
13	690	690	0

LAIV technology is not without issues. Though LAIVs exist, they have not been approved for those 60 years or older in North America and are contra-indicated for some patient groups, including the immuno-compromised, young infants and pregnant women. Some clinical and regulatory work remains to broaden the indication for LAIV-vaccines. Conversion from IIV to LAIV-production during a pandemic also requires some significant up-front preparation. Current LAIV-producers will need to share their proprietary technology and technical knowledge with non-LAIV producers, provided the necessary incentives to share their intellectual property can be arranged. If agreement on the intellectual property of the technology can be reached, technical skills and plant infrastructure in a few selected plants will need to be adapted. Contrary to what is is often stated, LAIV production does not require the use of specialised specific pathogen-free (SPF) eggs, so the existing supply chain of eggs can be used in the case of pandemic production. To prove their ability to produce high-quality LAIV-vaccine, convertible plants would have to produce trial batches of LAIV on a yearly basis to ensure an effective conversion at the time of the pandemic, maintain accreditation and receive regulatory approval.

Live attenuated influenza vaccines are administered through intranasal applicators or droppers rather than syringes. This would prove much easier for mass vaccination campaigns than injections, but the delivery chain would have to adapt accordingly.

The costs of enabling existing seasonal IIV facilities to convert to producing LAIV during a pandemic consist of development costs for pandemic LAIV, additional infrastructure costs to prepare the existing IIV-facilities for LAIV production, and a yearly production cycle of LAIV in these facilities for testing purposes. Since the development of pandemic LAIV is in an advanced stage, limited additional funding

[20] Assume that 1 dose of trivalent IIV yields 22.5 (mean of 15 and 30) pandemic LAIV immunizations. Seasonal production capacity of 400 million trivalent IIV doses translates to 800 million trivalent IIV doses at maximum continuous capacity. Assuming 9 producing months, monthly maximum production is 800/9 = 89 million trivalent IIV doses. 89 * 22.5 = 2,000 million pandemic LAIV immunizations per month. The remaining capacity of 290 million trivalent IIV doses (690 minus 400) would add 290*2 = 580 million trivalent IIV doses per year. 580 * 4.5 = 2,610 pandemic IIV courses per year. 2,610/9 = 290 pandemic IIV courses per month. In total, 2,000 (LAIV) + 290 (IIV) = 2,290 pandemic courses per month would be available, matching the target of 2,250.

of $25 million spread over five years is estimated to bring to market this type of pandemic vaccine.[21] Adapting production lines costs $5 million annually for each facility and another $5 million annually for each facility for the production and testing of 2–3 batches of LAIV. [22] For example, the overall cost of ensuring convertibility of 400 million doses of IIV to LAIV is estimated at $80–85 million annually (Table 4 in appendix). Similarly, creating and maintaining convertibility for 150 million doses of existing capacity would cost about $30–35 million annually.

It is an open question whether existing producers would be willing or able to make their current plants convertible. As a result, the cost of creating new, convertible plants also needs to be considered. New plants would have the added benefit that they could be located in regions where there is currently expected to be a production shortage. The cost of building a 50 million IIV dose plant would be approximately $50 million. **Factoring in yearly convertability costs, building 150 million IIV doses of new convertible capacity would cost about $30 million per year.[23] This is similar to the cost of converting existing capacity to LAIV production.**

Switch animal facilities to human production

Previous consultations have taken place between the World Health Organization (WHO), the World Organization for Animal Health (OIE), the Food and Agricultural Organization (FAO), animal and human vaccine manufacturers and national authorities responsible for the regulation of veterinary and human medicines about the feasibility of converting existing veterinary capacity to produce human pandemic vaccine. The same egg-based technology is used to produce animal vaccines against Newcastle disease and avian para-influenza and influenza. Surprisingly, the bulk of higher specification (SPF) eggs is currently used for the production of veterinary vaccines, while only a small proportion is used for the manufacture of human live attenuated influenza vaccine (LAIV) in the United States.[24] In addition, plants in North America and Europe tend to be compliant with good manufacturing practice (GMP) standards. Industry sources estimate the entire veterinary vaccine industry could handle 78 million embryonated eggs annually. Depending on the assumptions used, this could translate into 25–100 million doses of trivalent seasonal vaccine.[25]

However, there are significant technical issues with this option:

- The purification standards for animal vaccines are much less stringent than for human vaccines. Significant modifications to existing animal vaccine plants are needed, mainly in downstream processing.
- Adjuvants used are not registered for human use.
- Approval from regulatory authorities would be required for veterinary producers to produce human vaccine. Regulatory approval will be granted following a clinical trial that demonstrates that the produced vaccine is comparable in safety and efficacy to traditionally produced products.

[21] Estimation based on discussion with WHO and industry experts.

[22] Estimation of costs for adaptation of production lines and estimates of an industry expert on the production and testing of LAIV.

[23] $1 per IIV unit to build a new egg-based IIV facility (industry interviews) , depreciated over 10 years. In addition, yearly testing of LAIV production is estimated at $5 million (industry interviews) per facility. Assuming 3 facilities with a capacity of 50 million IIV doses each, yearly costs would amount to: $150 million/10 + 3x $5 million = $30 million.

[24] Interview with Charles River

[25] Current human influenza vaccine manufacturers in China require two or three eggs to produce a single dose of seasonal vaccine (McKinsey industry information). Using this estimate yields the lower end of the range of 25 million doses of trivalent IIV (78 million/3). On the other end of the spectrum, the mean yield per egg for European manufacturers is 0.7 egg/dose trivalent IIV. This would translate into a maximum of 100 million doses of trivalent IIV.

