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Options for the Design and Financing of an H5N1 Vaccine Stockpile: Key Findings and Study Methodology

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This document was commissioned by the Bill & Melinda Gates foundation and provides expert technical analysis in connection with the establishment of an international stockpile of H5N1 vaccines. (WHA resolution 60.28 requests, inter alia, the establishment of such a stockpile.) As such, the document does not present any official view attributable to WHO, its Member States or its Secretariat

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1. Executive summary

Rationale for considering the creation of an H5N1 vaccine stockpile

Three influenza pandemics occurred over the last century, with the most recent in 1968. Most influenza experts believe that another pandemic is inevitable, 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 60 million deaths worldwide by some estimates, with the majority of these occurring in developing countries.

Vaccines have the potential to dampen the impact of an influenza pandemic, but global demand for vaccine would far outstrip production capacity at the time of a pandemic. An analysis of the global capacity to produce influenza vaccines was recently completed by WHO and IFPMA, with the support of Oliver Wyman, and funding from the Bill & Melinda Gates foundation. Detailed results will be released in the Spring of 2009. This assessment shows that it could take years from the point of the identification of the pandemic strain to produce enough pandemic vaccine to satisfy global need. Based on outbreak modeling, experts agree that this response time is not sufficient to protect global populations during the first wave of a pandemic.

SAGE recommendation on the H5N1 vaccine stockpile

In May 2007, the World Health Assembly requested the WHO Director-General to develop an international stockpile of influenza A (H5N1) vaccines. In November 2007, after reviewing data on safety and immunogenicity of H5N1 vaccines, the WHO Strategic Advisory Group of Experts in Immunization (SAGE) recommended that WHO establish a stockpile of up to 150 million doses (full courses for 75 million people) of H5N1 vaccine for two uses.

SAGE recommended that up to 50 million doses be maintained to complement other interventions used in rapid containment of the earliest detected outbreak of H5N1 virus infections. This vaccine would be deployed if sustained human-to-human transmission of an H5N1 virus is identified and is considered by WHO and the affected country to have the potential to initiate an influenza pandemic. An additional 100 million doses was recommended for equitable distribution to low-income and middle-income countries, in amounts proportional to the size of the country's population, to help maintain those services considered most essential by the countries in the event of sustained human-to-human transmission of the H5N1 virus.

Manufacturers have responded with pledges to donate 110 million doses of vaccine to such a stockpile. Efforts are underway to secure the donation of an additional 40 million doses, and the analysis in this study assumes that all 150 million start-up doses will be donated.

Study objectives and approach

The following study was undertaken between April and September of 2008 to further define the details of the stockpile logistics and financing and was conducted as a collaboration between WHO, the Bill & Melinda Gates foundation, and Oliver Wyman. The objectives of this effort were to:

- **Define options for the logistical design of the H5N1 vaccine stockpile and associated tradeoffs.** This included an assessment of the form of the vaccine, strategies for storing the vaccine, and deployment considerations.
- **Develop potential strategies and mechanisms to finance the stockpile.** This included an assessment of the key drivers of cost and design of mechanisms to manage the costs and mitigate uncertainties.

An analytical and consultative process was pursued to initially identify potential options for the stockpile, evaluate the tradeoffs across those options, and then seek feedback on a prioritized set of options. The analytic evaluation utilized a custom-built, sophisticated model of the cost and service time tradeoffs across various options. In addition, the analysis was supported by nearly 200 interviews with potential recipient country representatives, WHO and UNICEF functional and regional experts, current holders of national H5N1 vaccine stockpiles, vaccine manufacturers, associated materials manufacturers, logistics providers (storage, transportation, and services), and various other experts.

Stockpile options were evaluated based on five key criteria:

- **Stockpile cost** – The total dollar cost of the stockpile, incorporating all costs of initiating, maintaining, and deploying the stockpile (assuming donation of the 150 million start-up doses).
- **Response time** – The complete time to deploy the stockpile from the start of an event (H5N1 outbreak or sustained human-to-human transmission of H5N1) until the last dose is delivered to the capital cities of recipient countries.
- **Management complexity** – The level of complexity of managing the stockpile (comprising nearly 2,000 pallets of vaccine and more than 9,000 pallets of ancillary supplies) and associated risks of deploying vaccine at the time of an H5N1 outbreak or sustained human-to-human transmission of H5N1.
- **Attractiveness to recipient countries** – Consistency of the design with the interests of the recipient countries (e.g., most countries voiced an interest in vaccine held in the regions and at least some portion in filled doses).
- **Supply certainty** – The likelihood that stockpiled vaccine will be deployed from the storage locations, given potential nationalization risks and local logistical capabilities.

Stockpile logistical design

A range of logistical design options were considered, each with tradeoffs across the five main criteria. The following strategy scored highest across the criteria: holding the stockpile in filled doses, in one-to-three strategic locations, with ancillary supplies (e.g., syringes, personal protective equipment) stored with the vaccine. However, other considerations may influence the final design decision.

The tradeoffs that drove the individual components of this strategy are the following:

- **The outbreak containment portion of the stockpile must be held in filled doses:** Vaccine for outbreak containment needs to be delivered within 3 – 4 weeks of the start of sustained human-to-human transmission (as each additional week considerably reduces the likelihood of containment). Vaccine stored in bulk form would require nearly 4 weeks for filling activities and delivery and, therefore, is not a viable option for the outbreak containment portion of the stockpile.

