

Influenza Vaccine Strategies for Broad Global Access

Key Findings and Project Methodology

October 2007

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Influenza pandemics in recent history have occurred in intervals of approximately 40 years, the most recent being 1968. Many experts believe that the next pandemic is imminent, with currently circulating H5N1 strains (“avian flu” or “bird flu”) representing a potential near-term threat. An outbreak of a virulent form of pandemic influenza could result in over 100 million deaths worldwide by some estimates. Vaccines represent an important opportunity among other global health interventions to reduce mortality and morbidity associated with such an outbreak. High-income countries are pursuing a range of strategies to provide their populations with access to pandemic influenza vaccines. However, providing global access to such vaccines, especially to those residing in lower-income countries, remains a true global challenge.

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1.) Executive Summary

This study was conducted by PATH and Oliver Wyman from January to June 2007. The overall objectives were two-fold:

- To develop strategies for increasing access to pandemic influenza vaccines among developing world populations (for use both before and during a pandemic).
- To identify and quantify potential investment opportunities for highest-priority strategies.

The study involved the following areas of evaluation:

1. Development of a current and future (5 to 10 year) global supply and demand picture.
 - For seasonal influenza vaccines.
 - For pandemic influenza vaccines.
2. Evaluation of current and planned vaccine technologies for influenza vaccine production.
 - Economics and operating characteristics (led by Oliver Wyman).
 - Clinical and other considerations (joint Oliver Wyman/PATH).
3. Identification of potential access strategies based on input from global stakeholders and evaluation of approaches taken by various governments.

The views represented in this paper are those of the authors. However, the study included close collaboration with the World Health Organization (WHO) and input from many key constituents from the influenza vaccine community. We would like to thank all of those individuals who dedicated their time to this effort as their input was invaluable.

Through the course of this effort, we obtained non-public information from various sources, including the vaccine manufacturers themselves. We are restricted from divulging some of this information based on non-disclosure agreements. Thus, we have either omitted or sufficiently obscured or aggregated such information in this report to adhere to these agreements.

Summary of Findings:

- The global need for a pandemic vaccine is large; high-income countries that have stated their intent to obtain pandemic vaccine access are pursuing strategies to provide universal coverage to their populations. Extrapolating a similar approach globally, the need represents approximately 13 billion doses (about 6.5 billion courses, assuming a two-dose course).
- Based on policies set by high-income countries and estimates from various outbreak scenarios, planning for availability of a pandemic vaccine should assume at most a six-month time horizon, and likely a shorter one. The horizon is defined as the time between WHO's declaration of an outbreak and the provision of vaccines to specific populations.
- Should an outbreak of pandemic influenza occur today, the doses available for global populations within this time frame would be well short of the need, given the state of preparedness and the level of existing capacity. Our estimate is that in a "best-case" scenario, only 1.2 billion courses (2.4 billion doses) could be produced from current capacity within six months, and current stockpiles are limited.

- Certain strategies would increase the amount of protection available to global populations over time through greater access to pandemic influenza vaccines. In addition, promising developments have begun to occur with respect to global capacity, technological innovation and global conviction to address the problem.
- The global community should distinguish between two time frames with respect to access strategies:
 - Short-term (i.e., next five years), which is limited by infrastructure and technology constraints that cannot be meaningfully altered in this time frame.
 - Longer-term (i.e., greater than five years), which has more relaxed constraints because new capacity can be created and more advantageous technologies may be available.

In our view, strategies suited to both the short-term and longer-term should be pursued in parallel to maximize protection for global populations. Pursuing one without the other would be an incomplete solution.

- In the short term, pre-pandemic measures will be required given the above-referenced shortfall in capacity relative to global need after an outbreak. Encouragingly, the overall supply and demand picture presents opportunities for pre-pandemic measures. Excess capacity (based on inactivated egg and cell-based technologies) already exists relative to seasonal demand, and that excess is projected to rise considerably as capacity grows faster than demand. Pre-pandemic use of this capacity could include stockpiling and pre-pandemic immunization of some populations based on the currently circulating H5N1 strains.
 - However, if this excess capacity is not used by pre-pandemic demand or other demand sources, it is reasonable to assume that this excess capacity will ultimately be rationalized by manufacturers (e.g., by closing older facilities). Thus, the time frame to utilize this excess capacity is limited.
- The proportion of the global population that can be protected in the short term from current H5N1 strains through these measures varies considerably, based on the following key factors: 1) production yields achievable for H5N1-based vaccines; 2) dosage requirements, including quantity of antigen per dose and number of doses; 3) broad access for all major influenza vaccine manufacturers to novel adjuvants that can be used to reduce vaccine dosage; and 4) the appropriateness and feasibility of pre-pandemic immunization, or conversely the opportunity to extend stockpile durations. In the best case scenario, it would take four years to satisfy the global need through pre-pandemic measures. In a worst case scenario, however, less than 20 percent of the global population would be covered by 2013. Considerable global coordination would be required to ensure that a best case is achieved.
- With respect to longer term strategies, newer technologies in development have the potential to make real-time access based on the actual pandemic strain (which could be H5 or other variants such as H2, H7, or H9) feasible and affordable for global populations. Live attenuated (egg or cell) technology (LAIV) has the potential to be the most economically viable, but recombinant technologies (proteins and Virus Like Particles) are also attractive. In particular, live attenuated vaccines may offer significant advantages relative to current technologies, such as improved facility efficiency (e.g., 60x

doses per unit of capacity), a one-dose course (versus two), and dropper-based administration that could be conducted by non-medically trained personnel. In other words, it could serve as a mass-campaign-oriented technology suitable for developing world populations, akin to oral polio vaccine. Given the potential productivity of these technologies, a modest investment in capacity could produce sufficient doses after the onset of an outbreak to cover global populations in an appropriate time frame (i.e., six months or less) after the onset of a pandemic. Vaccines based on these technologies could be produced (bulk and fill/finish costs) for less than \$0.25 per dose. However, since live attenuated pandemic vaccines pose a risk for recombination with wild type circulating influenza strains prior to the onset of a pandemic, widespread pre-pandemic vaccination campaigns would not be possible with this technology.

- In our view, efforts to accelerate further development of live attenuated and recombinant technologies are a global priority and studies are needed to demonstrate appropriate immunogenicity of these vaccines.
- Leveraging these technologies for real-time access in the longer term would require the creation of new bulk production facilities globally. We estimate that four to eight bulk production facilities using these technologies, located in the developing world, would be appropriate to balance investment requirements and risk diversification objectives. Use of these facilities during the pre-pandemic period would need to be addressed, and new seasonal programs in the developing world could serve that purpose.
- We estimate the investment requirements to implement both the short-term and long-term strategies to be in the \$2 to 10 billion range. This comprises upfront and ongoing costs, but does not incorporate an estimate of profit margins for commercial partners. Profit margins associated with these commercial arrangements would be determined by interactions with commercial partners.
- In addition to bulk manufacturing, preparations would need to be made in advance to secure the appropriate form/fill capacity, to make available effective adjuvants, and to stockpile appropriate delivery devices in advance of an outbreak. Additional investigation is required to select the appropriate delivery device – for example, an aerosol device for a LAIV vaccine may be cost prohibitive, but a nasal dropper may be more affordable.
- To successfully implement both the short-term and longer-term strategies, a number of issues need to be addressed in a concerted and coordinated way
 - Short-term strategies: facilitating novel adjuvant access to enable a “best case” scenario; establishment of product requirements and standards; establishment of commercial terms with suppliers; resolution of the suitability of pre-pandemic immunization and definition of the vaccination schedule
 - Longer-term strategies: accelerating development of LAIV and recombinant technologies for pandemic vaccine use; network design and distribution for bulk and finishing facilities; local supplier evaluation, selection, and potential technology transfer; and in-country logistics and administration planning
- Successfully addressing the access (i.e., supply-side) part of this problem is not sufficient. Countries must also prepare to administer the vaccine supplies that could be made available

through these access strategies. However, evaluating such programmatic issues and developing strategies to address them was beyond the scope of this effort.

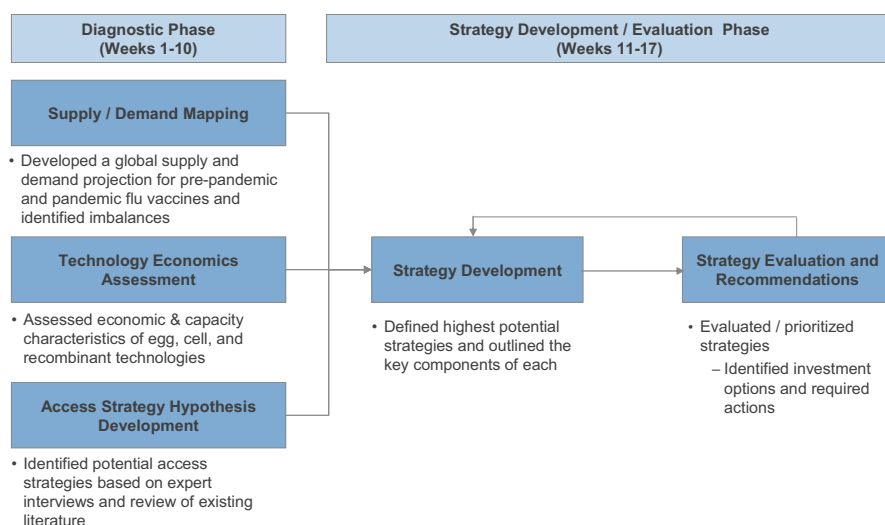
- Many organizations are working on individual pieces of this problem. Key stakeholders need to reach consensus on the holistic “answer” and then coordinate implementation and communication efforts.

We hope that this report makes a positive contribution to the global effort to increase access for pandemic influenza vaccines.

2.) Project Approach

This project was completed in two phases, as illustrated in Figure 1. The first Phase was a diagnostic and involved three sets of research and analysis: Supply/Demand Mapping, Technology Economics Assessment, and Access Strategy Hypothesis Development. The findings informed a second phase that involved Strategy Development, Evaluation and Recommendations.

Figure 1: Figure 1: Influenza vaccine strategies project phases.



2.1 Phase 1: Diagnostic Phase

The diagnostic phase comprised the following three sets of research and analysis activities, which were conducted in parallel.

2.1.1 Supply-Demand Mapping

The objectives of this component of the study were to develop a global supply and demand projection for seasonal and pandemic influenza vaccines and to identify excesses or shortages between supply and demand. These imbalances were estimated to determine whether there might be excess capacity for the developing world to access during the pre-pandemic period, and what magnitude of shortage might be expected during a pandemic outbreak.

Supply

To determine global influenza vaccine supply, we mapped the production and capacity characteristics of the 32 bulk manufacturing facilities globally that are currently approved to produce influenza vaccine. This provided a picture of the current capacity available to produce seasonal trivalent vaccine or monovalent pandemic vaccine, as the underlying infrastructure can be used for either product. We then identified manufacturers' plans to either expand existing bulk facilities or build new ones. Since the time frame for constructing and validating a vaccine

bulk production facility is typically five to seven years, this provided us with a robust picture of capacity through 2013.

This supply picture was developed through 1) secondary research, including manufacturer web sites, press releases, annual reports and analyst reports; 2) interviews with more than 40 experts in the areas of manufacturing processes, facility design and construction, and specific production technologies; and 3) direct discussions with current and prospective manufacturers of influenza vaccine. These manufacturers spanned the technologies evaluated in this effort and represent the majority of both current and expected future capacity (in doses and number of facilities).

While the physical infrastructure of a facility at any point in time is static, the number of doses that infrastructure can produce varies based on a number of parameters, such as the yields experienced in the process and the dosage requirement of the vaccine (will be discussed subsequently in greater detail). Therefore, we created a dynamic supply model that enabled variation in the levels of these key parameters universally or for individual facilities and assessed different production and output scenarios.

We also evaluated the fill/finish capacity associated with current seasonal influenza vaccines. However, unlike bulk production infrastructure, it is common for manufacturers to fill/finish multiple vaccines with the same capacity. Therefore, the global fill/finish capacity needed for pandemic influenza vaccine production were evaluated separately (as accessing fill/finish capacity being used for other vial-based drugs/vaccines is a possibility) in the context of specific access strategies, which are described in Section 5.

Demand

We projected global seasonal and pandemic demand under different scenarios and strategies utilizing a multi-step process. The first step was to build a global demographic data set based on the world's 187 countries, utilizing multiple databases to size the global population by country and sub-population (i.e., age, gender, health status, occupation). This data set formed the basis of all demand projections, which are based primarily on two key variables—assumed target sub-populations for vaccination and vaccine coverage levels by country—for both seasonal and pandemic vaccines.

The next step involved assessing historic seasonal vaccine coverage rates, based on research conducted by the Macroepidemiology of Influenza Vaccine (MIV) Study Group and additional expert interviews. These data were combined with the demographic data set to create estimates of the annual number of vaccine doses distributed, by country, from 1997 to 2003. The coverage rate trends observed in these historic data for 55 countries were then used to project seasonal influenza vaccine demand, by country, through 2016, based on various assumptions and scenarios described in Section 4.