- The co-operation of human vaccine producers is necessary to transfer the technical knowledge and skills to animal vaccine producers.
- Animal vaccine workers would have to acquire new skills and attend regular training to maintain new capabilities.
- Batches of human vaccine would have to be produced on a regular basis to ensure responsiveness at the time of a pandemic. This would disrupt the non-cyclical production cycle of animal vaccines.
- Veterinary vaccine plants are better used to produce influenza vaccine to protect chickens against H5N1 infection, as a means to reduce transmission to humans.

The costs of conversion from animal to human production are difficult to estimate. Assuming the same safety and regulatory standards are maintained in a pandemic, the combination of technical, clinical and regulatory costs will probably outweigh the potential benefit of being able to produce a relatively small increase in pandemic vaccine courses.[26]

Invest in R&D (GAP objective 3)

Research can play a major role in increasing the availability of pandemic vaccines. There are three major challenges to producing sufficient pandemic vaccine within 6 months. The first is the 3–4 month lag between characterization of the strain and the production of the first dose. The second is the speed of production. The third is the efficacy of vaccines and the limited cross-protection offered by previous vaccinations. The first two essentially call for new production methods while the third demands better vaccines.

A scan of current research efforts reveals that though technology shows much promise, most solutions are at least 10 years away from mass commercialization. Given that this business plan for the GAP covers the period from 2007 to 2017, this section touches some of the key research avenues under consideration. Overall, we estimate that $200–300 million per year should be dedicated to developing new production and vaccine technologies.

The vast majority of influenza vaccines are currently produced in embryonated eggs using a technology invented decades ago, with a well-established safety profile. This production technique is used specifically for a small number of products, limiting the flexibility of production facilities. In addition, egg supply needs to be planned 6–12 months ahead, introducing further constraints.

To circumvent the problems associated with egg-based production, several of the major producers are currently investing in new facilities to produce IIV in mammalian cell cultures. Production of LAIV in mammalian cell culture is also in the early stages of development. While cell-based production has the advantage of being independent from the egg supply, it requires higher investments than egg-based production. This results in higher vaccine production costs.

Production of recombinant vaccines in baculovirus-infected insect cell culture is a recently developed production technique with very promising results. A trivalent seasonal vaccine consisting of 135µg of rHA has been shown to induce acceptable seroprotection against circulating influenza strains.[27] Recombinant rHA seasonal vaccines are expected to be available commercially by autumn 2008.[28]

[26] In addition to the issues mentioned, animal vaccine production is highly fragmented, so that many plants would have to be convertible to achieve significant production capacity.

[27] Treanor JJ et al. JAMA 2007

[28] Interview with Dr. Manon Cox (CEO, Protein Sciences)

According to first experiences, the transfer of this production technology to manufacturers with a running insect cell culture production requires approximately 3 months with relatively small investments in infrastructure in the range of $2–3 million per facility. In the long term, this technology may therefore present a highly scalable alternative to current production technologies.

The production of recombinant proteins in bacteria (E.coli) is a well-established, highly scalable technique that can be operated at relatively low cost. However, it is less well developed than baculovirus-based technology.

An intensive area of research is the development of vaccines directed against antigens common to all influenza strains, such as the M2 protein. These vaccines should theoretically induce lasting immunity against all influenza strains.[29] However, such vaccines are still at an early stage of development. Similarly, DNA and virus-like particle (VLP) vaccines are experimental.

Summary

A combination of solutions emerges as the best way to increase availability of pandemic vaccine. There appears to be a strong cost/benefit case for high and middle income countries to increase their uptake of seasonal influenza vaccination. The cost of countries increasing their vaccination rates up to those of their best peers would be close to **$3 billion per year**. The seemingly high cost of increasing seasonal demand to the 600–800 million trivalent dose level needs to be placed in perspective. Much of the expenditure will be borne by individual countries and justified on stand-alone grounds. Further studies are required to fully characterize the benefits of seasonal flu vaccine, particularly in middle and low income countries.

The evolution of the seasonal flu market may likely result in excess capacity by 2012. This could be up to 200 million trivalent doses. Serious consideration should be given to maintaining the availability of this capacity for pandemic production. This would cost about **$100 million annually.**

Developing the capability to convert existing facilities from IIV to LAIV production during a pandemic appears to be the best option at our disposal over the next 10 years. It is the most cost effective. While there are important technical challenges to overcome, these appear to be soluble. Exactly how much convertible capacity will be required depends heavily on the titre required for an LAIV immunization and whether high income countries begin using LAIV for some of their seasonal demand. If a high expansion factor from IIV to LAIV can be achieved, then it may be feasible to contemplate creating somewhere in the range of 150 million trivalent IIV doses of convertible, seasonal capacity. This already represents about 20 per cent of forecast 2010 seasonal trivalent IIV capacity. Making a greater proportion of capacity convertible is likely to be challenging. The cost of building and maintaining **150 million IIV doses of convertible capacity would be about $30 million per year.** This capacity could be located in non-producing countries, thereby alleviating regional pandemic supply gaps.

Looking ahead, research holds out much promise, particularly in the area of improved production methods and new vaccine formulations. Between **$200 million and $300 million annually** will be required to support innovation in addressing the 3–4 month lag in production and the minimal cross-protection offered by previous influenza vaccinations.

[29] VaxInnate website

In sum, a package of solutions costing between $3.2 and $3.4 billion annually would allow the world to produce enough pandemic vaccine within 9 months of the receipt of the strain by industry. A significant proportion of that – $2.7–2.8 billion – would primarily be spent by governments of high and middle income countries on seasonal programmes. Donors could be called upon to annually fund $200 million towards seasonal programmes in low income countries, $100 million to maintain idle capacity, $25–100 million to ensure convertibility to LAIV, and up to $200–300 million for research. Donor contribution on production efforts would thereby be $525–700 million per year. This figure rises to between $1.1 billion and 1.4 billion per year when the enablers of this plan, discussed in the next section, are added to the total.