- **Logistical tradeoffs also favor holding the essential populations portion in filled doses, though this is less clear than the outbreak containment portion:** Holding the vaccine in bulk form would reduce the cost of a long-term stockpile as bulk vaccine is expected to have a longer shelf-life (5 years vs. 3 years for filled doses). However, these savings are not as significant as initially anticipated, accounting for only a 9% savings on the total stockpile cost if the stockpile is maintained for two vaccine replenishment cycles (approximately 9 years of stockpile life). Those cost savings are offset by significant non-cost tradeoffs that favor holding filled doses. Filling the bulk product at the time of need would increase deployment time by a minimum of 20 days and would increase management complexity by introducing steps to the deployment process. In addition, a bulk strategy was viewed as unattractive by some recipient countries and would increase nationalization risk as filling capacity is primarily located in countries with large populations.
- **Placing the stockpile in one-to-three strategic locations would balance country preferences and complexity concerns:** Stockpile costs and service times are not a major driver of the placement strategy as they are similar across options. The main tension is between the preferences of the recipient countries (to have the stockpile located within their regions) and the need to reduce management complexity (to improve the likelihood of successful deployment). Reducing complexity is most critical for outbreak containment, favoring the placement of the entire containment stockpile in a single site. For the essential populations component of the stockpile, a small set of locations (up to three) that are geographically dispersed would best balance the logistical and country-preference considerations.
- **The locations considered for stockpile placement should have superior logistical infrastructure, top tier cargo airports, and low risk of nationalization:** Locating the stockpile in countries with strong logistical infrastructure and air cargo capabilities would minimize response time and maximize supply certainty. In addition, countries should be selected with characteristics that suggest a reduced risk of nationalization. Countries with small populations and with existing H5N1 stockpiles would have a reduced incentive to nationalize (as minimal doses from the stockpile would not be needed to protect their populations). Balancing these considerations with recipient countries' desires for stockpile placement in their regions, cities such as Singapore, Dubai, and Panama City emerge as good examples of host cities. Final selection will need to be based on facility availability, host country preferences, and pricing.
- **Holding ancillary supplies (e.g., syringes, PPE) with the vaccine will increase the likelihood of success without raising costs:** Management complexity and supply certainty emerge as the most important criteria for the placement of the ancillary materials given that the vaccine cannot be administered without these materials. All other criteria, including cost, are similar across options. Therefore, holding and deploying these materials with the vaccine would maximize the likelihood of successful delivery.

Stockpile replenishment options

The most complex set of stockpile decisions relates to the replenishment of vaccine given the following issues:

- The donated vaccine from the manufacturers is only expected to maintain its potency for 3 years if held in filled doses (with ongoing testing potentially extending that time).

- Vaccine replenishment will be very costly relative to other stockpile costs, and decisions around replenishment will, therefore, drive the funding need. Estimates provided by the manufacturers suggest a vaccine price of \$1 – 5 per complete (i.e., filled, adjuvanted) dose. For modeling purposes, we have assumed \$3 per dose. Each full replenishment cycle of 150 million doses of vaccine would cost \$450 million in nominal terms. The average replenishment cycle would cost \$360 million (as adjuvant has a longer shelf-life and would not need to be replenished as often). In comparison, the cost of storage, maintenance, and transportation of the vaccine is only approximately \$7 million per year.
- The number of replenishment cycles required is not possible to predict up-front. While the antigen shelf-life is expected to be 3 years, considerable uncertainty exists given the current lack of data and variability by strain and manufacturer. In addition, the required timeframe for protection is unknown. The timing of the pandemic event is uncertain and new technologies may emerge that could change the stockpiling strategy.
- Establishing a stockpile of 150 million doses at a single point in time will not occur without some purchase of vaccine or changes to the manufacturer pledges and WHO's requirements. This is based on three factors: 1) manufacturers have pledged that they will stage vaccine donations over a three-year timeframe, 2) WHO has set initial requirements that donated vaccine be licensed and pre-qualified; 3.) Vaccines are at different stages of development with expected licensure timeframes varying. Vaccine would, therefore, be eligible from the manufacturers over different timeframes (i.e., one manufacturer from 2009 – 2011, another from 2011 – 2013). The resulting stockpile would never reach 150 million concurrent doses due to expiry.

The global community, therefore, must make a set of complex decisions around replenishment including: Whether to purchase any additional vaccine up-front? Whether to fund additional replenishment cycles beyond the expiry of donated vaccine? Whether to pursue innovative financing mechanisms to mitigate the risks associated with the funding uncertainty?

This study evaluated three major options, but recognizes that variants may exist on each option. Clear tradeoffs exist across the options that need to be weighed in finalizing the decision.

- 1) **“Pay-as-you-go” Physical Stockpile:** The most straightforward option would be to start with the donated vaccine and not commit to additional funding of replenishment cycles. The nominal cost of this option would be \$85 million (with a present value of \$70 million), primarily comprised of the purchase of ancillary supplies and storage / transportation costs. This option would allow for the vaccine to be held in physical form consistent with the optimal logistical design. The major tradeoff associated with this option is that it is only expected to provide an active stockpile for 3-5 years, at which point additional funding decisions would need to be made. Further, a stockpile of 150 million concurrent doses is not anticipated unless manufacturers alter their donation plans and/or WHO relaxes its stipulations to accept donated vaccine.

The available financing mechanisms for this option are fairly simple: funds will need to be provided up-front in the form of cash or in donated services to pay for ancillary materials and transportation (which comprise the majority of the cost).

- 2) **“Committed Replenishment” Physical Stockpile:** An alternate option would be to commit to some number of replenishment cycles up-front, still enabling the stockpile to be held in physical form. The total cost for the stockpile, including one replenishment cycle (of antigen only given the longer adjuvant shelf-life) would be \$360 million in nominal terms and \$280 million in present value terms for an approximately 5 year stockpile life. A choice would exist for the first replenishment cycle: the purchased vaccine could either be used to replace donated expiring vaccine or some portion of the vaccine could be purchased up-front to configure an initial stockpile of 150 million doses, which would not be possible from donated vaccine alone.