Finally, we analyzed pandemic vaccine demand for different population/country groups, utilizing a range of scenarios (also described further in Section 4). The purpose was to determine the capacity required to serve the developing world under different coverage strategies. The intent was not to determine which specific countries or sub-populations should be immunized upon outbreak of a pandemic, which is a policy question for others to consider.

The output of this overall stream of analyses includes a dynamic demand model, which enables adjustments to key drivers (e.g., coverage rates, population targets) under different scenarios and strategies for seasonal and pandemic vaccines.

2.1.2 Technology Economics Assessment

The objective of this component of the study was to assess the economics and capacity characteristics of egg, cell, and recombinant technologies. These technologies were selected due to their higher likelihood of availability within the next 10 years, as candidates exist for these technologies in Phase II clinical trials or beyond. Other technologies with earlier stage candidates, such as universal proteins, viral vectors, and DNA vaccines, were not evaluated.

To assess the economics and capacity characteristics of each technology (e.g., how many doses could be produced in a given time frame), we first mapped the production processes and timing associated with manufacturing seasonal and pandemic influenza vaccines. We then identified the key production drivers (e.g., yields, dosage, location, and scale) and analyzed the main cost components of each process, including the variable costs of inputs, and labor and equipment required. We also assessed some of the non-economic characteristics of these technologies, such as clinical performance, appropriate sub-population segments for use, and overall viability and risks given current stage of development.

The data to support these analyses were gathered through: 1) secondary research, including manufacturer disclosures, medical journal trial reports, and articles that have been published about each technology; and 2) primary research, including direct discussions with the manufacturers/developers as well as “proximate research” with knowledgeable technical experts.

The output of this set of analyses is a dynamic technology economics tool that enables adjustments to key drivers (e.g., yields, cost of inputs) of the production economics across a range of technologies and products to derive estimates of output levels, manufacturing costs, and investment requirements at different production scale points and locations.

2.1.3 Access Strategy Hypothesis Development

The objective of this component of the study was to identify potential influenza vaccine access strategies to both guide the scope and focus of the other diagnostic activities, as well as the strategy development and evaluation process in Phase 2.

Sources for ideas on pandemic influenza vaccine access strategies included: 1) discussions with policymakers from high-income countries such as the U.S. and UK, which have been developing and implementing their own access strategies; 2) review of published pandemic preparedness reports from more than 60 countries, which provided insight on coverage strategies for sub-population groups being considered by countries; 3) consultation with developing country representatives and multilateral organizations; and 4) discussions with influenza vaccine manufacturers and developers.

The findings were combined with a synthesis of the implications from the supply/demand and technology economics diagnostic activities to develop potential access strategies.

2.2 Phase 2: Strategy Development, Evaluation, and Recommendations

The objectives of this phase were to identify the highest potential strategies for broad global access to pandemic influenza vaccines, and then to evaluate and prioritize strategies and identify the investment requirements and actions associated with each strategy.

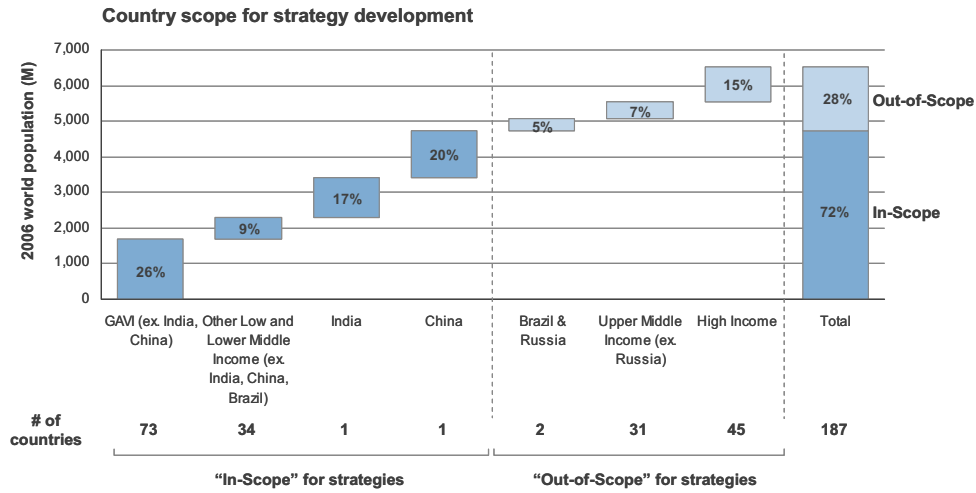
Developing, evaluating, and prioritizing these strategy alternatives involved a series of additional expert interviews; consultations with WHO and other key constituents; and additional analyses related primarily to specifics of certain technologies and ‘downstream’ considerations (e.g., syringe supply and fill/finish capacity).

2.3 Definitions

Throughout this document, several terms warrant clarification:

- **Vaccine courses (“courses”)**: A course represents the complete immunization regimen required to provide sufficient protection to an individual from either seasonal or pandemic influenza. For seasonal vaccines, a “course” is generally equivalent to a “dose” with the exception that young children require two doses per course. Therefore, as it relates to seasonal vaccine analyses in this document, “doses” are referenced in relation to supply and demand. For pandemic analyses in this document, all data are represented in “courses” because different technologies have different dosing requirements.
- **“Production” versus “capacity”**: “Production” refers to the number of doses/courses produced. In contrast, we define “capacity” as the expected output if facilities were run at maximum possible utilization (i.e., all year, with the exception of time for required maintenance). Most bulk facilities are currently underutilized (e.g., during Southern Hemisphere production schedule) and therefore “capacity” exceeds “production.”
- **“In-Scope” vs. “Out of Scope” countries**: The purpose of this effort was to develop access strategies for countries that are not currently well positioned to independently access pandemic vaccines. Therefore, we delineated countries in our analyses when sizing the demand for various access strategies. Countries considered ‘in scope’ for influenza vaccine access strategies included all low- and lower-middle-income countries based on World Bank Income Classification (including all GAVI-eligible countries). Those considered ‘out of scope’ for access strategies included all high- and upper-middle-income countries. Due to their size, India and China were generally considered ‘in-scope’ for strategies, but analyzed separately. Because they possess in-country vaccine manufacturing capabilities that could be used to serve their populations, Brazil and Russia were considered ‘out-of-scope’ for strategy development (see Figure 2).

Figure 2: Country classification for strategy development.



Source: "Country Classification" (World Bank website); GAVI Alliance website (as of January 2007).
 Note: World Bank classifies 208 countries into 4 income categories: High Income (>\$10,725 GNI/capita), Upper Middle Income (\$3,466-10,725 GNI/capita), Lower Middle Income (\$876-3,465 GNI/capita, Low Income (<\$876 GNI/capita).

3.) Technology Economics Assessment

This effort involved evaluating the economics of technologies available today or likely to be commercialized over the next 10 years. Our economic assessment consisted of three key steps:

- Description of each technology and associated production process.
- Assessment of the economics of each technology for seasonal vaccine production.
- Translation of the economics to potential pandemic production.

In addition, we identified important non-economic considerations (e.g., efficacy for different sub-populations) that will be discussed in Section 5.

3.1 Overview of Technologies

As seen in Figure 3, we considered three main technologies (egg-based, cell-culture, and recombinant), as well as several product variations for each (inactivated, inactivated using novel adjuvants, and live).

Figure 3: Set of technologies evaluated.

	Inactivated	Inactivated w/ Adjuvants	Live
Egg-based			
Cell-culture			
Recombinant			N/A

The following is a high-level description of each of the technologies, including the bulk production process, means of administration, and manufacturers with existing products or products in development.

Egg-based Inactivated

The upstream portion of the process consists of growing the virus in the allantoic fluid of hen eggs. After pre-incubation, the eggs are inoculated with the virus, incubated again (to allow infection to propagate), and harvested. The fluid subsequently undergoes several downstream purification steps. Initially the fluid is centrifuged and filtered to capture the desired antigen, remove any unwanted material, and concentrate the solution. Depending on the nature of the product, chemical agents may be introduced to disrupt the cell membrane, followed by size exclusion chromatography to help further purify the HA content (for split/sub-unit products). All

product variations then undergo an inactivation step where formaldehyde (or a similar agent) is added to kill the virus, followed by a final sterile filtration step to remove any remaining extraneous material and bacteria. The finished bulk is then formulated, filled, and packaged to be administered intramuscularly via syringe.

Cell-based Inactivated

Starting in roller flasks, host mammalian cells (e.g., Vero, MDCK, Per.C6) are placed into synthetic medium (note for microcarrier technology micro beads are also added) and the cells are gradually scaled up to the targeted fermenter size. Once desired cell density is reached in the final fermenter, the virus is introduced into the media to infect host cells. When propagation is complete the cells are harvested using centrifugation, and then a set of downstream steps similar to that described above for egg-based inactivated manufacturing is employed. A few additional steps exist to treat the host cell DNA which must be broken apart using chemical agents and then removed completely from the solution using additional purification steps. The finished bulk is then formulated, filled, and packaged to be administered intramuscularly via syringe.

Recombinant

Upstream production steps for recombinant proteins and VLPs (using baculovirus expression, the production platform for recombinant vaccines in furthest stages of development) are similar to mammalian cell. There are however a few major differences between the two systems. First, recombinant expression requires additional preparatory work related to the development of the initial seed strain (requires the development of an expression plasmid containing the target antigens). Second, antigen is expressed differently using baculovirus as compared to live virus; baculovirus infects cells which are in turn instructed to produce and secrete the desired antigen.

During downstream production the solution undergoes similar harvesting and filtration steps as inactivated mammalian cell, but splitting and inactivation are not required. Rather, the recovered antigen undergoes a series of column chromatographic steps to further purify the material. The solution is then passed through ultra filters and sterile filters to ensure all extraneous material and bacteria are removed. The finished bulk is then formulated, filled, and packaged to be administered intramuscularly via syringe.

Live Attenuated (Egg-Based and Cell-Culture-Based)

The production steps for live attenuated vaccines are similar to those of their respective inactivated processes (egg or cell-based). However, the reference strain is developed to be cold-adapted (i.e., so that the viral propagation is limited to the upper respiratory system). In addition, egg-based production for live attenuated vaccine currently requires the use of specific pathogen-free (SPF) eggs as opposed to the standard clean eggs used for inactivated vaccine (note this difference in consumables does not exist for cell-culture, in which the same medium is used for producing both live and inactivated vaccines). The major difference in downstream processes for live attenuated vaccines is that the antigen does not undergo either splitting or inactivation, but rather passes directly from initial filtration/centrifugation to sterile filtration. The finished bulk is then formulated, filled, and packaged to be administered via intranasal spray or drops.

Adjuvants

Adjuvants have been developed to improve both the efficacy and antigen-sparing nature of influenza vaccines. Thus far, the most commonly used adjuvant, alum, has proved relatively ineffective in both regards. Much effort has therefore been devoted by the major manufacturers and others to develop novel adjuvants that will better serve these objectives. For example, both Novartis and GlaxoSmithKline (GSK) have developed novel adjuvants that have demonstrated promising results. The manufacturing process for these oil-in-water emulsions require the combination of an oil and an aqueous phase using a homogenizer and then purification using a microfluidizer. The mixture is then filtered before formulation with final bulk.

See Figure 4 for a list of the manufacturers with licensed products or products in development for each technology.

Figure 4: Manufacturers across technologies.

	Seasonal		Pandemic	
	Licensed	In-development	Licensed	In-development
Egg Inactivated	<ul style="list-style-type: none"> CSL, GSK, Novartis, Sanofi, Solvay, and other smaller manufacturers (e.g., Berna Biotech) 	<ul style="list-style-type: none"> Most existing manufacturers are currently developing improved products Several emerging suppliers are attempting to enter the market 	<ul style="list-style-type: none"> GSK (with Alum), Novartis (with MF59), and Sanofi 	<ul style="list-style-type: none"> CSL (phase 2), GSK (phase 2 with AS03), Solvay (phase 1), and other smaller manufacturers (e.g., Berna Biotech)
Cell Inactivated	<ul style="list-style-type: none"> Solvay (MDCK – free suspension, Netherlands only) and Novartis (MDCK – free suspension) 	<ul style="list-style-type: none"> Nobilon (phase 1 in 2006 in MDCK), Sanofi (phase 1 in 2006 in Per.C6), GSK (pre-clinical in MDCK), and other small manufacturers (e.g., Vivalis / HepaLife (pre-clinical in embryonic chicken cells)) 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Baxter (start phase 3 in 2007, wild-type in Vero), Nobilon (phase 1 in 2006 in MDCK), Sanofi (phase 1 in 2006 in Per.C6), Solvay (started phase 1 in 2007 in MDCK), GSK (pre-clinical, MDCK), Novartis (Pre-clinical, MDCK), and other small manufacturers (e.g., Vivalis / HepaLife (pre-clinical in embryonic chicken cells)).
Recombinant	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Protein Sciences (to start phase 3 in 2007), Novavax (to start phase 1 in 2007), and others (e.g., Lentigen) 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Protein Sciences (pre-clinical) and Novavax (pre-clinical), and others
Live Attenuated	<ul style="list-style-type: none"> MedImmune (egg-based) and Products Immunologicals (egg-based) 	<ul style="list-style-type: none"> MedImmune (pre-clinical cell-based) and Nobilon (pre-clinical cell-based) 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> MedImmune (currently in phase 1 for both egg and cell), Nobilon (pre-clinical in cell), and Products Immunologicals (phase unknown egg-based)

Source: Oliver Wyman Analysis

3.2 Seasonal Economics

It is important to evaluate costs at the bulk production and finishing levels separately. Bulk manufacturing consists of all steps prior to formulation, and finishing consists of all remaining steps (from formulation to final packaging). The differences in bulk manufacturing described above lead to a wide variation in bulk costs. Variation in finishing costs is not technology-driven, but rather is affected by other factors. We will first review bulk manufacturing costs by technology and will then assess finishing costs cross-technology.