5. ENABLERS

During the preparation of this business plan, three enablers of overall preparedness surfaced consistently:

1. Create a robust supply and delivery chain (GAP objective 1)
2. Protect essential services with H5N1 and antiviral stockpiles (addition to the GAP)
3. Resolve policy, regulatory and intellectual property issues (enablers to GAP objectives 2 and 3)

This chapter briefly considers each enabler and its implications for pandemic preparedness.

Create a robust supply and delivery chain

The worldwide delivery of billions of pandemic vaccines will require a supply chain that guarantees cold chain distribution and administration with syringes (IIV) or droppers (LAIV) by qualified healthcare personnel. There is a considerable risk of failure to deliver vaccines if the necessary resources are not in place ahead of time. Key actions to consider include:

1. Fill/finish capacity
Filling and finishing in developed countries accounts for a substantial proportion of production costs. Therefore, fill and finish capacity is designed to avoid surplus. Since the number of adjuvanted pandemic vaccine doses that would be produced is over ten times greater than current doses of seasonal vaccines, fill and finish capacity will be insufficient. This shortfall could be met by finishing in larger vials such as 10-dose vials rather than single dose vials. An alternative solution is to fill and finish the vaccines regionally, with the bulk antigen still being produced by the established manufacturers. For this purpose, fill and finish facilities capable of handling influenza vaccines need to be identified, licensed and periodically tested. Optimally, these additional fill and finish facilities would be spread out in across all six WHO regions.

The regional fill and finish of polio vaccines sets a precedent for such a scheme. The successful eradication of polio could result in a reduction of regional fill and finishing capacity, as packagers will not keep up their polio fill and finish capacity. The quantity of regional fill and finish capacity needed will depend on the chosen scenario and can be obtained partially from existing factories.

Other crucial vaccine packaging components, namely glass vials and rubber stoppers, are forecast to be in short supply during a pandemic. The current annual global production capacity of sterile glass vials amounts to 3 billion units for all vaccines. The overall need for and the cost implications of maintaining stockpiles of glass vials and rubber stoppers remain to be defined.

2. Cold chain
The distribution of pandemic vaccines will require a cold chain, albeit with limited need for warehousing, since pandemic vaccines will be used with minimal delay. While in some developing countries there is limited operational experience in cold-chain distribution, the polio vaccination campaign delivered and administered 2 billion vaccine doses to 500 million people per year including those in remote regions. A practical solution to secure a functional cold-chain network for the delivery of pandemic vaccines would be the maintenance of the existing network beyond the eradication of polio, which is estimated at around $150 million annually.

3. Production capacity for syringes
IIVs are currently administered by injection while LAIVs are delivered intra-nasally. If the majority of pandemic vaccines are IIV, 13.4 billion syringes would eventually be required to meet GAP goals. It is estimated that 20 billion disposable syringes are used annually in the world and approximately 40 per cent (8 billion syringes) of these are in sizes suitable for pandemic immunization. Current supply is closely matched to demand and, in the event of a pandemic, it would only be the syringes in manufacturers' and distributors' inventory that could be diverted for the use of pandemic immunizations. The global inventory is estimated at 2–3 months' supply (1.3 to 2.0 billion appropriately sized syringes) and without advanced planning, the actual numbers available to the global population could be even lower. Maintaining a stockpile of 13 billion syringes would cost about $180 million annually.

4. Human resources needed to distribute the vaccines
Assuming a time of 2 minutes to administer a vaccine, approximately 300,000 medically qualified people (doctors, nurses and pharmacists) will be needed to vaccinate 6.7 billion people. While countries with a highly developed health care system will be able to vaccinate their entire population within a few days of the vaccine's becoming available, several countries in East Asia and in Africa lack the necessary human resources for this campaign.[30]

The total cost of upgrading and maintaining a viable supply chain would be $300–400 million per year.

First line response

Stockpiling H5N1 vaccine is being pursued or considered by several countries and organizations. Given the likely 3 or 4 month delay between the beginning of a pandemic and the initial supply of pandemic vaccine, the appeal of stockpiling is clear. If the stockpiled vaccine were effective against a specific pandemic strain, there could be an immediate response, protecting thousands or even millions of lives. SAGE (Strategic Advisory Group of Experts) recently recommended that WHO continue development of an H5N1 stockpile. More specifically, SAGE calls for two uses for stockpiled vaccine. First, 50 million doses, enough to vaccinate 25 million people, should be reserved for the containment of outbreaks that would have the potential to cause a pandemic. Second, a further 100 million doses should be maintained for use in low and middle income countries in the event of a pandemic. One vaccine producer will contribute 50 million doses of H5N1 vaccines over a 3-year period to WHO to create an international stockpile, and other manufacturers have pledged to contribute to the stockpile.

Some affluent countries have also started to develop national stockpiles of vaccines against novel influenza strains. Other nations, such as Canada, have chosen not to develop stockpiles, following in-depth consultations. Some corporations have developed pandemic influenza kits for staff that include courses of antiviral drugs such as oseltamivir®. According to available information, no corporation has yet to purchase a stockpile of novel strain vaccines.

The potential drawbacks of stockpiling vaccine are unfortunately significant when considered against the goal of ensuring a global supply of effective vaccine. There is no guarantee that the stockpiled vaccine will protect against the pandemic strain. Due to the antigenic drift of circulating strains and limited shelf life of vaccines, such stockpiles also have to be replaced regularly.[31]

[30] The costing of additional human resources was not a part of this plan. Given the magnitude of human resource shortages in some countries, the cost to train sufficient staff to deliver vaccinations could run into the hundreds of millions of dollars each year.