The greater the number of replenishment cycles committed up-front, the longer the expected stockpile life, but the higher the cost. For example, the cost of a stockpile including two replenishment cycles (two antigen replenishments and one adjuvant) with an expected life of 9 years, would be \$880 million in nominal terms and \$610 million in present value terms.

This option would enable the use of innovative financing mechanisms to manage the costs and risks associated with a longer-term stockpile. One mechanism, a “product warranty” could be used to guarantee the shelf-life of the vaccine for a specific length of time. The manufacturers would guarantee the shelf life and potency of their vaccine for a period of time in exchange for an upfront or annual payment. Funding could then be committed for a fixed period of time rather than for a number of replenishment cycles with unknown length. This mechanism would transfer the uncertainties around the shelf life of the vaccine from the stockpile holder to the manufacturers, who are best equipped to manage those risks.

Another mechanism, a “pandemic annuity,” could be purchased from an insurer or group of insurers to mitigate the risks associated with unknown pandemic timing. In exchange for an upfront fee, the insurers would provide annual payments to the stockpile to cover management and replenishment costs until the stockpile is fully deployed (or the contract term expires). This mechanism would provide funding certainty to the stockpile, as well as an attractive financial hedge to insurers against other pandemic risks they are carrying. The financial hedge value could result in discounted pricing (as much as a 15-30% discount). This mechanism is most applicable for longer intended timeframes of the stockpile.

- 3) **Virtual stockpile:** A third option would be to adjust the logistical design of the stockpile and hold the vaccine in virtual form with the manufacturers. This option is currently not feasible since H5N1 vaccine is not in regular use during the inter-pandemic period. If at some time in the future, H5N1 vaccine is put into regular use, a stockpile could be comprised as part of manufacturers’ regular, revolving stock of inventory (with vaccine being sold before it expires). The vaccine could be held in filled doses or bulk form and would considerably reduce the cost of the stockpile by eliminating the need to store and replenish vaccine. The estimated cost of a virtual stockpile is \$70 million in nominal terms and \$65 million in present value terms. This option would have significant non-cost tradeoffs, including increased nationalization risks (driven by the manufacturer locations), increased management complexity (driven by storing vaccine at multiple manufacturing sites), and increased deployment

time (if the vaccine is held in bulk form, which may be required given potential differences in vaccine presentation / packaging from other demand sources).

Stockpile deployment options

Throughout our consultations, there was clear consensus that measures should be taken in advance to ensure that funds are in place for deployment and delivery (given the size and immediacy of the requirement). However, there was considerable debate as to whether the global community or the countries themselves should fund these activities.

One argument is that deployment and delivery is a critical element of any vaccination strategy, and assistance should be provided by the global community in advance to maximize the likelihood that vaccine makes it into the targeted arms. Given the size and immediacy of the funding need at the time of a pandemic, countries may not be prepared to fund these activities on their own. If required in year 10, the cost to deploy and deliver 150 million doses of vaccine to potential recipient countries is estimated to be over \$300 million in nominal terms and \$170 million in present value terms. Further, all countries (not just those covered by the H5N1 vaccine stockpile) will benefit from the timely deployment and use of the stockpile.

The counter-argument is that individual countries' interests will be aligned with the funding need at the time of deployment and they should therefore fund these activities. While the total burden is large, the average cost per country is only \$2 million. In addition, approximately 95% of the cost is driven by delivery within the country itself, with human resources accounting for the majority of that cost. A hybrid argument is that assistance should only be provided to those countries that are least likely to be able to self-finance. For example, GAVI-eligible countries represent approximately half (\$150 million in year 10 nominal terms, \$80 million in present value) of the cost of deploying and delivering the H5N1 vaccine stockpile. Support could be provided to these countries by GAVI itself or other donors.

Regardless of whether the global community or the countries themselves fund the deployment and delivery, a set of financing mechanism options exist:

- **Cash financing:** Traditional, cash financing in which funds would be reserved up-front or guarantees would be made to ensure that funds are available when needed.
- **Deployment insurance:** Purchase of an insurance policy that would cover deployment and delivery costs at the time of a pandemic event. This policy would add to an insurers' already substantial pandemic influenza risk exposure and therefore the attractiveness of the terms are unclear.
- **Guaranteed line of credit:** Pre-negotiated lines of credit that can be drawn upon at the time of a pandemic event. Depending on how the policy is backed, the ongoing costs could be minimal. The counter-party risk would need to be managed to ensure that funds are available if financial havoc ensues during the pandemic.

Next steps

We recommend that several next steps be pursued to finalize the selection and pursuit of the logistics and financing options:

- **Test critical assumptions:** The costs are highly sensitive to assumptions around the vaccine price and shelf-life that should be further tested. Also, this work was completed prior to the recent financial crisis and assumptions around discount rates / inflation and the viability of specific financing options should be revisited.
- **Decide on logistics and replenishment design:** The global community needs to consider the options presented in this document and determine which best fits with the goals of the stockpile and the current financial environment. This may include a set of consultations with potential donors, contributors, and recipient countries.
- **Finalize detailed logistics and build stockpile:** Once the stockpile design has been selected, the remaining detailed elements of the logistical design should be finalized (e.g., site selection, vaccine purchase, stocking / deployment procedures).
- **Finalize financing mechanisms and raise funding:** The selection of the specific financing mechanisms should be evaluated within the context of the logistics and replenishment options pursued and funding should be raised.

We would like to thank the individuals and organizations that contributed to this effort – without you, this work would not have been possible. We hope that this work continues to advance the global agenda around H5N1 vaccine stockpiling. Please forward any questions or comments to the authors:

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2. Rationale for considering the creation of an H5N1 vaccine stockpile

Three influenza pandemics occurred over the last century, with the most recent in 1968. Most influenza experts believe that another pandemic is inevitable, 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 60 million deaths worldwide by some estimates, with the majority of these occurring in developing countries¹.