Bulk manufacturing cost differences can be evaluated at the highest level in two ways:

- **Cost per liter:** The cost to process a given number of liters of biologic material. For egg-based vaccines, liters are measured in terms of allantoic fluid, and for cell/recombinant in terms of fermentation broth. This cost figure represents the fully burdened production cost, comprised of material costs (e.g., medium cost, chromatography consumables), production labor, overhead (e.g., quality assurance/quality control, utilities), and facility costs (depreciated over 10 years). This is consistent with common accounting principles used in manufacturers’ financial disclosures.
- **Courses per liter:** The number of courses of the vaccine generated from each liter of biologic material. This metric is driven by the antigen yield from each liter [measured in terms of micrograms (ug) of HA for inactivated vaccines and number of infections for live vaccines], the required antigen dosage per strain, the number of strains per dose, and the number of doses in a full course.

3.2.1 Base Case Bulk Cost Estimate

As summarized in Figure 5, the doses per liter and cost per liter differ for each of the technology and product variations. We have indexed each of the cost drivers relative to the average Egg Inactivated vaccine (produced in a high-income country with approximately 600K liters of capacity in an eight-month production cycle). We assume that all facilities are fully utilized with the exception of required downtime for maintenance. These estimates exclude the cost of manufacturing the adjuvants, but our estimates suggest that the adjuvant costs are negligible relative to the bulk cost (for the adjuvants currently being explored for flu vaccines).

Figure 5: Seasonal cost driver summary (columns indexed to egg inactivated at 1,000¹)

Technology	Cost per liter	Doses per liter	Bulk cost per dose
Egg Inactivated	1,000	1,000	1,000
Egg Inactivated w/ Adj.	1,000	7,600	130
Egg Live	2,300	58,000	30
Cell Inactivated	740	450	1,750
Cell Inactivated w/ Adj.	740	3,300	210
Cell Live	740	25,000	30
Recombinant	710	450 – 3,600	1,510 – 200
Recombinant w. Adj.	710	10,000 – 87,000	70 – 10

Source: Oliver Wyman Analysis

¹ Indexing (in this case to 1,000) allows us to display metrics for other technologies relative to the egg inactivated vaccine level. For example, Egg Inactivated with an Adjuvant exhibits the same cost per liter as Egg Inactivated, but doses per liter are 7.6 times higher, resulting in a bulk cost per course that is 87% lower (870 divided by 1,000)

Egg-based inactivated with adjuvant: While the cost per liter remains the same, novel adjuvants have the potential to considerably increase the doses per liter achieved by reducing the dosage requirement. As novel adjuvants are only beginning to be evaluated for incorporation into seasonal products, we used benchmarks from pandemic vaccines in development to infer a potential impact on seasonal dosage. These benchmarks suggest a dosage level per strain from <.1ug to ~4ug, with a midpoint of 1.9ug. This represents an eightfold increase in doses per liter relative to a non-adjuvanted, inactivated vaccine.

Egg-based live: The cost per liter for live products is ~2.5 times greater than egg-based inactivated costs. While labor, overhead, and facility costs are lower due to the removal of several downstream processing steps, the egg costs are almost quadruple given the current requirement of using SPF eggs. WHO is leading an evaluation of whether clean eggs can be substituted for SPF eggs, but currently this requirement remains in place. The doses-per-liter level achieved, however, are ~60 times that of egg-based inactivated due to a significantly reduced dosage requirement. Relatively few infections (and therefore low dosage) are needed since the virus continues to replicate in the nose following administration of the vaccine.

Cell-based inactivated: In this analysis, we have assumed a free suspension-based cell system, which is expected to account for the greatest proportion of cell-based capacity. While free suspension has the potential to be the lowest cost among cell-based systems, it still costs at least 50 percent more than egg-based inactivated vaccine. While the cost per liter is lower (since medium cost is below egg costs), the number of doses per liter is also lower given expected yields in the process.

Cell-based inactivated with adjuvant: The impact of using novel adjuvants for cell-based technology is similar to the impact for egg-based. Cost per liter remains the same, but the doses per liter are projected to increase eightfold.

Cell-based live: The impact of cell-based live vaccine is comparable to the effect described above for egg-based live vaccines.

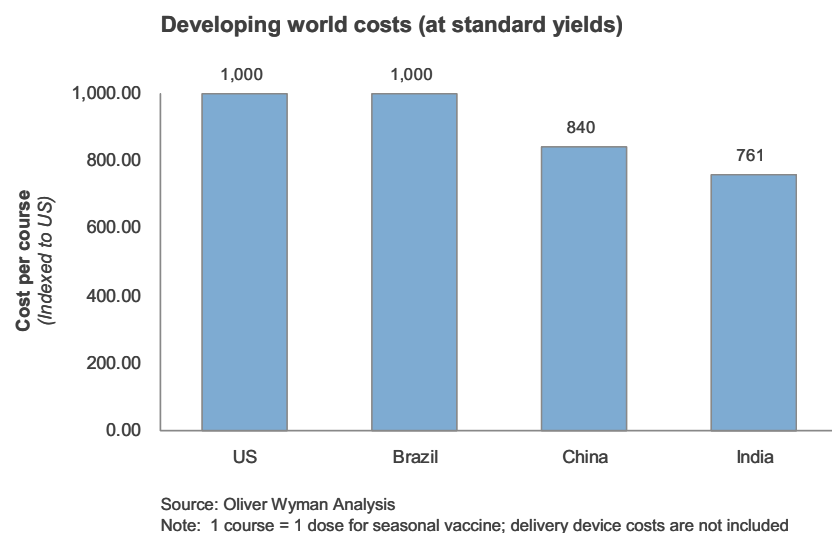
Recombinant: For recombinants, we must evaluate both the experience of current developers as well as analogies from other recombinant systems to infer the potential productivity and cost structure of this technology. In general, the cost per liter should be relatively comparable to cell-based systems. However, doses per liter could be characterized by a large range—anywhere from levels comparable to current cell-based systems to a ~10-fold improvement, based in large part on yields achieved in the process. Note that the most studied current influenza recombinant vaccine has dosage levels of 135ug, versus 45ug for traditional egg-based and cell-based inactivated vaccines. Achieving the high-end of the potential yield range and lower dosage could reduce the cost to similar levels as live.

Recombinant with adjuvant: Assuming that adjuvants can have a similar impact on recombinant technologies (reducing dosage levels to 1.9ug per strain), cost per liter will remain the same, but doses per liter will increase considerably. Please note that no such vaccines are currently in development.

3.2.2 Impact of Location and Scale on Bulk Production

Unlike some other vaccines, location does not have a major impact on manufacturing costs for influenza vaccines. Location is meaningful for vaccines in which labor represents a large portion of the cost structure since costs can then be reduced by manufacturing in low labor-rate locations. However, for influenza vaccine production, labor represents a minority portion of the cost structure across the technologies evaluated. In fact, for egg-based manufacturing, the impact of location is even smaller since clean eggs (~50 percent of the cost structure) are more expensive in many developing countries due to higher agricultural feed costs. As shown in Figure 6, the difference in manufacturing costs for egg-based production between the U.S. and India is only ~20 percent. Of course, this gap in absolute terms becomes even smaller for lower-cost vaccines.

Figure 6: Bulk indexed cost sensitivity to location.



Scale also has a minimal impact on manufacturing costs for influenza vaccines for two reasons. First, materials represent 40 to 50 percent of the cost structure and cannot be reduced by increasing the size of the facility—each incremental liter processed requires a proportional increase in material usage (egg or medium) and associated costs. Second, machine size (e.g., inoculator/harvester speed and cell fermenter size) reaches a constraint at 30 to 50M doses of annual output for most of the technologies. Below that level, scale has a more meaningful impact as the size of the machine can be increased with only a marginal increase in labor and equipment costs. However, as most of the existing manufacturers are above that point, increasing capacity requires adding machines, which offers a much lower degree of scale benefit.

3.2.3 Finishing Costs for Developing World Formulations

As we did with bulk costs, we first established a base case estimate for finishing costs and then analyzed the sensitivity to several key parameters. While this does not have a major bearing on technology choice, these economics were incorporated into our overall assessment of spending and investment requirements to implement the recommendations described in Section 5.

This base case assumed that the vaccine is formulated, filled, and packaged in a facility of average size and configuration globally (one high-speed, 30K vial-per-hour line operating three

shifts). In addition we have assumed that this facility would be located in a high-income country and the product would be filled in 10-dose vials. Given this configuration, the cost per dose would be quite low, with materials representing half the cost, and production labor, facilities, and overhead accounting for the remainder. The material costs are comprised of vials, stoppers, caps, labels and basic packaging.

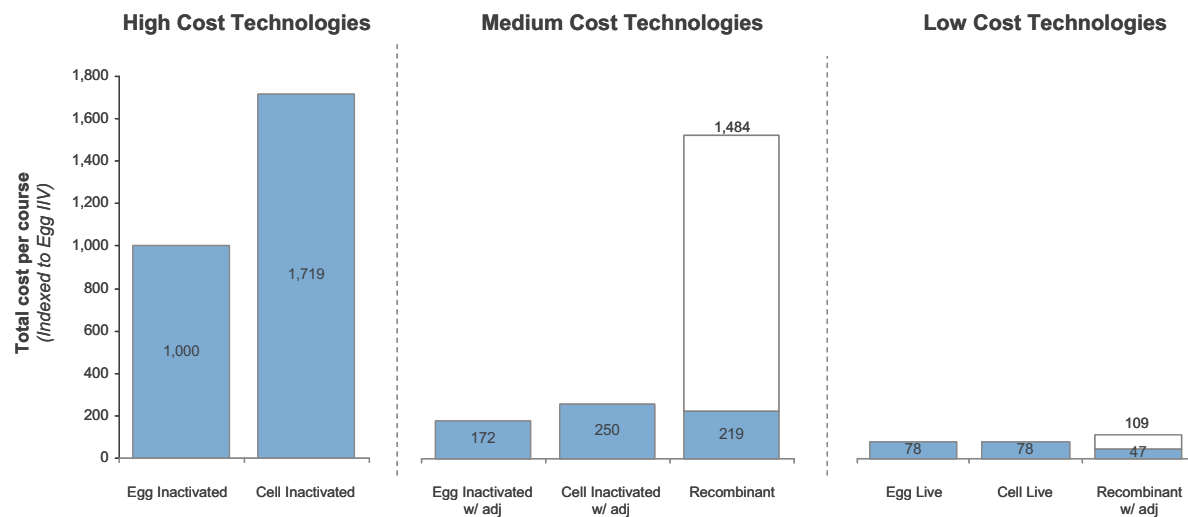
Our estimate for fill/finish costs is different than cost levels experienced by many of the current manufacturers of seasonal influenza vaccines—finishing costs are 10-fold to 30-fold of our estimate for those manufacturers. These manufacturers have made operating choices and formulation decisions for high-income markets, which are quite different than choices that would be made for developing world markets. The majority of existing seasonal vaccine is filled in single-dose vials, manufacturers use additional primary packaging for high-income markets (box and label around the vial) and some manufacturers operate fewer than three shifts. Our base-case assumptions seem reasonable for developing world populations as the presentation level we assume (10-dose vials) is consistent with other developing world vaccines. At high volumes one would expect these vaccines to be produced in large facilities operating three shifts (especially in a pandemic situation).

3.2.4 Total Manufacturing Costs—Seasonal

Figure 7 summarizes the total cost for each of the technologies, including finishing costs. The technologies are grouped in three segments based on their total cost:

- High-cost: egg-based and cell-based inactivated.
- Medium-cost: egg-based and cell-based with use of novel adjuvants and recombinant.
- Low-cost: egg-based and cell-based live, recombinant with the use of novel adjuvants.