[31] Experts estimate the medical lifetime of a stockpile to vary between 6 months and 2 years. This plan assumes stockpiles are replaced every 2 years.

Antiviral drugs reduce transmission, duration of hospitalisation and illness when given within 48 hours of exposure.[32] However, their use as a definitive treatment for a mass population is limited by restricted manufacturing capacity, need for an efficient health system to deliver treatment rapidly, and inability to generate host immunity. In addition, there are some reports of H5N1 strains demonstrating resistance to oseltamivir.[33] Circulating seasonal influenza strains are already highly resistant to earlier antiviral drugs such as amantidine.[34] The acquisition of resistance to neuraminidase inhibitors by the pandemic strain might render stockpiles of antiviral drugs ineffective.

The overall cost of maintaining a stockpile of vaccine and antiviral drugs to cover 75 million people would be $240 million annually.[35]

Regulation and intellectual property

The resolution of regulatory and IP-issues will require the alignment of all stakeholders. There is a range of issues related to policy, regulations and intellectual property that need to be resolved to improve the preparedness for an influenza pandemic:

1. Agreements on import and export conditions for vaccines during a pandemic
Import and export of pandemic vaccines will be required because they are produced in only a limited number of countries. During a pandemic, however, governments of influenza vaccine-producing countries may impose an export ban for pandemic vaccines until their own immunization needs are satisfied. This would prevent the optimal use of vaccines from a global perspective, and exacerbate the pandemic. To avoid such uneven distribution, there is a need for agreement on free movement of vaccines during a pandemic.

2. Licensing and approval of pandemic vaccine production technology and vaccines
An important factor for reducing the time between the emergence of a human pandemic influenza virus and the availability of pandemic vaccine is optimizing and possibly harmonizing national regulatory pathways. In order to help regulatory authorities prepare and to support countries without their own regulators, WHO and some key regulatory authorities are currently preparing guidelines for "Regulatory Preparedness for Human Pandemic Influenza Vaccines". Important issues to resolve include the possibility of pre-licensing mock vaccines, a path that has been followed by two manufacturers in Europe (EMEA), as well as the licensing and testing of regional fill-and-finish manufacturers.

3. Sharing of vaccine production technology or the use of proprietary adjuvants during a pandemic
Between pandemics, NGOs, governments and the industry need to agree on the conditions for the transfer of production technology and adjuvants. In addition, the technology and adjuvants to be used by secondary producers who are considered for pandemic production need to be tested and licensed. Two of the major vaccine producers have communicated their willingness to share their adjuvants with other producers during a pandemic. Another manufacturer has publicly announced its willingness to share its production technology for pandemic LAIV. These examples demonstrate the readiness of important IP holders to help prepare for a pandemic. Since the

[32] Jefferson et al, Lancet, 2006

[33] Reece et al, J Med Virol, 2007

[34] Deyde etl al, J Infect Dis, 2007

[35] $2 per dose of vaccine; $1 per adjuvant; rotate one-third of stockpile each year. A course of antiviral drugs would cost $12 with an assumed validity of 10 years.

pandemic vaccines of all producers will need to be approved by regulatory authorities, further steps along the regulatory pathway will need to be initiated, including testing and licensing of these vaccines. The issue of indemnity for the mass use of proprietary technology also needs to be addressed. It is unrealistic to expect secondary producers, who do not routinely use proprietary technology belonging to another producer, to be able to make use of such technology effectively at the time of a pandemic. Even after regulatory approval and licensing, batches of "mock" pandemic vaccines would have to be made on a regular basis and inspected for quality and adherence to standards. Such activities are likely to disrupt secondary manufacturers' production cycles and be financially unattractive. Overcoming these obstacles will require significant further coordination and facilitation and, most likely, the substantial involvement of WHO. WHO has mapped the intellectual property related to the production of pandemic influenza vaccines.[36] The acquisition of some key patents by the international community may present an alternative to the sharing of technology free of charge and remains to be investigated.

Resolving policy, regulatory and intellectual property issues would cost $5–10 million annually.[37]

[36] Study on "Mapping of Intellectual Property Related to the Production of Pandemic Influenza Vaccines", Martin Friede, WHO (IVR), August 2007

[37] WHO estimate

6. CONCLUSIONS

The analysis underpinning this report clearly reveals that the world is far from prepared to supply enough vaccine to respond to a full-scale avian influenza pandemic. The summary of key facts is stark:

- There remains a 3–4 month delay between the receipt of the reference strain and the production of the first pandemic immunization. This time is not likely to shrink much in the next 5–10 years.
- In 2007, maximum pandemic capacity would be 2.7 billion monovalent, adjuvanted immunizations per year (two 5µg doses), rising to 6.2 billion annually in 2010
- Many new technologies are promising but not yet ready for mass production
- The supply and delivery chain is patchy, with significant gaps in fill/finish, syringe/dropper, and human resource availability

A combination of three solutions can greatly boost global supply of pandemic vaccine:

- Increase demand for seasonal vaccine (GAP objective 1)
- Increase and maintain production capacity beyond seasonal need after 2010 (GAP objective 2)
- Prepare for converting some IIV capacity to LAIV at the onset of a pandemic (GAP objective 2)

While these three solutions in combination could provide enough vaccine for 6.7 billion people within 9 months of the start of a pandemic, achieving the GAP goal of 6 months is not feasible with current technology.

New technologies offer the potential to dramatically shorten the time required to generate vaccine, but appear to be at least 10 years away from mass production. More research is needed to develop new production techniques and delivery mechanisms (GAP objective 3).