In May 2007, the World Health Assembly requested that the WHO Director-General, in close consultation with Member States, identify and propose frameworks and mechanisms aimed at ensuring fair and equitable sharing of benefits, in support of public health, taking into consideration the specific needs of developing countries² (WHA 60.28), specifically:

- To foster the development of capacity for influenza vaccine production, including facilitating acquisition by developing countries of capacity for manufacturing influenza vaccines
- To develop an international stockpile of influenza A (H5N1) vaccine

One year earlier, due to growing concern over the risks of pandemic influenza, WHO launched a global action plan for increasing the supply of pandemic influenza vaccines (GAP) in order to reduce the anticipated gap between potential vaccine demand and supply during an influenza pandemic³.

Both these initiatives are based on the premise that vaccines may have the potential to lessen the impact of an influenza pandemic. The ideal influenza vaccine is a broad spectrum vaccine protective against all influenza strains; second to that is the ability to produce a real-time “pandemic” vaccine based on the emerging pandemic strain and to produce this in sufficient quantity to vaccinate the global population within a very short period of time. An analysis of the global capacity to produce influenza vaccines was recently completed by WHO and IFPMA, with the support of Oliver Wyman, and funding from the Bill & Melinda Gates foundation. Detailed results will be released in the Spring of 2009. This assessment shows that it could take years from the point of the identification of the pandemic strain to produce enough pandemic vaccine to satisfy global need. Based on outbreak modeling, experts agree that this response time is not sufficient to protect global populations during the first wave of the pandemic^{4,5}.

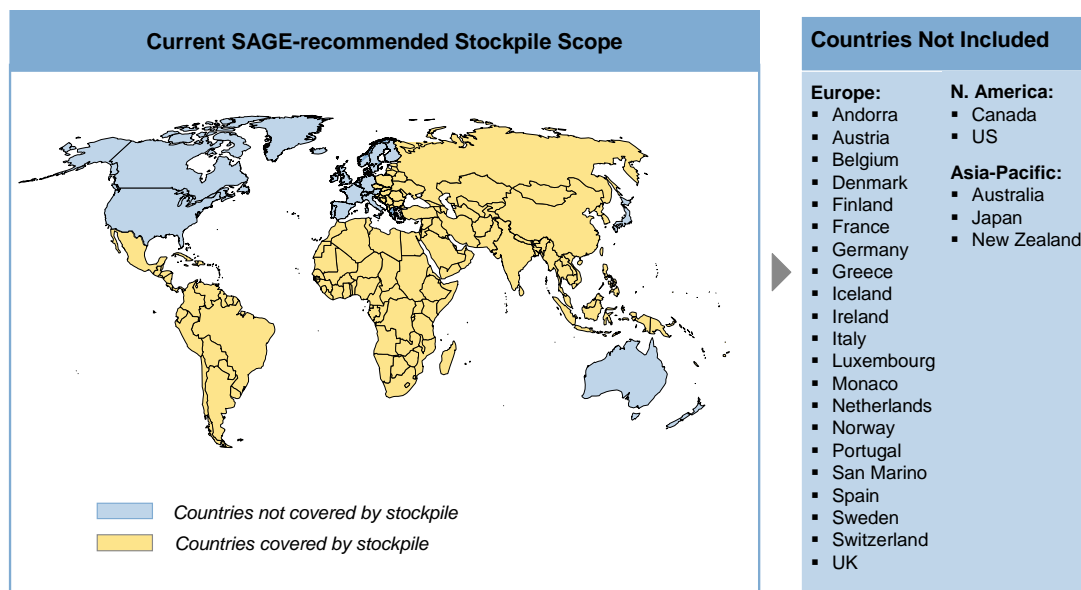
3. SAGE recommendation on the H5N1 vaccine stockpile

The World Health Assembly in May 2007 requested the WHO Director-General to develop an international stockpile of influenza A (H5N1) vaccines. Following this, in November 2007, after reviewing data on safety and immunogenicity of the H5N1 vaccine, the WHO Strategic Advisory Group of Experts in Immunization (SAGE) recommended that WHO establish a stockpile of up to 150 million doses (full courses for 75 million people) of H5N1 vaccine. This included consideration of logistical aspects and sustainability; development of associated procurement, management, governance, regulatory and deployment procedures; as well as procurement of necessary ancillary supplies such as syringes and needles. The uses of this stockpile were defined as follows:

- For the first use, up to 50 million vaccine doses to complement any interventions used in operations to try to contain the earliest detected outbreak of H5N1 virus infections in which sustained human-to-human transmission of the H5N1 virus is identified and which is considered by WHO and the affected country to have the potential to initiate an influenza pandemic.
- For the second use, SAGE recommended that WHO work towards stockpiling as much as 100 million additional doses of the H5N1 vaccine. If sustained human-to-human transmission of the H5N1 virus occurred, this stockpiled vaccine and any additional stockpiled vaccine that had not been used for containment should be equitably distributed to low-income and middle-income countries (totaling 167 countries, shown in Figure 1). The allocation would be in amounts proportional to the size of the country's population to help maintain those services considered most essential by them.

Manufacturers have responded with pledges to donate 110 million doses of vaccine to such a stockpile. Efforts are underway to secure the donation of an additional 40 million doses, and the analysis in this study assumes that all 150 million start-up doses will be donated.

Figure 1: Countries Covered by the H5N1 Vaccine Stockpile.



In November 2008, WHO, through SAGE, convened a Working Group on uses of H5N1 vaccines to analyze the most up-to-date data to determine if evidence-based policy recommendations can be made on uses of H5N1 vaccine by Member States in the current inter-pandemic period. SAGE will review this work and possibly issue recommendations on this topic by mid-2009. The working group will consider, in particular, whether enough evidence is available to recommend:

- Use of H5N1 influenza vaccines in high-risk or other groups selected by Member States prior to a pandemic. Switzerland, Japan, and perhaps other countries are

currently engaging in large scale volunteer demonstration studies of H5N1 immunization to assess safety of specific vaccine products.