Figure 7: Total seasonal cost summary (indexed to egg inactivated at 1,000).



Source: Oliver Wyman Analysis
 Note: 1 course = 1 dose for seasonal vaccine; delivery device costs are not included

3.3 *Pandemic Economics*

To translate seasonal costs into potential pandemic costs, we need to assess how the key drivers of bulk and finishing costs may change.

3.3.1 *Bulk Cost & Courses Per Liter*

The cost per liter should remain the same for cell-based and recombinant technologies, as the underlying facilities and materials are the same to produce a pandemic vaccine as they are to produce a seasonal vaccine. However, we have assumed that the cost per liter for egg-based inactivated products increases given the need to bio-secure the flocks that produce the eggs. The cost of bio-secured eggs is expected to be approximately triple that of clean eggs (i.e., similar to the cost of SPF eggs), resulting in an overall doubling of cost per liter.

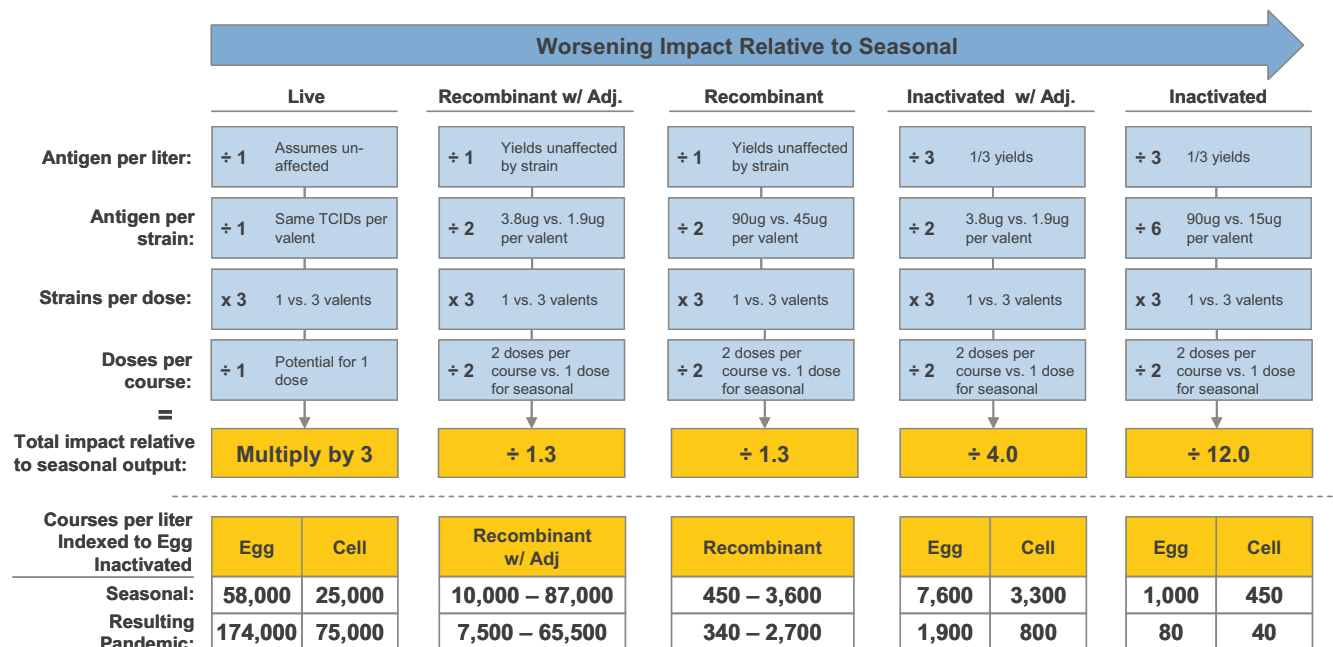
Bulk courses per liter differ considerably from seasonal production and vary by technology. To evaluate the potential change, we must analyze the factors that affect courses per liter: antigen yield per liter, required antigen dosage per strain, the number of strains per dose, and the number of doses per course. We will use manufacturers' experiences with H5N1 as a proxy for a pandemic product, even though the pandemic may actually be associated with another strain.

For example, for egg-based inactivated vaccines, the pandemic courses per liter are one-twelfth that of seasonal production driven by the following factors:

- Antigen yield per liter: Expected to be approximately 1/3 that of seasonal production. Over the last several years of experimenting with H5N1, manufacturers have seen yields range from an initial level of ~10 percent of seasonal up to ~80 percent, with an average of ~1/3 of seasonal. For a new strain, it seems appropriate to assume yields at 1/3 seasonal levels as sufficient time may not be available to optimize yields.
- Required antigen per strain: Expected to be six times that of seasonal given Sanofi's Pasteur's approved 90ug dosage without the use of adjuvants.
- Number of strains: Assumed to be 1/3 that of seasonal given a pandemic monovalent product (versus the seasonal trivalent).
- Number of doses per course: Expected to be two times that of seasonal as two doses are required to achieve sufficient immunogenic response (given lack of prior exposure to a pandemic strain) as compared with one dose for current seasonal vaccines.

Figure 8 summarizes the translation of courses per liter for each of the technologies considered. In summary, the variation in courses per liter between the high-cost and low-cost technologies only increases. Inactivated products (already highest cost) have the largest reduction in courses per liter, recombinant products remain the same (medium cost) and courses per liter actually increase for live products (already lowest cost). Please note on possible exception, which is that at least one manufacturer is exploring a cell-based, inactivated wild-type vaccine (non-adjuvanted) with dosage requirements and corresponding courses per liter that more closely resemble levels associated with adjuvanted inactivated products. Unlike inactivated products, the yields are expected to remain at least constant for live vaccines, the dosage is expected to remain the same, and potential exists to use a single dose.

Figure 8: Pandemic courses per liter translation (indexed to seasonal egg inactivated at 1,000)



Source: Oliver Wyman Analysis
 Assumptions: Pandemic strain is H5N1 (impacts output of each technology)

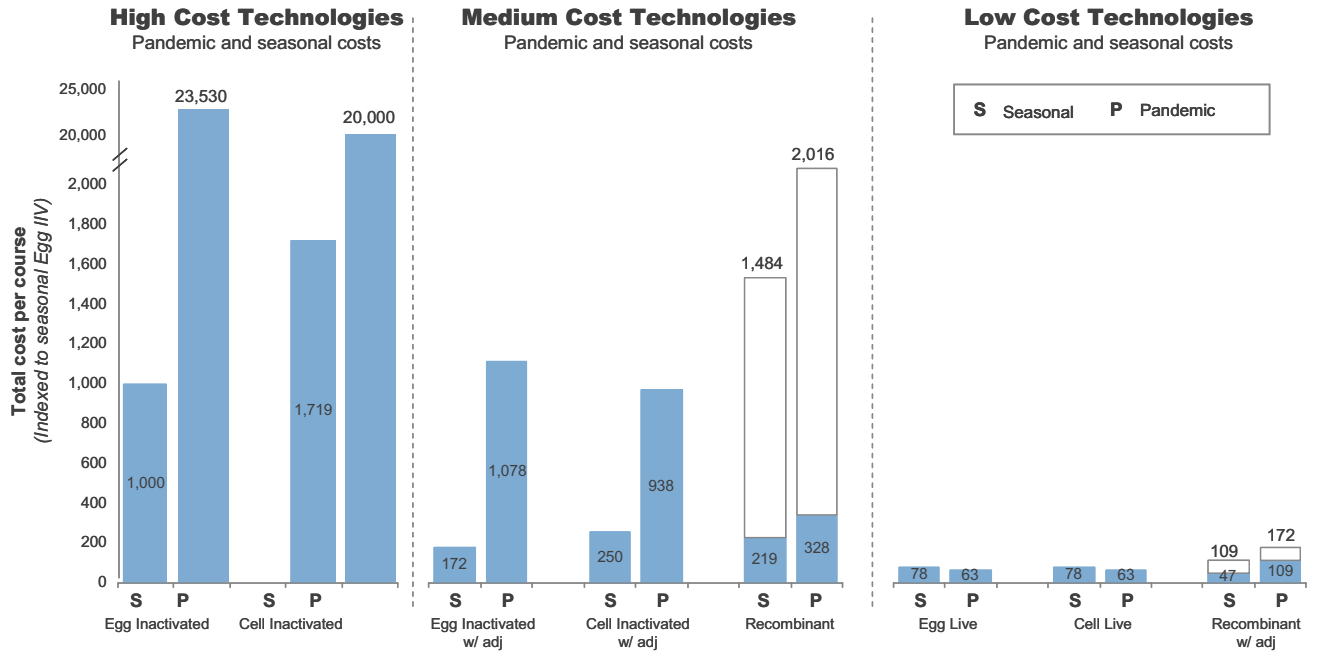
3.3.2 Finishing Costs

The finishing cost per dose is assumed to be the same for seasonal and pandemic products (given that similar facility configurations and presentation would be applied). However, the cost per course is different for pandemic vaccines because all of the technologies with the exception of live are expected to require two doses.

3.3.3 Total Manufacturing Costs—Pandemic

Figure 9 summarizes the total indexed cost per course for each technology. In summary, variation in the cost profile across technologies is even more significant. The high-cost technologies (egg-based and cell-based inactivated, and recombinant with current yields) become even more expensive. Pandemic vaccine costs for medium-cost technologies more closely resemble seasonal levels. Egg-based and cell-based with the use of novel adjuvants become moderately expensive for pandemic, while recombinant only increases slightly. All of the low-cost technologies (egg-based and cell-based live, recombinant with the use of novel adjuvants) remain low-cost.

Figure 9: Total pandemic cost summary (indexed to seasonal egg inactivated at 1,000).



Source: Oliver Wyman Analysis

Note: 1 course = 1 dose for seasonal vaccine; delivery device costs are not included; pandemic strain is assumed to be H5N1

4.) Supply-Demand Map

We now turn to supply and demand scenarios for pandemic vaccine. We have evaluated two scenarios in this analysis:

- Pre-pandemic: Production of pandemic vaccine prior to the onset of a pandemic for stockpiling or pre-pandemic immunization, using excess capacity for seasonal influenza vaccines
- Real-time access: Production of the pandemic strain upon outbreak, using all available capacity at that time (i.e., assuming production of seasonal vaccines would cease)

4.1 Pre-Pandemic Supply and Demand

First, we consider production and capacity of seasonal influenza vaccine and compare that to current and projected demand for seasonal influenza vaccine globally to determine excess capacity that may be available for pandemic vaccine production prior to a pandemic outbreak.

4.1.1 Seasonal Supply Base and Levels

Current Supply Base

Currently, there are 26 manufacturers with influenza vaccine capacity, but four manufacturers represent the majority of current influenza vaccine production and capacity: Novartis, GSK, Sanofi Pasteur, and MedImmune. Bulk manufacturing facilities across these manufacturers are located in the U.S., Canada, UK, Germany, France, and Italy. Other producers include Solvay, CSL, Denka Seiken, and Products Immunologicals; production facilities for these manufacturers are located in Europe, Australia, Japan, and Russia. Finally, there are a number of manufacturers in China that produce vaccine for the local Chinese market.

Current Production

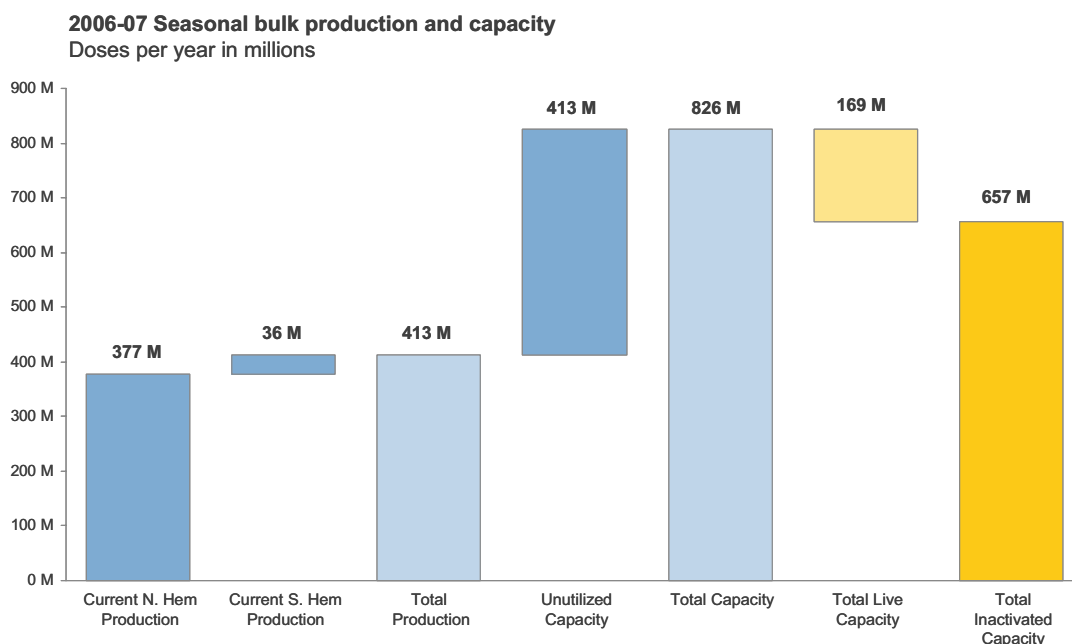
For the 2006-2007 influenza season, there were approximately 413 million doses of seasonal influenza vaccine produced, 407 million of which are inactivated and 6 million of which were live attenuated. Approximately 377 million of these doses are used in Northern Hemisphere countries, with the remaining 36 million doses used in Southern Hemisphere countries. This distinction is significant, as time frames for production between hemispheres are different.