In addition to ensuring the capacity to produce sufficient vaccine in a pandemic, there is a need to address the broader enablers of preparedness. These include:

- Creating a robust supply and delivery chain (GAP objective 1)
- Developing stockpiles of H5N1 vaccines, ancillary supplies and antivirals (addition to the GAP)
- Resolving policy, regulatory and coordination issues (enablers to GAP objective 2 and 3)

Promote seasonal vaccination programmes

A key conclusion is that encouraging greater uptake of seasonal vaccination is not a viable solution by itself. While every effort should be made to maximize the uptake of seasonal influenza vaccine in countries where there is a strong cost/benefit logic, this strategy alone is not a viable pandemic preparedness solution. The expense is prohibitive when compared to pressing priorities in middle and low-income nations. The implication is that without intervention, the market for seasonal vaccination is highly unlikely ever to create sufficient “surge” capacity to cater for the global population during a pandemic.

Maintain capacity beyond seasonal need

Were it not for the possibility of amplifying existing capacity, the only option would be to create new, excess capacity and keep it idle prior to a pandemic. This is also costly, making it difficult to justify in the face of pressing priorities, particularly in low-income countries. However, maintaining existing surplus capacity available for pandemic use is a viable solution.

Convert IIV- to LAIV-capacity during a pandemic

While several experts claim that developing the capability to convert an existing IIV facility to LAIV is possible, it is hard. Industry may not be particularly favourable given its investment in existing technology platforms. Additional up-front investment and annual maintenance costs would be incurred. Establishing new convertible plants is likely to be more feasible.

Promote R&D on new production technologies and vaccine formulations

The most tenable benefits of increased pandemic vaccine supply are likely to come from finalising the development of recombinant vaccines and adjuvants that are more powerful, and streamlining the ability to switch from IIV to LAIV production. In the longer term, novel vaccines have strong potential.

Build a viable supply chain

There is also a pressing need to ensure sufficient fill/finish, syringe or dropper and administration capacity. Critically, recipient countries will need to prepare this infrastructure. These elements were not strictly in the remit of this report but are noted because of their importance in achieving full preparedness.

First line response

The development of a limited stockpile to safeguard the delivery of essential services during a pandemic is sound policy. The cost of $240 million annually seems reasonable in the event that the stockpiled vaccine is indeed effective. Again, equity of access is an important issue. In order to ensure its equitable distribution, the stockpile should be maintained and administered by a neutral body such as WHO.

Ensure timely delivery and access to all

Converting IIV facilities in producing countries to LAIV production will not fully address the issue of getting vaccines to different parts of the world on time. Several non-producing countries fear that they will initially be shut out of supply until producing nations have vaccinated their own people. Many also lack faith that pre-existing supply agreements would be upheld in a crisis. As a result, there has also been a call to regionalize production, in the hope that this would create a fairer distribution of vaccine during a pandemic.

Understandably, some countries might choose to invest in developing their own capacity to produce pandemic vaccine. In practice, this would mean developing seasonal IIV or LAIV capacity. Indeed, countries such as Thailand are already doing this and WHO is operating a grant programme (with

financial support from some G8 countries) to assist developing country vaccine manufacturers who wish to acquire the capacity to produce influenza vaccines. A more balanced global distribution of vaccine production would be beneficial on the one hand to guarantee equitable access in all regions to pandemic vaccine and on the other to increase cost-competitiveness in the production and marketing of seasonal vaccine. Where possible, consideration should be given to developing new facilities in countries or regions that currently do not produce such vaccines, while having in place the technical capacity to produce vaccines of assured quality. Figure 5 shows that there are countries in every WHO region that would be capable of hosting production facilities.

Figure 5: Evaluation of countries applicable for the setup of production facilities per region

SEVERAL COUNTRIES ARE ABOUT TO START OR HAVE EXPRESSED INTEREST IN PRODUCING SEASONAL INFLUENZA VACCINE

Factors associated with successful production

- Sufficient regional population to generate future demand for seasonal vaccine
- Technical expertise in vaccine manufacturing
- Political stability
- High GNI per capita
- Rapid economic growth

Countries due to start production of seasonal influenza vaccine

- Republic of Korea
- Brazil

Countries awarded grants to assess feasibility

- Viet Nam
- Mexico
- Thailand
- Indonesia
- India

Countries expressing interest (not exhaustive)

European Region	African Region	South-East Asia Region	Western Pacific Region	Region of the Americas	Eastern Mediterranean Region
• Croatia • Serbia	• South Africa	• Malaysia	• Philippines	• Argentina • Cuba	• Islamic Republic of Iran • Morocco • Egypt

Develop stronger coordination mechanisms

Many of the proposed solutions are interdependent and none is sufficient on its own. For instance, IIV delivery will require syringes while LAIV will call for droppers. Part of the coordination challenge will be to link interdependent solutions and ensure that they are developed in parallel. In particular, it will be important to identify the main players, their role in delivering each solution, and what is expected from each of them.

Achieving preparedness will require significant coordination. There is a strong case to be made for greater focus. This does not necessarily imply, however, that yet another separate and independent body should be created. There is a real concern that the proliferation of independent organizations focused on single issues has led to a silo-approach to healthcare delivery at country level. Therefore, the key questions are:

1. What tasks need to be completed initially and on an ongoing basis?
2. What resources and capabilities are required to accomplish this?
3. Where should these resources be hosted and to whom should they be accountable?