- Use of H5N1 vaccine nearing the end of its shelf-life that is in the WHO stockpile for non-pandemic uses.
- Enlarging the size of the stockpile. Consultations with experts and with WHO Member States have indicated that the definition of "essential populations" varies in size across low and middle-income countries, ranging between 1% of their population (covered by the current stockpile design) and 3%. Increasing the size of the stockpile to cover the broadest definition of "essential populations" would entail increasing the stockpile size to 350 million doses.

4. Study objectives

This study was undertaken between April and September 2008 to further define the details of the H5N1 vaccine stockpile logistics and financing. It was conducted as a collaboration between WHO, the Bill & Melinda Gates foundation, and Oliver Wyman. The objectives of this effort were to:

- **Define options for the logistical design of the H5N1 vaccine stockpile and associated tradeoffs.** This included an assessment of the form of the vaccine, where the vaccine and ancillary supplies should be held and how the stockpile could be deployed. A detailed cost, service time, and broader tradeoff analysis was conducted to assist stakeholders in prioritizing options for the stockpile.
- **Develop potential strategies and mechanisms to finance the stockpile.** This included an assessment of the key drivers of cost and design of potential mechanisms for the efficient financing of the costs of a stockpile, taking into account a range of factors, notably the uncertainties associated with stockpile costs.

5. Study methodology

Evidence to inform the stockpile logistical and financing options was developed through a four step process.

- **Define a set of initial logistical hypotheses.** These hypotheses were used to bound the options under consideration and provide a basis for early discussions. They were developed based on preliminary interviews with experts in pandemic planning, vaccine stockpiling, and influenza (a full list of contributing organizations is available in Appendix I); a review of relevant publications; and analysis of preliminary tradeoffs. The hypotheses were then shared with a set of top pandemic influenza and public health experts as part of a meeting conducted as an adjunct to the Pacific Health Summit in June of 2008⁶.
- **Narrow options based on quantitative and qualitative tradeoffs.** Once hypotheses were established, a detailed tradeoff analysis based on extensive primary and secondary research as well as rigorous logistical and cost modeling was used to narrow the options.
- **Refine options, test sensitivities, and seek feedback.** The final options were then refined through an iterative review process that included feedback from a number of

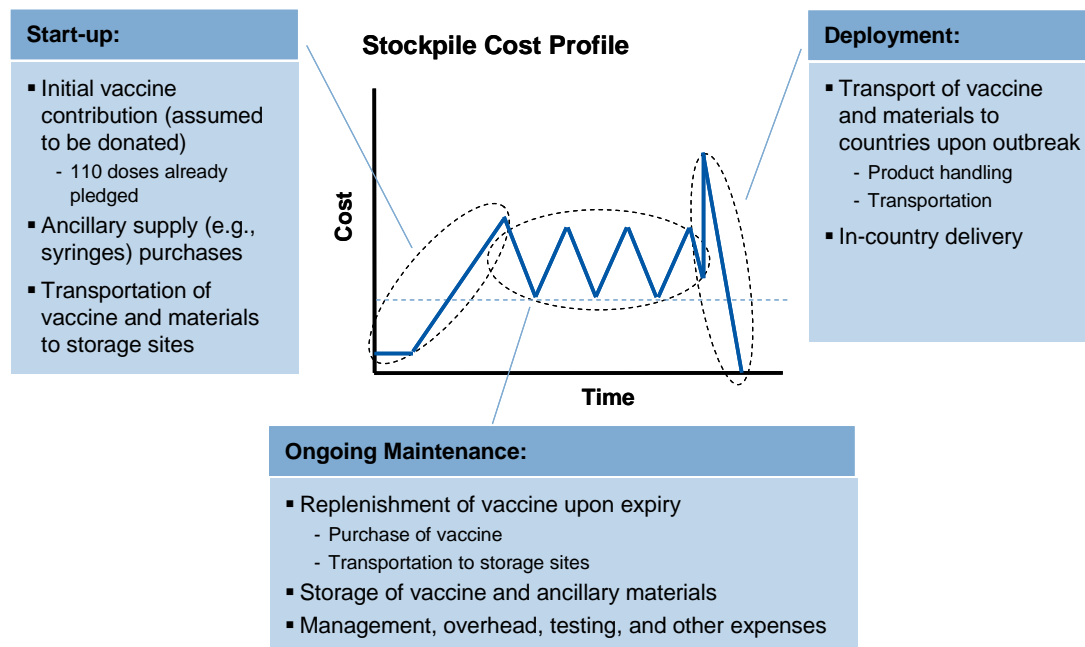
key stakeholders and public health experts. As part of this effort, sensitivities were calculated and analyzed for each option to understand the range of possible cost and non-cost outcomes.

- Evaluate financing mechanism options:** To develop the stockpile financing mechanisms, initially the funding needs were quantified and key uncertainties associated with the financing of the stockpile were identified. Options to address those needs and risks were then defined, tested, and refined, including an evaluation of the applicability to specific logistics options. This assessment was completed with input from experts on the use of innovative financing mechanisms in the global health arena, financing and capital markets experts, vaccine manufacturers, and risk assessment experts (a complete list of the contributing organizations can be found in Appendix I).

To refine and evaluate the logistical design options, five key criteria (stockpile cost, response time, management complexity, attractiveness to recipient countries, and supply certainty) were used.