Current Capacity

As illustrated in Figure 10, the current global capacity of approximately 826 million seasonal influenza vaccine doses (inactivated and live) is double the current production of 413 million doses. In addition, global capacity for inactivated influenza vaccines of approximately 657 million doses is ~60 percent greater than current production of 407 million doses. The primary factor contributing to this inactivated capacity excess is that most manufacturers currently produce bulk antigen for 8 to 9 months of the year, relative to a possible 11 months given one month of required maintenance down time. This largely stems from the fact that most manufacturers only serve Northern Hemisphere markets, for which all bulk production needs to occur during an 8-month time frame (starting with WHO strain identification in January and ending in August, when fill/finish activities must begin in order to ship doses in time for the influenza season). Note that this excess could be made available for Southern Hemisphere seasonal demand or pre-pandemic demand (e.g., stockpiling) primarily (i.e., capacity for these

manufacturers as it relates to serving Northern Hemisphere demand is highly utilized)—unless manufacturers further speculate on next season’s strains.

Figure 10: Bulk production and capacity.



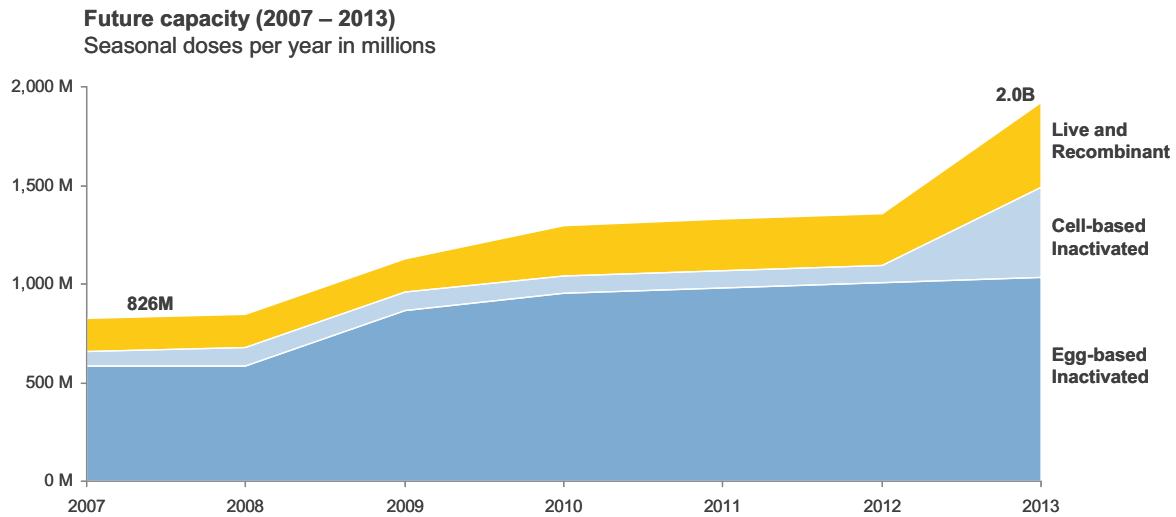
Source: Oliver Wyman Analysis; expert interviews; company statements; UBS Report: "Flu Vaccine Capacity Outstripping Demand" – Nov. 2006
Note: Doses generally equivalent to courses (1 dose / person = 1 course, except for young children, for whom 2 doses = 1 course); assumes trivalent vaccine (15ug per valent per course).

Projected Capacity

Based on manufacturers’ disclosed expansion plans, influenza vaccine capacity is expected to more than double by 2013, reaching 2B doses globally, of which 1.5B will be inactivated (see Figure 11). This growth will come from several sources:

1. Sanofi and GSK are either expanding current egg-based production facilities or constructing new ones. This additional capacity is expected to be available in the 2009 time frame.
2. Other manufacturers located primarily in emerging markets, such as Institute Butantan and Sinovac, are adding egg-based capacity. This new capacity will come online between 2008 and 2013.
3. Novartis and GSK each have a new cell-based manufacturing facility in the later stages of construction and validation. In addition, five new cell-based manufacturing facilities in the U.S. are expected in response to the U.S. government’s pandemic contracts. These facilities are expected to come on line in 2012 and 2013.

Figure 11: Expected capacity growth by technology.

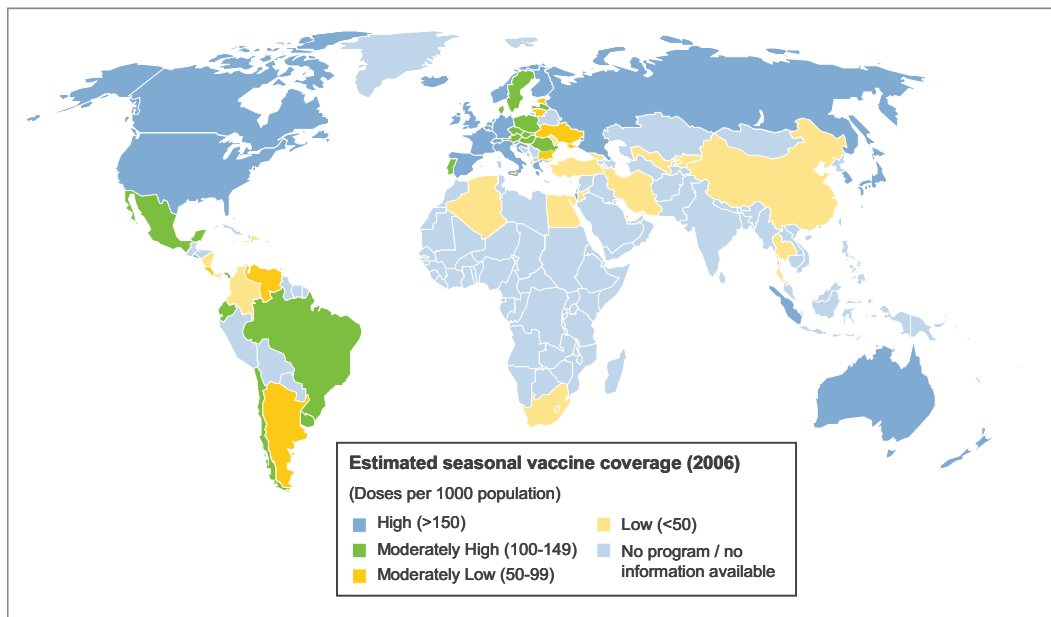


Source: Oliver Wyman Analysis; expert interviews; company statements; UBS Report: "Flu Vaccine Capacity Outstripping Demand" – Nov. 2006
 Note: Doses generally equivalent to courses (1 dose / person = 1 course, except for young children, for whom 2 doses = 1 course); assumes trivalent vaccine (15ug per valent per course).

4.1.2 Seasonal Influenza Vaccine Demand

Not surprisingly, seasonal influenza vaccine coverage rates are highest among high- and upper-middle-income countries (see Figure 12). In fact, only 20 'in-scope' countries are believed to have vaccination programs for seasonal influenza as of 2006 and, among these countries, average estimated coverage in 2006 is low (~25 doses/1000 population).

Figure 12: Current global coverage map.



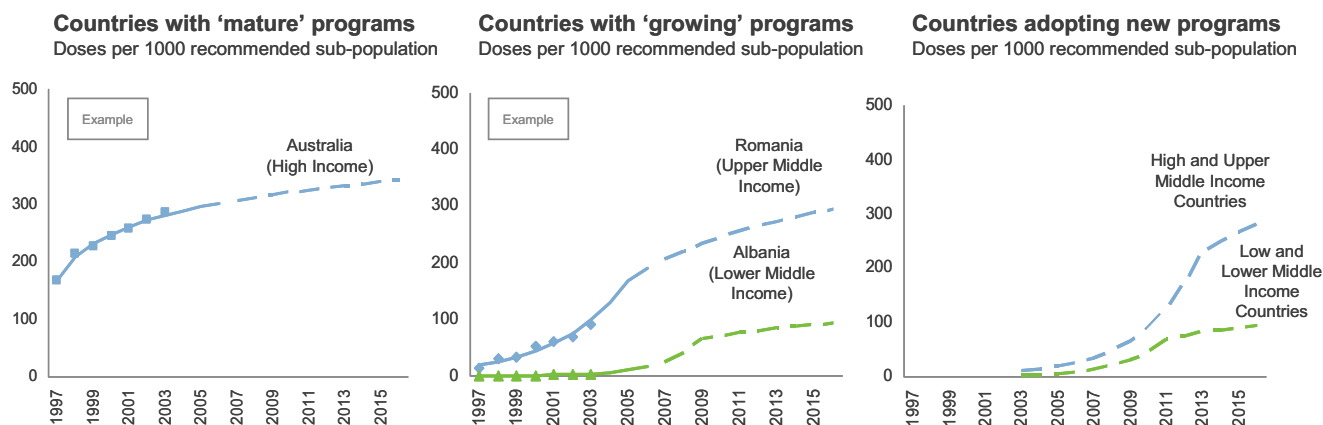
Source: Macroepidemiology of Influenza Vaccination (MIV) Study Group; PAHO

Applying historic coverage rate trends to country population sizes, we estimate that global seasonal influenza vaccine distribution grew from 160M doses to 310M between 1997 and 2003, representing a 12 percent compound annual growth rate.

Projected Seasonal Demand (Base Case)

Our base case estimate of seasonal demand is based on an extrapolation of historic demand trends by country. Strong time-series patterns (R-Squared of $>.80$ in ~ 80 percent of the countries) were identified in historic coverage levels and segmented into two groups of countries: those with ‘mature’ programs characterized by plateaus in coverage growth rates and those with ‘growing’ programs characterized by accelerating coverage growth rates. As illustrated in Figure 13, these patterns were used to project future coverage levels for all countries with existing programs, and for those assumed to adopt new programs in the coming years. Future coverage rates within each country with a ‘mature’ program were projected based on that country’s historic trajectory. For countries with ‘growing’ programs and all countries assumed to introduce new programs in the future, average aggregate coverage rate growth curves were derived based on observations from historic patterns among high-/upper-middle-income countries and low-/lower-middle-income countries.

Figure 13: Historic seasonal influenza vaccine demand trends.



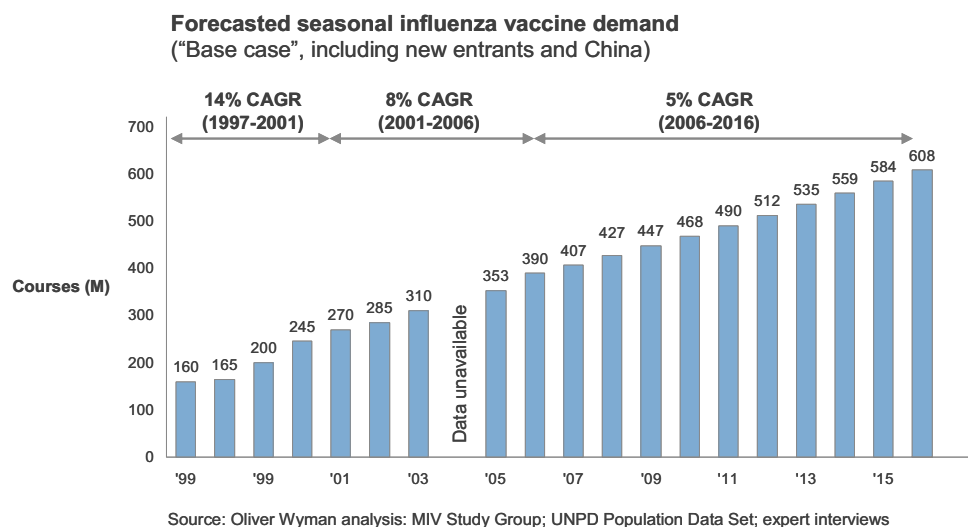
Source: Oliver Wyman analysis; MIV Study Group; UNPD Population Data Set; CDC
 Note: Doses generally equivalent to courses (1 dose / person = 1 course, except for young children, for whom 2 doses = 1 course).