It is beyond the scope of this report to make a specific recommendation on which body would be best to coordinate overall pandemic preparedness. The analysis focused specifically on production as opposed to the entire preparedness chain. Nonetheless, several key tasks requiring coordination are important to mention. From a supply of vaccine point of view, successful coordination will result in:

1. Multi-stakeholder agreement on the business plan to increase capacity
   - Governments will need to be satisfied that they can obtain vaccine in timely fashion.
   - Industry will need to agree to build sufficient convertible capacity, to consider regionalising production, and to share intellectual property.
2. The development of a clear funding strategy
   - Donors and governments will be needed to support any strategy to vaccinate 6.7 billion people.
   - Funding will have to be long-term and may be challenging to secure given that it is insurance rather than part of a definitive solution.
3. Clarity on the roles of respective stakeholders.
4. The achievement of a state of preparedness on the ground.

The coordinating function would ideally need to be able to:

- Secure, manage and distribute long-term financing
- Monitor, evaluate and performance manage individual stakeholder activities
- Plan strategically, with a particular emphasis on understanding markets, supply, and the implications of emerging technology
- Advocate and communicate on behalf of pandemic preparedness
- Arbitrate on disputes between stakeholders
- Be accountable for the maintenance and distribution of any stockpile

While the objectives of the GAP fit squarely with WHO's mission, WHO itself may face challenges in hosting a pandemic preparedness group. Moreover, it may be limited in its ability to bring together, monitor and performance manage all stakeholders effectively given its traditional advisory role.

Cost

The total cost of a plan including the three identified solutions, and funding for research and enablers would rise to $3.8–4.1 billion annually by 2012 and continue at that level through the end of the plan in 2017.

The initiatives to increase supply would account for $3.2–3.4 billion annually. The enablers would cost between $0.6 billion and $0.7 billion annually. Most of the total cost of the plan – $2.7–2.8 billion – would be spent by governments of high and middle income countries on seasonal vaccination programmes. **The incremental costs to global health donors would be $1.1–1.4 billion annually** (Table 11). This is in the same range as the amount spent annually on HIV by the Global Fund.

Next Steps

There is an urgent need to convene stakeholders to agree on a strategy to increase timely availability of vaccine during a pandemic and a mechanism to coordinate future efforts. The technology exists to be prepared and mount an effective response. To fail to do so due to collective inaction could be tragic indeed.

7. KEY RISKS

Reliability of information

In developing this report, every effort was made to source the latest and most reliable information. An exhaustive literature review was supplemented by interviews with over 30 industry experts, manufacturers, public health professionals and policymakers. The breadth and depth of this research provides a robust, though not perfect fact-base. There were several instances where certain parties, for understandable reasons, chose not to reveal confidential or privileged information. In these cases, we have done our best to develop estimates based on alternative sources.

Several estimates underpin the models used to calculate the impact of various options and scenarios. Each of these estimates was verified with a panel of industry experts. However, given the confidentiality of the industry data on one hand and the scope of change to the industry dynamics (volume, sources of supply, destination of production) implied in the scenarios proposed, there is a potential margin for error. Other parties should not rely on the figures and estimates in this report to make decisions as it is critical to understand the underlying assumptions that were used to generate the estimates.

Financial risk

The implementation of an integrated approach to ensure global supply of pandemic vaccine carries financial risk. Investments will be required by the international community, individual countries and industry. The level of investment required may be different from what is described in this report due to the nature of information available to-date, industry developments and challenges in implementation.

Technical/scientific risk

The analyses and recommendations in this report are based on existing technology and the views of experts on likely future developments. New or disruptive technologies could dramatically alter the relative merits of specific analyses and recommendations. Extensive literature searches as well as expert interviews help ensure that the information provided in this report is as robust as possible.

Timing risk

By definition, a pandemic preparedness plan will stretch over many years. Political, economic, and scientific conditions may change over time and alter the validity of current analyses and recommendations. In addition, it may take longer to achieve preparedness than implied by the analyses in this report if external conditions change.

APPENDIX 1: METHODOLOGY AND ACKNOWLEDGEMENTS

This report has been written by the management consulting firm of McKinsey & Company, in collaboration with the staff of the WHO Initiative for Vaccine Research (IVR).

The findings in this report are based on a combination of literature research on the subject matter, existing experience in the field of vaccines and, importantly, the insights gathered from more than 35 interviews with leading experts and industry representatives. In order to protect confidential information shared, the information in the report is shown on an aggregated level without specifically mentioning names or organizations.

We would like to thank the following interview respondents for their time, their insights and their high degree of openness:

Dr. Jon K. Andrus	Pan American Health Organization
Dr. John Boslego	PATH
Dr. Peter Carrasco	WHO
Sian Clayden,	GSK Biologicals, Vice President, Portfolio Strategy
Dr. John Clemens	International Vaccine Institute
Dr. Stephen Cochi	CDC
Dr. Alejandro Costa	WHO
Dr. Manon Cox	Protein Sciences
Dr. Bruce Gellin	HHS
Dr. Giuseppe Del Giudice	Novartis
Dr. Nico Drager	WHO
Dr. Pierre Duplessis	International Red Cross Federation
Prof. Rajae El Aouad	National Institute of Hygiene, Morocco
Dr. Martin Friede	WHO
Dr. Keiji Fukuda	WHO
Stephen Gardner	GSK Biologicals, Director Market Access Flu Vaccines
Birgit Girshick	Charles River
Renuka Gadde	Becton Dickinson
Dr. Paul Gully	WHO
Prof. Ian Gust	University of Melbourne
Dr. Luc Hessel	IFPMA
Dr. David Heymann	WHO
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Dr. David Nabarro	United Nations
Prof. Albert Osterhaus	Erasmus University Rotterdam
Dr. Bram Palache	Solvay
Dr. Laszlo Palkonyay	WHO
Dr. Rino Rappuoli	Novartis
Dr. Alex Ross	WHO
Dr. Fadia Saadah	World Bank
Dr. Bijan Sadrizadeh	MOH Islamic Republic of Iran
Prof. David Salisbury	UK Health Protection Agency
Dr. Pathom Sawanpanyalert	MOPH Thailand
Dr. Klaus Stohr	Novartis
Chris Strutt	GSK Vice President Government Affairs, Corporate and Europe
Dr. Georges Thiry	PATH
Dr. Lara Wolfson	WHO
Dr. David Wood	WHO