- Stockpile cost** – *the total dollar cost of initiating, maintaining, and deploying the stockpile (assuming donation of 150 million doses).* Costs were broken into three categories corresponding to different stages of the stockpile lifecycle and modeled for all relevant factors within those periods (see Figure 2). These costs were analyzed over various stockpile maintenance timeframes (short, intermediate, and long) to understand how costs and tradeoffs are likely to change over time.

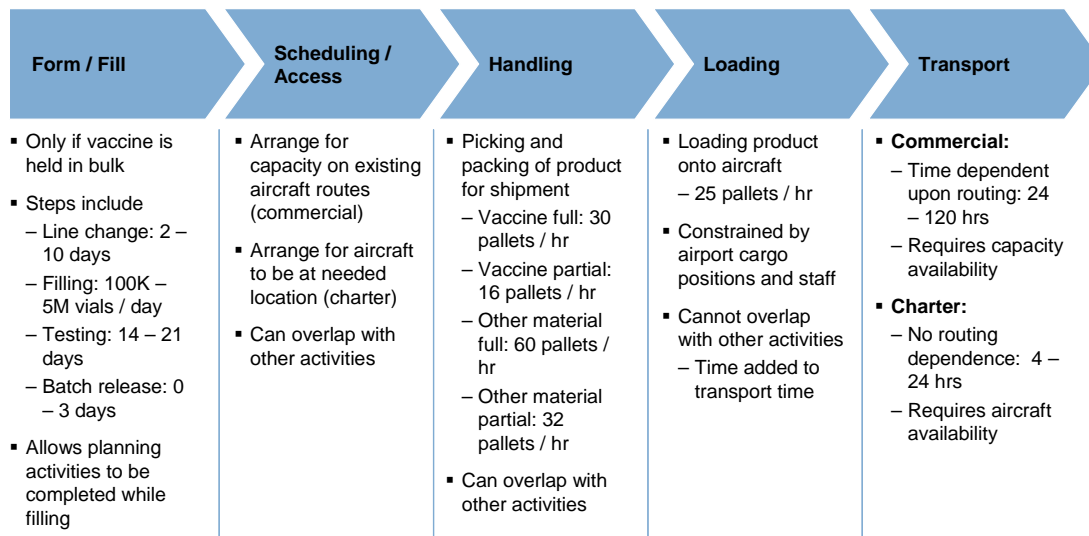
Figure 2: Description of Stockpile Stages and Associated Costs



- Response time** – *the time to deploy the stockpile from the start of an event (H5N1 outbreak or sustained human-to human transmission of H5N1) until the last dose is*

delivered to the capital city of each recipient country⁷. This includes vaccine fill / finish time (if required), warehouse pick / pack time, contracting and loading of cargo aircraft, and transit time to the recipient countries (See Figure 3). It was assumed for modeling purposes that the stockpile would be deployed via air using a combination of charter and commercial aircraft. Though it is possible that alternative deployment approaches may be used (e.g., the use of military aircraft), these were considered uncertain and/or similar to existing modes from a response stand-point and were, therefore, not explicitly modeled.

Figure 3: Factors that Drive Delivery Time to Countries⁸



- Management complexity** – *the difficulty of managing the stockpile and deploying it.* Given the scale of a 150 million dose H5N1 vaccine stockpile – comprising nearly 2,000 full pallets of vaccine and more than 9,000 pallets of ancillary supplies to be delivered (see Figure 4)⁹ – and the likely disruptive environment in which the stockpile will be deployed, it was considered critical that the logistical design be streamlined and efficient. Significant complexity in the form of multiple steps in the deployment process, an unwieldy number of stockpile locations, or an overly complicated deployment strategy increases the risk of failure in both stockpile maintenance and deployment. This could result in vaccine being delivered too late to be effective, vaccine not being properly handled or tested, or vaccine not being properly monitored to ensure appropriate administration and incident tracking.
- Attractiveness to recipient countries** – *the specifications or requirements of countries that would receive the stockpiled H5N1 vaccine.* As one of the objectives of the stockpile is to provide assurance to countries that some vaccine will be available to protect their populations in the case of an H5N1 influenza outbreak or sustained human-to-human transmission, it was crucial to understand what elements in the design are most relevant to providing that assurance. This was accomplished through a set of interviews with representatives from recipient countries and with WHO regional experts who spoke on behalf of potential recipient countries within their regions¹⁰. Though representative countries have different perspectives on this issue,

the broadly defined preference was for the H5N1 vaccine stockpile to be placed close to each region and for at least a portion to be held in filled doses (see Figure 5). However, most countries were flexible regarding the exact placement and configuration as long as the stockpile is configured in a way to provide the highest likelihood that the vaccine will be available and delivered in a timely manner when needed.

Figure 4: Storage requirements of stockpiled products

Storage Requirements: Vaccine (2 - 8° C)

Product	Doses per Pallet	Total Pallets	Footprint (M ²)
H5N1 Vaccine	82,000	1,835	918

Storage Requirements: Materials (<25° C)

Product	Required per dose	Total Req. (M)	Units per Pallet	Total Pallets	Footprint (M ²)
Ice packs	1 / 1,250	0.12	4,800	25	8
Case shippers	Varies	0.001	12	84	21
Syringe	1.1 / 1	165	42,900	3,846	962
Mixing syringe	1 / 10	15	27,190	552	138
Safety boxes	1 / 100	1.5	1,515	990	248
Masks	1 / 20	7.5	27,346	274	69
Gloves	2 / 1	300	360,000	833	208
Alcohol Swabs	1 / 1	150	105,495	1,422	355
Band Aid	1 / 1	150	2,057,143	73	18
Cotton	1 / 1	150	507,357	296	74
Paper	1 / 1	150	200,000	750	188
Total Materials				9,137	2,290

Figure 5: Select recipient country design preferences

Country	Preferred Placement	Preferred Vaccine Form	Comments
Country A	Regional	Filled Doses	"I think regional is best. . . . Pick a location that can access all the countries in the region."
Country B		Filled Doses	"WHO regional offices know the regions and can help coordinate."
Country C		Filled Doses	"It is difficult to travel around Africa. . . . Stockpile should be at sub-regional or regional level."
Country D	Central	Filled Doses	"Centralized would be best."
Country E	Regional	Filled Doses	"It must be regional."
Country F		Filled Doses	"The regional office is a good coordinator."