Overall, we project seasonal influenza vaccine demand growth to continue, but to level off in the coming decade. As seen in Figure 14, we estimate that historic demand growth has slowed in recent years and project that this growth rate decline will continue over the next decade (from a compound annual growth rate of 14 percent from 1997-2001 to 8 percent in 2001-2006 to 5 percent from 2006-2016). We see several reasons for this expected slowing in the growth of seasonal influenza vaccine demand. First, high- and upper-middle-income countries’ programs are maturing and therefore the growth in their demand is slowing down. In addition, there are relatively few of these high-/upper-middle-income countries that have yet to introduce new programs.

Further, it is assumed that additional ‘in-scope’ countries will not introduce new programs without assistance, due to the significant challenges of launching and expanding these programs. These challenges include:

- Unknown seasonal influenza disease burden, particularly in the developing world.
- Minimal vaccination infrastructure in place beyond EPI programs, making it difficult to reach sub-populations other than infants.
- Financial and programmatic burden, given the annual administration requirements.
- Other competing demands for health resources.

Figure 14: Projected base case seasonal influenza vaccine demand²

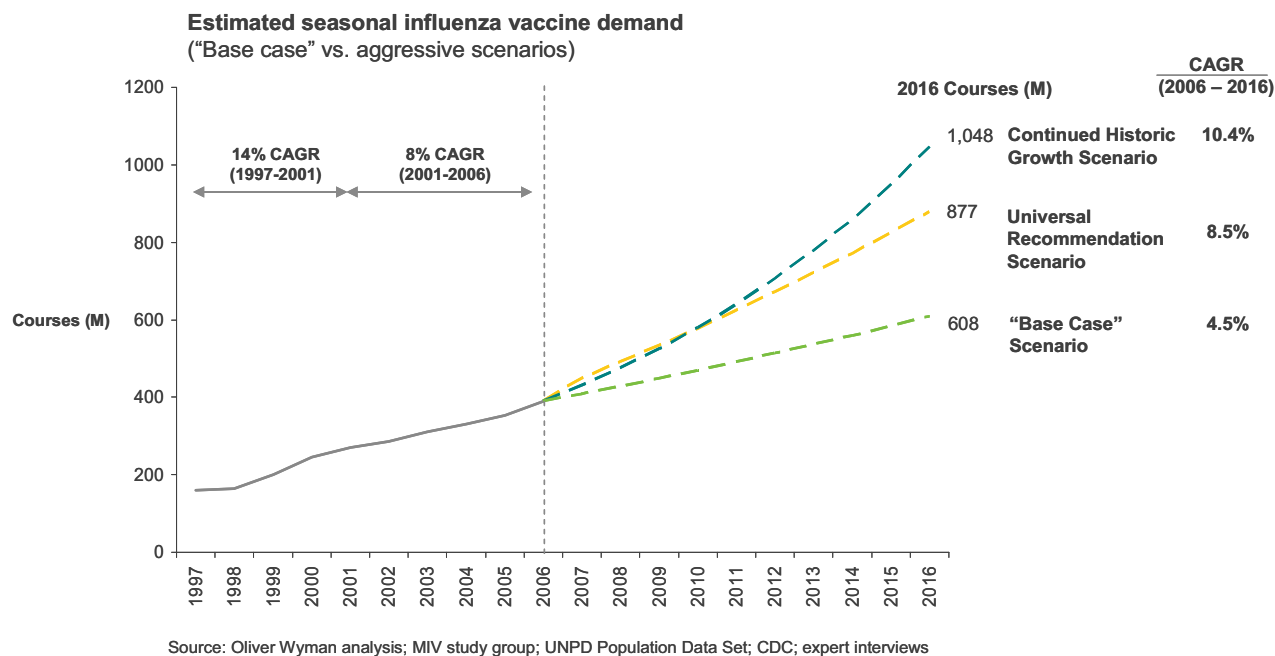


Aggressive Projections—Seasonal Demand Scenarios

In order to create conservative estimates of excess capacity, we also developed two more aggressive demand projections. The first of these is a A “Universal Recommendation” scenario, which is loosely based on the United States’ “Healthy People 2010” goals. In this scenario, we assume that all “mature” countries reach these goals. We believe this scenario is aggressive—for example, it would represent a near-doubling of the current 28 percent overall population coverage in the U.S. In the second, even more aggressive scenario, aggregate historic growth rates of ~10 percent are assumed to continue over the next decade. The demand projections from these scenarios are shown in Figure 15.

² CAGR stands for “Compound Annual Growth Rate”

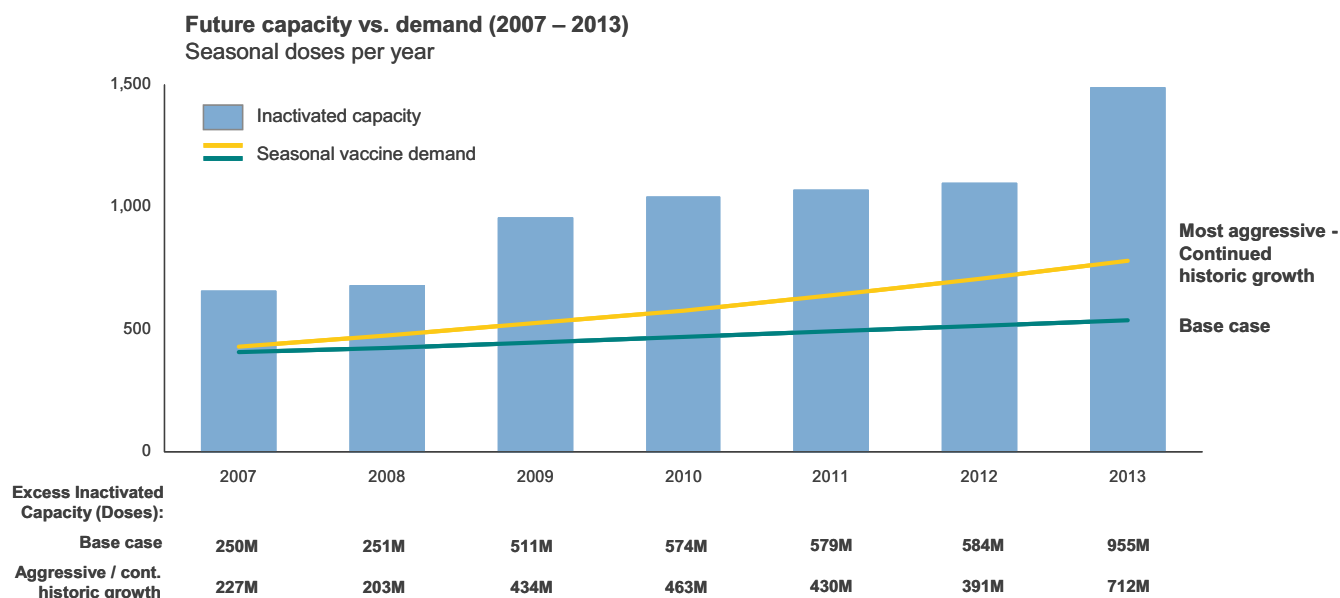
Figure 15: Base case vs. aggressive seasonal influenza vaccine demand projection.



4.1.3 Seasonal Excess Inactivated Capacity

For the 2006-2007 season, we estimate inactivated vaccine capacity exceeded demand for inactivated vaccines by 250 million doses (i.e., 657 million doses of capacity versus 407 million doses of demand). Going forward, we forecast this excess capacity for inactivated vaccines to grow. As illustrated in Figure 16, even under the most aggressive demand assumptions (i.e., a continuation of a historic 10 percent annual growth rate), expected inactivated capacity will exceed demand by approximately 710 million doses in 2013. Even more dramatically, if demand grows according to the 'base case' projections, manufacturers' excess capacity will exceed 950 million doses in 2013. These estimates assume that newer technologies such as live and recombinant do not capture any of the incremental demand (which is conservative). More likely, capacity for these technologies, particularly live attenuated, will absorb some of this demand, meaning that excess inactivated vaccine capacity will be even larger (as much as an additional 500 million doses, which is the expected capacity for newer technologies by 2013).

Figure 16: Overall seasonal supply-demand map—inactivated capacity and demand only.



Source: Oliver Wyman Analysis; expert interviews; company statements; UBS Report: "Flu Vaccine Capacity Outstripping Demand;" MIV Study Group; UNPD Population Data Set

As cited previously, some level of excess capacity is inevitable due to the imbalance between northern and southern hemisphere demand. Nonetheless, it is reasonable to ask why market forces would allow for such an imbalance of supply and demand over time. There are several explanations for this specific situation. First, the U.S. government is affecting the market for seasonal supply to create surge capacity in a pandemic situation. This policy has taken the form of direct subsidies to manufacturers to create excess capacity. Second, the picture above is at a macro level, whereas individual manufacturers have their own objectives and strategies to maximize individual market share. Third, vaccine manufacturing is highly inflexible—capacity takes many years to put in place, regulatory requirements and oversight are significant, and units of capacity exist in large discrete pieces (i.e., a manufacturer must shut down an entire facility to reduce capacity, which may represent half or all of its available capacity). Thus, while capacity over the long term should be balanced with demand, in the short term and medium term significant positive and negative imbalances can exist.

Notwithstanding these explanations, it is reasonable to assume that manufacturers with significantly underutilized assets will reduce capacity over time to better match their individual demand levels. Of particular significance will be the start-up of new cell-based facilities, which could trigger a shut-down of older, egg-based facilities if sufficient demand does not exist. Therefore, the ongoing availability of this capacity will likely require some alternative use, perhaps serving pre-pandemic influenza vaccine demand or demand for other vaccines or biopharmaceuticals that can be produced with this infrastructure.

4.1.4 Pre-Pandemic Supply and Demand

To determine how many pandemic courses can be produced using this excess capacity, we must translate capacity expressed in seasonal terms to pandemic terms. We have isolated inactivated capacity, as live attenuated and recombinant technologies are not yet sufficiently developed for

pandemic vaccines. To estimate excess capacity in pandemic terms, we made a series of “base case” assumptions regarding the key translational factors, which are as follows:

- All current inactivated egg-based technologies and associated production facilities are available to produce pandemic vaccine; the existing GMP-approved cell-based facilities without widely licensed products, however, are not available to produce pandemic vaccine.
- All future inactivated egg-based and cell-based facilities are available to produce pandemic vaccines when those facilities have licensed products.
- Production yields will be 1/3 of the levels associated with current seasonal vaccine, as described in Section 3.
- Manufacturers who have developed novel adjuvants will use them to minimize dosage levels and thereby increase the amount of effective doses that can be produced in a given time frame; GSK and Novartis are in advanced stages of clinical development with candidates at the following dosage levels:
 - GSK course = 3.8ug x 2 doses.
 - Novartis course = 7.5ug x 2 doses.
- All inactivated-product manufacturers without access to novel adjuvants use alum to also reduce their dosage requirements; as context, Sanofi’s recently licensed H5N1 vaccine is approved at 90ug per dose, but it is testing a reduced dosage candidate with alum:
 - Inactivated course = 30ug x 2 doses.
- Stockpiles would need to be regenerated every two years (the commonly believed shelf-life); this assumes that stockpiles are generated, but only administered in the event of an outbreak (i.e., doses are disposed of following expiration).

In contrast, we developed a more ‘aggressive case,’ for which the following different assumptions were made:

- Existing GMP-approved cell-based facilities (for Baxter and Solvay) are available for pandemic production even though they currently do not have widely licensed products.
- Production yields reach 80 percent of current seasonal vaccine levels. It is our understanding that this is feasible, and with time for process development and collaboration among manufacturers this may be broadly achievable.
- GSK/Novartis provide access for proprietary adjuvants to all inactivated-product manufacturers, and other manufacturers successfully refine their products with lower dosage levels. Alternatively, other manufacturers successfully develop and incorporate their own adjuvants:
 - Inactivated course = 3.8ug x 2 doses.
- Stockpiles do not need to be regenerated; prior to expiration, the vaccine would be administered to individuals in the pre-pandemic period, or stockpile durations can be extended significantly.

In addition, we must make estimates for high- and upper-middle-income country demand for pre-pandemic products, to determine the remaining capacity that may be available for other countries. To date, a number of governments have announced their intentions to stockpile doses of pre-pandemic vaccine for their populations, with coverage ranging from protection of 1 percent to 100 percent of their populations. However, we are aware of active discussions with various countries for additional stockpiling. As pre-pandemic products continue to be successfully

developed and dosage requirements are reduced through the use of adjuvants, we expect coverage targets to increase. Therefore, for demand planning purposes, it is reasonable to assume 100 percent coverage in these countries in planning for excess capacity that might be available to serve the pre-pandemic needs of broader global populations.