APPENDIX 2: OVERVIEW OF KEY CALCULATIONS

Table 3: Activities and associated costs for the promotion of seasonal vaccination programmes (in $ million 2007)

Activity	2007	2012	2017
High income countries	**273**	**1,223**	**1,260**
Social mobilization	37	5	6
Vaccine administration	158	811	836
Vaccines	79	406	418
Middle income countries	**318**	**1,473**	**1,525**
Social mobilization	34	5	5
Vaccine administration	113	587	608
Vaccines	170	881	912
Low income countries	**66**	**192**	**208**
Burden of disease studies	20	0	0
Social mobilization	11	2	2
Vaccine administration	11	60	65
Vaccines	24	130	141
Total	**657**	**2,887**	**2,993**

Assumptions: Duration of programme is 5 years (until 2012) to reach the target (30 per cent coverage in high, 15 per cent coverage in middle, and 2.5 per cent coverage in low income countries). Costs for social mobilisation are $0.70, 0.30, and 0.10 per additional dose and costs for vaccine administration are $15, 5, and 0.50 in high, middle, and low-income countries, respectively. Vaccine costs in high- and middle income countries are $7.50. Vaccine costs for low-income countries are $1.24. Burden of disease studies are projected to cost $100 million over 5 years.

Table 4: Activities and associated costs for switching from IIV to LAIV (in $ million 2007)

Activity	2007	2012	2017
Yearly testing of LAIV products	40	40	40
Infrastructure costs	40	40	40
Development of pandemic LAIV	5	0	0
Total	**85**	**80**	**80**

Assumptions: Development costs for pandemic LAIV: $25 million spread over a period of 5 years. Infrastructural adaptations of IIV facilities are estimated at $5 million per year and facility. The production of 2–3 batches of LAIV per convertible facility is estimated at $5 million per year and facility. Calculations are for 8 convertible facilities with a production capacity of 50 million IIV doses each.

Table 5: Regional availability of pandemic immunizations in 2012 assuming 400 million LAIV-convertible IIV capacity

WHO Region	African Region	Eastern Mediterranean Region	European Region	Region of the Americas	South-East Asia Region	Western Pacific Region	GLOBAL
Population (millions)	820	620	890	950	1,800	1,820	6,900
IIV capacity (million doses)	0	0	135	110	0	45	290
LAIV convertible capacity (million doses)	0	0	175	175	0	50	400
Time (months)	**Number of vaccination courses available (millions)**						
3	0	0	0	0	0	0	0
4	31	23	**890**	**950**	67	329	2,290
5	425	321			933	1,061	4,580
6	**820**	**620**			**1,800**	**1,820**	**6,900**

Assumption: Conversion of seasonal IIV capacity to pandemic LAIV production results in a yearly production of 22.5 pandemic LAIV courses (as compared to 4.5 pandemic IIV courses) per seasonal IIV capacity. See main text for details.

Table 6: Regional availability of pandemic immunizations in 2012 assuming 140 million LAIV-convertible IIV capacity

Region	African Region	Eastern Mediterranean Region	European Region	Region of the Americas	South-East Asia Region	Western Pacific Region	GLOBAL
Population (millions)	0	0	0	0	0	0	6,900
IIV capacity (million doses)	0	0	250	225	0	75	550
LAIV convertible capacity (million doses)	0	0	60	60	0	20	140
Time (months)	**Number of vaccination courses available (millions)**						
3	0	0	0	0	0	0	0
4	0	0	550	525	0	175	1,250
5	61	46	**890**	**950**	134	418	2,500
6	274	207			601	829	3,750
7	486	368			1,067	1,239	5,000
8	698	528			1,533	1,650	6,250
9	**820**	**620**			**1,800**	**1,820**	**6,900**

Assumption: Conversion of seasonal IIV capacity to pandemic LAIV production results in a yearly production of 22.5 pandemic LAIV courses (as compared to 4.5 pandemic IIV courses) per seasonal IIV capacity. See main text for details.

Table 7: Regional availability of pandemic immunizations in 2012 assuming 30 million LAIV-convertible IIV capacity

Region	African Region	Eastern Mediterranean Region	European Region	Region of the Americas	South-East Asia Region	Western Pacific Region	GLOBAL
Population (millions)	0	0	0	0	0	0	6,900
IIV capacity (million doses)	0	0	295	270	0	95	660
LAIV convertible capacity (million doses)	0	0	15	15	0	0	30
Time (months)	**Number of vaccination courses available (millions)**						
3	0	0	0	0	0	0	0
4	0	0	370	345	0	95	810
5	0	0	740	690	0	190	1,620
6	60	46	**890**	**950**	132	352	2,430
7	202	152			442	604	3,240
8	343	259			753	855	4,050
9	484	366			1,063	1,107	4,860
10	625	473			1,373	1,359	5,670
11	767	580			1,683	1,611	6,480
12	**820**	**620**			**1,800**	**1,820**	**6,900**

Assumption: Conversion of seasonal IIV capacity to pandemic LAIV production results in a yearly production of 22.5 pandemic LAIV courses (as compared to 4.5 pandemic IIV courses) per seasonal IIV capacity. See main text for details.

Table 8: Costs for creation and maintenance of supply chain (in $ million 2007)

Activity	2007	2012	2017
Stockpile 13 billion syringes	182	182	182
Maintain polio distribution network	150	150	150
Total	**332**	**332**	**332**

Assumptions: Shelf-life of syringes 5 years, costs per syringe of $0.07. Yearly total costs for polio distribution network $150 million.