- **Supply certainty** – *the likelihood that stockpiled vaccine will reach the recipient countries*. The political and logistical environment that is likely to exist (if an event grows in intensity) could pose several challenges to accessing and delivering the stockpiled vaccine to recipient countries. In particular, two possible challenges are foreseeable: 1) the “nationalization” of the stockpile and inability to export the H5N1 vaccine; and/or 2) the closure of airports and consequent limitations in air transport that would delay or inhibit shipment of the H5N1 vaccine. The first of these challenges was recently demonstrated during a communicable disease outbreak in which a vaccine-producing country closed its borders to export, thus cutting off access to half of global emergency supplies¹¹. Similar outcomes are easy to imagine in an influenza pandemic. One approach to mitigate this risk would be to place the stockpile in countries with very small populations and/or with their own H5N1 stockpiles as the portion of the stockpile at risk if these host countries use the vaccine for their own populations would be minimized. An example of the second challenge is the disruption that the SARS outbreak had on global air cargo transport^{12,13}. Global air cargo experts, crisis responders, and pandemic planners – many of whom lived through SARS – categorically recommend the placement of the stockpile in major transportation hubs to best ensure access to air transport during a major health emergency¹⁴. The logic is that those hubs, having the best infrastructure to deal with emergencies and being integral to even the most basic movement of goods, are most likely to remain open in the case of an outbreak. Further, those hubs are most likely to have a large fleet of aircraft available at the time of an outbreak, making it possible to access aircraft for the special purpose of stockpile deployment even if air traffic is severely restricted.

To support the assessment of the first two criteria (cost and response time), an expansive logistical model was constructed, which allowed quantification of costs and response times across all hypothesized stockpile configurations. The model is customized to the parameters of known or likely H5N1 vaccine manufacturers, taking into account differences in the configuration of products and the locations of production facilities, and accounts for all ancillary supplies. This model can be run across countless combinations of 25 different stockpile locations and customized across the entirety of the stockpile supply chain – from manufacturer to stockpile to recipient country (for more details on the cost and logistics model, see Appendix IV).

The stockpile logistics costs and service times data used in the model were estimated based upon guidance provided by potential service providers (e.g., third party logistics providers (3PLs), cargo air carriers, freight forwarders) as part of a sample Request for Information (RFI) process¹⁵. Non-logistic cost and service time data (e.g., testing vaccine, management costs) were derived from interviews with manufacturers, service providers, and other stockpile holders. All costs represent those likely to be paid by WHO (or the stockpile host) for a stockpile of this nature intended for lower and middle-income countries. Aside from donated vaccine, no other form of donations were factored into this effort, but it may be possible to reduce some of the estimated costs through corporate or government donations of critical stockpile materials or services.

Analysis of other criteria was supported by nearly 200 interviews / consultations with potential recipient country representatives, WHO and UNICEF functional and regional experts, existing H5N1 vaccine stockpile holders, vaccine manufacturers, ancillary supplies manufacturers, logistics providers (storage, transportation, and services), and various

academics, regulators, and related government agencies (see Appendix I for a complete list of contributing organizations).

6. Stockpile logistical design

A range of logistical design options were considered, each with tradeoffs across the five main criteria. The following strategy scored highest across the criteria: holding the stockpile in filled doses, in one-to-three strategic locations, with ancillary supplies (e.g., syringes, personal protective equipment) stored with the vaccine. However, other considerations may factor into the final design decision.

The tradeoffs that drove the individual components of this strategy are the following:

a) The outbreak containment portion of the stockpile must be held in filled doses

There are two basic storage options for the stockpiled H5N1 vaccine: filled doses or bulk. "Filled doses," in this case, means holding vaccine in filled vials (a 10 dose presentation is assumed throughout). "Bulk" means large, non-filled quantities of vaccine which must be filled into vials prior to stockpile deployment.

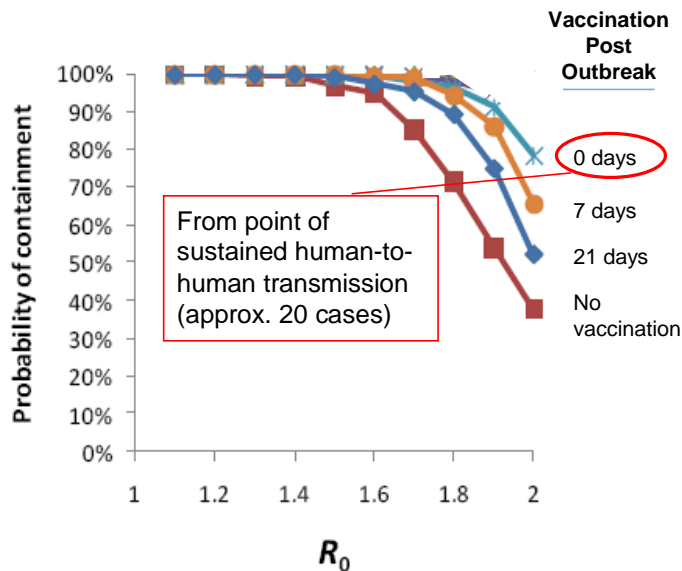
To understand the vaccine form decision for the outbreak containment portion of the H5N1 vaccine stockpile, it is important to first understand what will be required to contain an H5N1 outbreak when it occurs. Outbreak modeling conducted at Imperial College (see Figure 6) shows vaccine needs to be delivered within 3 – 4 weeks of the start of sustained human-to-human transmission (about 20 cases) to have any benefit in containment efforts (with each passing week lowering the potential that the outbreak will be contained)¹⁶. As the minimum time required to deliver vaccine held in bulk form is nearly four weeks¹⁷, the only viable solution is to hold outbreak containment vaccine in filled doses that are immediately ready for deployment.

b) Logistical tradeoffs also favor holding the essential populations portion in filled doses, though this is less clear than the outbreak containment portion.