As seen in Figure 17, the opportunity for pre-pandemic measures to be a means for broad global protection is mixed. Under our base case assumptions for pre-pandemic capacity, a stockpile could be generated that totals ~110 million courses in 2008 and rises to nearly 970 million courses by 2013. However, this is small relative to potential demand in high- and upper-middle-income countries of 1.8 billion and 1.9 billion courses in those years, respectively. In this scenario, the capacity available for other countries is likely to be limited. Under our aggressive case assumptions, however, pre-pandemic coverage would be 1.2B courses in 2008, rising to 9.0B courses cumulatively produced by 2011. This exceeds global need across all countries.

Figure 17: Base case and aggressive scenarios for 2007 to 2013 (cumulative courses).

Cumulative H5N1 Courses		
Year	Base Case	Aggressive Case
2008	111 M	1.2 B
2009	389 M	3.6 B
2010	623 M	6.3 B
2011	688 M	9.0 B
2012	684 M	11.8 B
2013	967 M	16.4 B

Source: Oliver Wyman Analysis

4.2 Real-time Access Pandemic Supply and Demand

As with pre-pandemic vaccine measures, we evaluated the degree to which global demand for real-time access could be served by using existing capacity for seasonal programs, assuming all capacity was diverted to pandemic production upon outbreak.

4.2.1 Real-time Access Pandemic Supply

As with pre-pandemic interventions, it is important to express capacity in pandemic vaccine terms. Most of the assumptions for the base case and aggressive cases remain the same for real-time access. However, assumptions regarding stockpile regeneration are not applicable, as real-time access would involve production and administration upon outbreak. In addition, there are several parameters that need to be incorporated in a real-time access assessment that pertain to the lead time for producing a vaccine based on an emergent strain. These factors are as follows:

- In both the base case and aggressive case, all manufacturers would have access to reverse genetics (based on announcements by MedImmune). Reverse genetics is used to develop reference strain material by cloning the desired HA and NA proteins and combining them in a plasmid with six additional genes from a backbone strain. This process is typically

one to two weeks faster than classical reassortment, the process used for most seasonal vaccines today.

- In the base case, regulatory authorities require pathogenicity testing, which increases the time to produce the first batch of bulk vaccine by six weeks; in the aggressive case, pathogenicity testing would not be required, as testing would be completed with high potential clades prior to a pandemic outbreak.
- In the base case, cell-based manufacturers do not continuously regenerate biomass and therefore require an additional six weeks to scale up biomass; in the aggressive case, biomass is continuously regenerated, and therefore infection of the biomass with the vaccine strain can begin immediately.

The final key difference between pre-pandemic and real-time measures relates to the targeted protection time frame (i.e., the time from outbreak to vaccination of the full population). Countries that have signed contracts with manufacturers for real-time access have different time frame targets—ranging from two months to six months. Simulation models predict that all countries are likely to experience a first peak of infection within six months of outbreak, but potentially sooner. For the remainder of this analysis, we will use a six-month protection time frame but will show the sensitivity to shorter time frame targets.

As shown in Figure 18, even in the aggressive scenario by 2013, only 2.8B courses could be produced in a six-month time frame.

Figure 18: Real-time access pandemic supply: number of pandemic courses.

		Pandemic Courses Produced			
		Base Case		Aggressive Case	
		2007	2013	2007	2013
Bulk through finish production window (# of months post-outbreak to complete production)	3	0M	0M	300M	700M
	4	20M	50M	600M	1400M
	5	60M	160M	900M	2100M
	6	90M	250M	1200M	2800M

Source: Oliver Wyman Analysis

4.2.2 Real-time Access Pandemic Demand

As it relates to real-time access, we have assumed that high- and upper-middle-income countries will have first access to the influenza vaccine capacity described above to produce pandemic

vaccines in the event of an outbreak. This is based on both the financial resources of these countries and the fact that the vast majority of this capacity is located in high- and upper-middle-income countries; it is reasonable to expect that nationalization of capacity will occur in the event of an outbreak, and populations in those countries will be served first. Therefore, demand for these countries is estimated first and compared to projected pandemic production capacity.

One way to estimate demand in high- and upper-middle-income countries is to infer coverage strategies based on countries' pandemic preparedness reports. Based on our review of such reports for 63 countries, coverage of broadly prioritized sub-populations such as health workers, military personnel, essential services workers, and the elderly would translate into ~450 million courses demanded upon outbreak. However, we do not believe that this provides an accurate portrayal of pandemic demand in these countries for several reasons. First, the preparedness plans seem to reflect a seasonal vaccine protection strategy, which may not be appropriate in a pandemic situation. Second, other indicators of governments' intent suggest that high-income countries' strategies will be to secure vaccine for their entire populations in a pandemic. Significantly, of the 15 countries known to have entered into contracts with manufacturers for access to pandemic vaccine production capacity to date, 10 have contracted for courses to cover essentially their entire populations.

If all high- and upper-middle-income countries (including Brazil and Russia) sought vaccines for their entire populations in a pandemic, nearly 2 billion courses would be required. If China pursued this goal as well, more than 3 billion courses would be required to serve these populations.

4.2.3 Real-time Access Supply-Demand Map

Comparing expected developed-world pandemic vaccine demand with the 'base case' and 'aggressive' supply scenarios creates a picture of the expected magnitude of excess/shortages of capacity under different circumstances. This analysis concludes that, assuming high-resource countries secure capacity for their entire populations in a pandemic, developing world demand would not be addressed in a sufficient time frame under any supply scenario based on current inactivated technologies.

As illustrated in Figure 19, under 'base case' supply assumptions, if the pandemic outbreak were to occur in 2007 and high-resource countries sought vaccines for their entire populations, developing countries' demand would not begin to be met for nearly five years after the onset of an outbreak. The populations of these countries would not be fully served for more than ten years. Under our aggressive supply assumptions, if the pandemic outbreak were to occur in 2007, developing-world demand would not begin to be addressed until approximately eight months after the outbreak and would not be fully served for approximately two years. Even under our most aggressive supply assumptions and assuming the pandemic does not occur until 2013, developing-world demand would not begin to be addressed until five months after the outbreak and would not be fully served for approximately one year.

Figure 19: Time frame to serve developing-world pandemic demand during an outbreak (real-time access).

Year	Base Case		Aggressive Case	
	Time to 1 st Dose	Time until Demand Served	Time to 1 st Dose	Time until Demand Served
2007	5 years	>10 years	8 months	25 months
2008	4 years	>10 years	8 months	24 months
2009	3 years	9 Years	6 months	17 months
2010	3 years	9 Years	6 months	16 months
2011	3 years	9 Years	6 months	16 months
2012	3 years	9 Years	6 months	15 months
2013	2 years	6 years	5 months	12 months

Source: Oliver Wyman Analysis

5.) Strategy Recommendations

5.1 *Strategy Definition*

We have defined an access strategy for pandemic vaccine across four dimensions:

1. Which populations?
 - a. Specific regions or groups of countries.
 - b. Specific sub-population groups within countries.
2. Which technologies?
 - a. Inactivated egg or cell.
 - b. Live.
 - c. Recombinant.
 - d. With or without novel adjuvants.
3. Which intervention?
 - a. “Real-time” doses of vaccine (i.e., produced after declaration of outbreak and identification of pandemic strain).
 - b. Doses for pre-pandemic interventions (stockpiling and/or pre-outbreak immunization based on most likely pandemic strain—e.g., H5N1).
4. What capacity?
 - a. Number and location of facilities.
 - b. Leveraging existing capacity or creating new capacity.

Access strategies defined by these dimensions can apply to any time frame, as the timing for a pandemic outbreak is, of course, unknown. For planning purposes, we have used five years as a key demarcation point in setting strategy—i.e., less than five years is a “short-term” planning horizon, and greater than five years (2012 and beyond) is a “longer-term” planning horizon. There are two key drivers of this distinction. First, new capacity for vaccine production is generally characterized by a five-year lead-time; therefore, only facilities currently being constructed and validated can be considered available during that time frame, and in this respect available capacity is static. Second, it is not clear whether achieving a proven and licensed pandemic product (i.e., based on H5N1) via technologies beyond egg and cell inactivated is feasible in the next five years. Overall, short-term strategies are designed within current constraints, whereas longer-term strategies can be designed around interventions to create new capacity and develop new technologies.

5.2 Short-Term Strategies

5.2.1 Technology and Capacity

Given the technology and supply constraints described above that characterize the short-term time frame, options for the technology and capacity elements of an access strategy in the short-term are defined a priori. Adjuvanted products are in the process of being licensed for egg-based technologies that, in addition to requiring lower dosage, have demonstrated high levels of direct seroprotection and seroconversion and the ability for good cross-protection (i.e., protection against other clades). Similarly, questions of capacity are moot in the short-term; capacity used for short-term strategies will have to be the existing or already planned infrastructure, which for bulk production is predominantly egg-based inactivated, located primarily in high-income countries such as the U.S., UK, and Germany.

5.2.2 Populations for Coverage

We have segmented developing world populations into three groupings from a pandemic protection perspective. The definition of these groupings and the segments within each were derived from interviews with key policy makers and a review of country pandemic preparedness reports, where countries established priority levels for various subgroups within their populations. Our objective in conducting this segmentation was to evaluate and develop various access strategies, as opposed to assessing the merit of covering one group versus another, which is a separate policy question. These groupings are as follows:

- “The Essentials” (~140MM people): Sub-populations in this segment include frontline health workers and essential public service employees. In covering this group, the objectives are to minimize economic and social disruption in addition to preserving their individual well-being.
- “The Many” (3-5B people): Sub-populations in this segment include young children (6 to 59 months), children and adolescents (5 to 19 years), and young (20 to 34) and middle-aged (35 to 59) adults. These sub-populations represent the majority of individuals in the developing world, and protecting them would represent an attempt to achieve high impact in terms of mortality and morbidity reduction.
- “The Vulnerable” (600MM people): Sub-populations in this segment comprise elderly (65+) and chronically ill/immuno-compromised persons. This group could be viewed as those most in need of protection given their current health condition—i.e., potentially experiencing the highest mortality and morbidity rates absent health interventions (although this has not necessarily been the case in past pandemics such as the 1918 “Spanish” flu). Conversely, in a world of limited resources, immunizing health populations may be a priority in order to minimize disability-adjusted life years (DALYs) lost, if this were to be a policy objective.

Given their role in maintaining order and function in societies and caring for those who become ill in a pandemic, protecting The Essentials segment either prior to outbreak or immediately thereafter would seem to be a requirement of any strategy. Covering additional segments in the short term is clearly a function of feasibility (what populations can reasonably be reached and served), resources (how much funding is available), and available capacity. There is nothing

inherent in the segmentation characteristics themselves to rule out specific segments or overall groupings as candidates for potential coverage in the short-term.

5.2.3 Interventions

The analysis in the pandemic supply-demand section previously demonstrates that real-time access is not a viable intervention in the short term, given current and planned infrastructure and existing technologies. Therefore, the only viable intervention in the short term is a pre-pandemic approach such as stockpiling or pre-pandemic immunization with an H5N1-based adjuvanted vaccine. The viability of this approach would depend on how several factors are addressed:

1. *Providing broad access to novel adjuvants.* Adjuvants play a critical role in reducing the dosage requirement for pandemic influenza vaccines. Clinical trials have demonstrated the ability to reduce dosage requirements from as much as 90 mcg to as little as 3.8 mcg—a ~25 times increase in the effective number of doses for a given amount of physical infrastructure. Currently, both GSK and Novartis have developed novel adjuvants, and candidates incorporating these adjuvants have been able to achieve these levels of dosage sparing and acceptable immunogenicity in late-stage clinical trials. Ensuring that other manufacturers have access to these adjuvants (and resulting development occurs) would have a significant impact on the number of doses that could be produced through the use of excess capacity during the pre-pandemic period. Sufficient capacity appears to also exist for the key building blocks of these adjuvants. Assuming production can be diverted from existing uses for these adjuvants, sufficient supply could be made available.
2. *Broad achievement of high production yields.* Enabling all manufacturers to achieve the high end of potential yield levels in the production of H5N1-based vaccines through sharing of operating practices, techniques, and potentially re-assorted strains is also a critical way to increase the number of pandemic doses that can be produced with excess seasonal capacity for pre-pandemic interventions.
3. *Pre-pandemic immunization or extending stockpile “shelf lives.”* If pre-pandemic doses are administered to individuals prior to a pandemic outbreak, either immediately after production or after an intermediate stockpiling step (i.e., stockpiles are administered prior to expiration), only a single course needs to be produced to protect a given individual. Alternatively, if the duration of vaccine stockpiles can be significantly extended through technological innovation, the effect on access may be comparable—i.e., less capacity is required per individual targeted by the pre-pandemic measure. Conversely, pursuing a stockpiling-only approach based on the current expected shelf-life of approximately two years would make broad access less achievable. Therefore, opportunities to enhance stockpile duration, and/or resolution of the appropriateness of pre-pandemic immunization, need to be explored and addressed.

If these issues are successfully addressed, the entire global population could be protected through pre-pandemic vaccine measures within a four-year period, subject to the constraints cited above of feasibility of reach and availability of funding. Therefore, the viability of this strategy is predicated on resolution of the above-cited issues. In addition, other challenges would need to be addressed, such as:

- Accessing required syringes (our initial assessment indicates considerable current production, but limited excess capacity).