Table 9: Costs to protect essential services (in $ million 2007)

Activity	2007	2012	2017
Stockpile antigen for 75 million people	100	100	100
Stockpile adjuvants for 75 million people	50	50	50
Stockpile antiviral drugs for 75 million people	90	90	90
Total	**240**	**240**	**240**

Assumptions: Shelf life of antigen and adjuvant is 3 years, of antiviral drugs 10 years. The costs are $2.00, $1.00, and $12, respectively.

Table 10: Reconciliation of business plan to GAP

GAP Objectives and Strategies	Business Plan
Objective 1: Increase in seasonal vaccine use	
1.1 Develop regional and national plans for seasonal influenza vaccination Programmes *Activity 1.1.1*: Map the landscape *Activity 1.1.2*: Estimate disease burden *Activity 1.1.3*: Develop regional plans of action	Not included
1.2 Mobilize resources for the implementation of seasonal influenza vaccination programmes *Activity 1.2.1*: Mobilize resources for resource-constrained countries	$2.9 billion/year for promoting seasonal vaccine programmes
Objective 2: Increase in vaccine production-capacity	
2.1 Increase capacity for inactivated influenza vaccines (IIV) *Activity 2.1.1*: Improving production yields and immunogenicity for vaccines based on H5N1 influenza strains; *Activity 2.1.2*: Building new production plants in both developing and industrialized countries; NEW: Incentivise industry to maintain idle capacity	$100 million to build and maintain idle capacity
2.2 Explore formulations of influenza vaccine other than those commonly used for seasonal vaccination *Activity 2.2.1*: Conduct clinical trials with alum and MF-59 adjuvanted vaccine; *Activity 2.2.2*: Explore the opportunity to scale-up production of live attenuated influenza vaccines (LAIV); *Activity 2.2.3*: Further evaluate whole-virus based inactivated vaccines;	$25–100 million to stimulate industry to build capacity that is convertible from IIV to LAIV
2.3 Assessment of alternative delivery routes *Activity 2.3.1*: Test the intradermal route of administration;	$70-100 M
Objective 3: Promote research and development for new influenza vaccines	
3.1 Enhance protective efficacy and immunogencity of existing vaccine types *Activity 3.1.1*: Evaluate novel adjuvants; *Activity 3.1.2*: Assess the molecular basis of immunogencity to design more potent vaccines; *Activity 3.1.3*: Predict viral evolution;	$70–100 M
3.2 Develop novel vaccines that induce broad-spectrum and long-lasting immune response *Activity 3.2.1*: Develop new generation vaccines; *Activity 3.2.2*: Determine potential benefits of immune priming;	$70–100 M
3.3 Improve evaluation of vaccine performance *Activity 3.3.1*: Define correlates of protection; *Activity 3.3.2*: Standardize immunogenicity assays;	Not included
NEW	
H5N1 vaccine and antiviral stockpiles	$240 M
Resolution of policy, regulatory, and IP Issues	$5–10 M
Strengthening of supply chain, including cold chain	$300–400 M

Table 11: Donor Costs

GAP Objectives and Strategies	Business Plan
Objective 1: Increase in seasonal vaccine use	
1.1 Develop regional and national plans for seasonal influenza vaccination Programmes *Activity 1.1.1*: Map the landscape *Activity 1.1.2*: Estimate disease burden *Activity 1.1.3*: Develop regional plans of action	Not included
1.2 Mobilize resources for the implementation of seasonal influenza vaccination programmes *Activity 1.2.1*: Mobilize resources for resource-constrained countries	$200–300 million/year for promoting seasonal vaccine programmes in low income countries
Objective 2: Increase in vaccine production-capacity	
2.1 Increase capacity for inactivated influenza vaccines (IIV) *Activity 2.1.1*: Improving production yields and immunogenicity for vaccines based on H5N1 influenza strains; *Activity 2.1.2*: Building new production plants in both developing and industrialized countries; NEW: Incentivise industry to maintain idle capacity	$100 million to build and maintain idle capacity
2.2 Explore formulations of influenza vaccine other than those commonly used for seasonal vaccination *Activity 2.2.1*: Conduct clinical trials with alum and MF-59 adjuvanted vaccine; *Activity 2.2.2*: Explore the opportunity to scale-up production of live attenuated influenza vaccines (LAIV); *Activity 2.2.3*: Further evaluate whole-virus based inactivated vaccines;	$25–100 million to stimulate industry to build capacity that is convertible from IIV to LAIV
2.3 Assessment of alternative delivery routes *Activity 2.3.1*: Test the intradermal route of administration;	$70-100 M
Objective 3: Promote research and development for new influenza vaccines	
3.1 Enhance protective efficacy and immunogencity of existing vaccine types *Activity 3.1.1*: Evaluate novel adjuvants; *Activity 3.1.2*: Assess the molecular basis of immunogencity to design more potent vaccines; *Activity 3.1.3*: Predict viral evolution;	$70–100 M
3.2 Develop novel vaccines that induce broad-spectrum and long-lasting immune response *Activity 3.2.1*: Develop new generation vaccines; *Activity 3.2.2*: Determine potential benefits of immune priming;	$70–100 M
3.3 Improve evaluation of vaccine performance *Activity 3.3.1*: Define correlates of protection; *Activity 3.3.2*: Standardize immunogenicity assays;	Not included
NEW	
H5N1 vaccine and antiviral stockpiles	$240 M
Resolution of policy, regulatory, and IP Issues	$5–10 M
Strengthening of supply chain, including cold chain	$300–400 M