- Resolution of product-related questions, such as appropriate standards.
- Accessing required form/fill capacity for either pre-pandemic administration or post-outbreak usage of bulk stockpiles.
- Development and agreement on an administration plan—how to reach populations, which countries and in what sequence, etc.
- Commercial terms with manufacturers and associated funding.

5.3 *Longer-Term Strategies*

5.3.1 *Technologies*

In the longer term, live-attenuated and recombinant/VLP-based vaccines are among the options for consideration. With these technologies added to the mix, there are different roles for each of the existing and newer technologies to play given their economic, clinical, and other distinguishing characteristics, as follows:

- *Inactivated (egg or cell)*. Even with the use of novel adjuvants, inactivated vaccines will still be the most costly of these vaccines to produce. However, adjuvanted vaccines have demonstrated the ability to protect against antigen drift, an important characteristic for pre-pandemic use or early-stage outbreak use given the potential for continuing drift of the pandemic strain. For egg-based systems, any strategy (especially for real-time access) would need to consider the merit of bio-securing flocks given the avian nature of H5N1, the most threatening strain today. In addition, the complexity of cell-based manufacturing systems may make cell-based technologies less suitable for new bulk capacity that could be created in the developing world by emerging suppliers with less experience in these systems.
- *Live attenuated*. As described in the technology section, live attenuated vaccines have potentially low bulk production costs and, perhaps more importantly, have the capability to generate a sufficient number of courses in a six-month window to serve large portions of the global population following the onset of an outbreak. This distinction reflects both the high effective output per production run and the potential to generate sufficient immunogenic response with a single dose. Therefore, this technology is suitable for a real-time access solution that could serve large population sub-groups such as “The Many.” It is less suitable, however, for longer-term solutions involving pre-pandemic measures, as immunization with a live attenuated vaccine prior to outbreak could itself trigger a pandemic through reassortment with circulating strains. For real-time access, the potential for multi-dose, dropper-based administration offers advantages in reduced reliance on trained personnel in-country and lower cost/stockpiling requirements for the delivery device. However, live attenuated technology requires further development for pandemic purposes, as H5N1-based vaccines have not yet proven successful clinically. Furthermore, live-attenuated vaccines may not be as effective in sub-population groups within “The Vulnerable” segment.
- *Recombinant*. Recombinants have the potential to be relatively low-cost and therefore more affordable for providing access to large populations. Like live-attenuated vaccines, further development of recombinant vaccines is required to achieve high production yields and effectiveness against H5N1, although theoretically recombinant proteins or

VLPs may be better matched than current technologies and may offer good cross-protection. Like inactivated technologies, recombinants would still require syringes and a two-dose course.

5.3.2 Interventions and Populations

Given these technology characteristics, a combination of interventions with specific technologies is recommended for each of the three population groups (“The Essentials,” “The Many,” and “The Vulnerable”) as follows:

- **Pre-pandemic interventions (either stockpiling or immunization) for “The Essentials” using inactivated technologies, and potentially recombinants over time.** Ensuring that these groups are protected before the onset of an outbreak is critical to their role in preventing broader mortality and morbidity, and societal disruption. As noted above, live attenuated is not a feasible option for pre-pandemic use, and the relatively high cost of inactivated vaccines is mitigated in absolute terms by the limited number of courses required for these sub-populations. Individuals in this segment could be immunized multiple times based on the most likely pandemic strain in circulation at the time (e.g., H2, H5, H7, or H9), or with a combination vaccine if one were developed.
- **Real-time access for “The Many” and “The Vulnerable” using live attenuated and potentially recombinants.** Providing pre-pandemic protection on an ongoing basis to the large segments of the global population is less necessary if a viable real-time access solution exists. Having an established real-time access program would preclude the cost and complexity of pre-pandemic interventions for several billion people and the risk that the wrong strain is used. As noted above, live-attenuated is most suited for mass-scale, real-time access, given its cost advantages. However, exploring recombinant technologies is also attractive as a risk-spreading strategy for two reasons. First, it is a low-cost alternative in case development of a live attenuated pandemic vaccine is not successful. Second, recombinant vaccines offer an alternative solution for “The Vulnerable” in case live attenuated vaccines are shown to be less effective in this population.

5.3.3 Capacity (New versus Existing, Location, and Number)

Like the short-term approach, existing bulk and fill/finish capacity could be leveraged to provide pre-pandemic interventions to “The Essentials.” However, providing real-time access to the vast majority of the global populations will require “surge” (and therefore new) bulk production capacity. With respect to fill/finish capacity, sufficient infrastructure may exist today in the developing world to enable diversion of that capacity for filling and finishing bulk vaccine during a pandemic. A wide range of estimates exist for developing world vaccine fill/finish capacity, from ~5 to 20B annual doses. In addition, other injectables capacity may exist which could be multiples of that which is currently dedicated to vaccines. Therefore, establishing new fill/finish capacity solely for this purpose seems less necessary and appropriate.

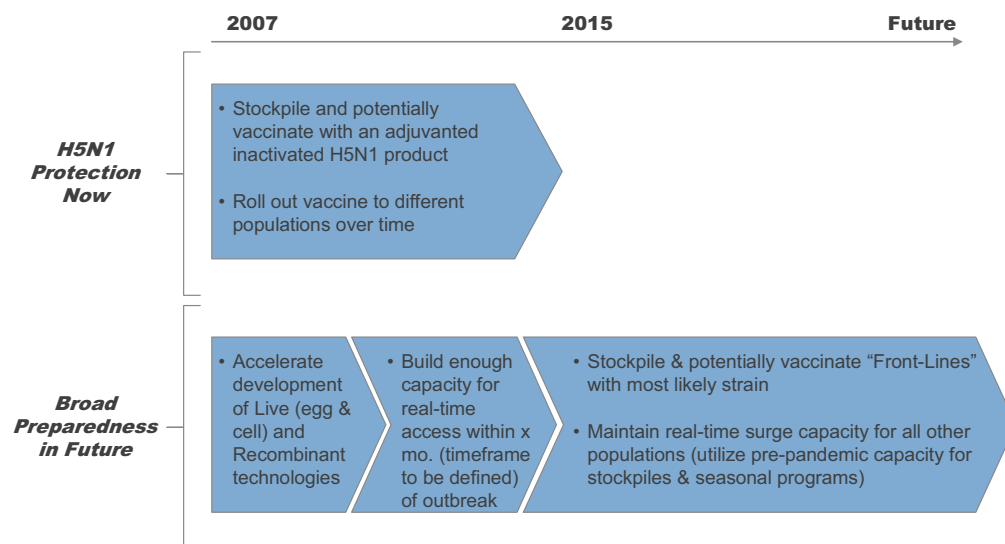
Given that the majority of pandemic vaccine demand will be located in the developing world, new bulk production facilities for providing real-time access should likewise be located in these countries. In terms of the number of facilities, there will be a trade-off between investment efficiency and diversification. More facilities for a given amount of global demand means smaller facilities, resulting in higher investment cost per dose (given scale economies); for example, 16 live attenuated production facilities to serve 3 billion courses of pandemic demand

would require an investment of more than triple what would be spent on 4 facilities to serve the same level of demand. One could argue, however, that this approach (i.e., fewer facilities) could lead to nationalization by countries with production facilities. A possible solution that balances these considerations is four to eight facilities in total, with one located each in India and China (given their large size) and the other two to six located in smaller countries in different regions to provide more regionally balanced access.

5.4 Considerations Within and Across Short-Term and Longer-Term Strategies

While different, both short-term and longer-term strategies are mutually reinforcing, and pursuing one without the other is not ideal. Specifically, protecting global populations from H5N1 in the short term using existing capacity does not allow for protection against other strains that may ultimately emerge as the source of a pandemic. In addition, H5N1 strains may drift over time such that protection afforded by current H5N1-based vaccines (even adjuvanted) may not be sufficiently effective. On the other hand, enabling real-time access for large portions of the global population to vaccines based on the strain that has become the source of a pandemic is not an option in the next five years, given requirements for further development of the appropriate technologies and time frames for new capacity build-out. Pursuing both paths in parallel provides the greatest opportunity to minimize the impact of an influenza pandemic. This approach is summarized in Figure 20.

Figure 20: Summary of the overall approach.



6.) Investment and Implementation Considerations

6.1 *Investment Required*

Expenditures required to implement these access strategies (not accounting for spending on administration) can be broken down into several categories:

- Product development costs
- Manufacturing costs
 - Upfront capital investment outlays for new capacity
 - Bulk production costs
 - Fill/finish production costs
- Profit margin realized by vaccine suppliers
- Delivery device costs (includes manufacturer margins)

All figures quoted below pertain only to the manufacturing and delivery device cost elements of this expenditure. Profit margins incorporated into the ultimate vaccine pricing are determined by interactions with suppliers and are therefore less ascertainable, and we have made no attempt to estimate these levels. In addition, product development costs to successfully advance existing and newer technologies will need to be accounted for but have not been estimated as part of this exercise.

In the short term, the total cost is highly sensitive to product and operations parameters. In the best case, sufficient courses of H5N1 vaccine to serve the developing world (approximately five billion people) can be produced by our estimate for \$1 to 5 billion. Manufacturing costs to implement the short-term strategy comprise bulk and fill/finish production costs, as no additional capital investment is required (because existing excess capacity is used). Not achieving parameters associated with the best case scenario described in Section 4 will not only reduce the number of doses available, but will also raise this cost estimate considerably.

Costs to implement the longer-term strategy are more complicated to estimate. These costs include:

- Upfront investment to build new bulk facilities.
- Annual cost of producing vaccines for pre-pandemic use for “The Essentials” group.
- Annual cost to operate bulk facilities during the pre-pandemic period. There are several alternatives for utilizing the facilities in the pre-pandemic period, such as serving new seasonal influenza programs in the developing world (not in our demand forecast) or contract manufacturing other vaccines or biopharmaceuticals. Interestingly, live attenuated facilities could be used to produce inactivated vaccines during the pre-pandemic period, resulting in much more limited quantities that could be suitable for new, modestly-sized developing-world seasonal programs.
- In the event of an outbreak, the cost to produce doses and provide delivery devices for broad developing world coverage.

Total costs for the long-term strategy over a 25-year period (assuming an outbreak in that time frame) would be \$1 to 5 billion, with the range driven by assumptions about the alternative uses for new live attenuated and recombinant capacity during the pre-pandemic period.

6.2 *Implementation Considerations*

Implementation of both the short term and longer term access strategies will require a concerted and carefully orchestrated effort. First and foremost, communications are needed to build broad consensus among the key constituents, such as manufacturers, developing world governments, donors, and agencies with critical responsibilities. Based on our interaction with various stakeholders, we do not believe broad consensus yet exists. We believe that implementing a carefully orchestrated communication plan to achieve broad-based buy-in, followed by a thoughtfully designed implementation plan that addresses the wide range of required activities across the areas of supply, demand, and finance, are required for these access strategies to be realized.

Implementation can generally be organized around three areas: supply, demand and finance. Below is a table for the short-term and longer-term access strategies that provides examples of some of the key implementation steps within each of these areas; however, these are by no means comprehensive. Furthermore, careful consideration will need to be given to how these are staged and linked, and how responsibilities are divided and assigned.

Table 1. Example implementation areas for supply, demand, and finance.

	Short-Term Strategy	Longer-Term Strategy
Supply	<p>*Bulk issue resolution: enabling adjuvant access/reduced dosage, optimizing yields.</p> <p>*Product definition: requirements for inactivated approach (split vs. whole vs. wild type) and specific adjuvants, clade selection.</p> <p>*Establishment of commercial terms with suppliers.</p> <p>*Plan to access fill/finish capacity.</p> <p>*Resolution of syringe constraints.</p>	<p>*Bulk supply development: technology development plan for live attenuated and recombinant/VLP technologies, arrangement of tech transfers as appropriate, achieving access to key enablers (e.g., adjuvants).</p> <p>*Network design for new bulk facilities: specific location and number of facilities.</p> <p>*Identification of appropriate fill/finish capacity and establishment of commercial terms for access; specific location and number for new fill/finish facilities as appropriate.</p> <p>*Formulation and delivery device development.</p>
Demand/Policy	<p>*Administration plans within countries (which sub-population groups, in what sequence).</p> <p>*Access plans across countries.</p> <p>*Resolution of appropriateness of pre-pandemic immunization.</p> <p>*In-country logistics plan.</p>	<p>*Administration plans within countries following outbreak (which sub-population groups, in what sequence).</p> <p>*Access plans across countries following outbreak.</p> <p>*In-country logistics plan for distribution during pandemic.</p>
Finance	<p>*Funding plan and mechanisms for pre-pandemic measures.</p>	<p>*Funding plan and mechanisms for real-time access measures.</p>