As discussed above, the 50 million doses allocated to outbreak containment must be held in filled form. For the remaining 100 million doses, holding bulk vaccine is possible. The key tradeoff in this decision is the cost advantage of holding bulk versus the response time and logistical flexibility provided by a filled dose solution. The following assumptions were used to evaluate this tradeoff:

- **Replenishment:** Replenishment, in this case, refers to the need to replace vaccine when it has reached expiry and can no longer be used (vaccine could also require replenishment because it has been used in outbreak containment operations, but that type of replenishment does not factor into the form decision). This further assumes that the stockpile will be maintained for longer than the eventual shelf life of the start-up vaccine, and additional vaccine will, therefore, need to be purchased (or donated) to replace the start-up vaccine¹⁸.

Figure 6: Impact of vaccination timing on probability of successful outbreak containment¹⁹



- Antigen shelf life and rates of degradation:** Interviews with current H5N1 vaccine stockpile holders, H5N1 vaccine manufacturers, and other experts on these vaccines made it clear that there are no easy answers to the question of H5N1 antigen shelf life. To start, these vaccines are all recently developed²⁰, with the result that extensive data have not yet been collected on their stability. Further, data that have been collected have shown that shelf life and degradation rates vary based on the reference strain used (e.g., shorter for the Vietnam strain, longer for Indonesia), the manufacturer, the production process, and the vaccine presentation²¹. That being said, the general consensus around the best assumption for antigen shelf life is that if held in filled vials it is likely to retain its immunogenic properties for three years. If held in bulk form, the protein content is expected to degrade 10% per year (with that 10% loss replaced each year). This degradation can continue for five years before the remaining antigen must be discarded and replaced. This degradation schedule results in an effective bulk antigen shelf life of approximately four years.
- Adjuvant shelf life and storage:** Most of the H5N1 vaccine expected to be used in the stockpile utilize “novel” adjuvants that can be purchased and stored separate from the antigen²². This means that adjuvant shelf life can be considered separately from antigen shelf life. With respect to adjuvant shelf-life, uncertainty exists, but the best assumption is that it will be viable for five years and that the form in which it is held (filled vials or bulk) will not meaningfully impact the shelf life²³. Given the longer shelf life of adjuvant, it is expected that it will be held separate from the antigen (for applicable vaccines) and mixed at the time of delivery (i.e., “bedside mixing”).
- Vaccine Cost:** A review of the H5N1 vaccine purchases that have been made by other stockpile holders (in high-income countries) suggests a pricing of approximately \$7 – \$20 per complete vaccine dose (i.e., filled antigen and adjuvant)^{24,25,26,27,28,29}. However, based on discussions with vaccine manufacturers, it is reasonable to assume that vaccine will be offered to the H5N1 vaccine stockpile at a substantial discount to the prices charged to high-income country stockpiles. Discussions with the vaccine manufacturers provided a range of \$1 - \$5 per complete dose³⁰. For modeling purposes, we have assumed \$3 per

complete dose (with a 2.5% annual inflation rate – this rate applies to all costs throughout the cost modeling work³¹).

- **Adjuvant cost:** Vaccine manufacturers have indicated that the adjuvant (in the case of manufacturers who are using “novel” adjuvants) will be a significant portion of vaccine cost³². For modeling purposes, it was assumed that adjuvant will make up half (50%) of the price of each complete vaccine dose.

Since the adjuvant represents half of the expected price of the vaccine and the adjuvant shelf life is not affected by the form in which it is stored (filled doses or bulk), nearly half of the cost of vaccine replenishment will not be affected by decisions around vaccine form. Further, since the outbreak containment portion of the stockpile must be held in filled doses, only the 100 million dose essential populations portion is eligible for cost savings from bulk storage. Taken together, the cost savings associated with holding vaccine in bulk as opposed to filled doses is relatively modest – a difference of only 9% of the total stockpile cost if the stockpile is maintained for two replenishment cycles (i.e., approximately 9 years).

Though a 9% savings on a stockpile of this scale deserves serious consideration, this must be weighed against the substantial non-cost benefits of holding vaccine in filled vials:

- **Faster stockpile response time.** Based on interviews with vaccine manufacturers and contract fillers, formulation and filling of bulk vaccine is expected to add a minimum of 20 days to the stockpile response time in the best case. That additional time could actually exceed 40 or more days if lower volume filling sites are selected or there are any delays in the filling or testing processes³³.
- **Certainty of successful access to and deployment of the vaccine.** The majority of viable fill and finish capacity is in countries with large populations³⁴. In order to be filled, the vaccine would have to be stored in or pass through one of these countries. As discussed earlier, countries with large populations carry an increased risk of stockpile nationalization. Vaccine held in filled doses, on the other hand, provides the ultimate flexibility in stockpile placement, allowing the selection of locations with low risk of supply disruption, ideal logistical capabilities, and attractive geography.
- **Lower management complexity.** The need to formulate and fill the bulk vaccine adds complexity to the management and deployment of the stockpile. In the inter-pandemic period, contract fillers (if used) would have to be certified by the manufacturers to fill their vaccine and associated technology transfers would need to be facilitated. These certifications would be complex for the vaccine manufacturers to establish and for WHO to maintain³⁵. At the time of deployment, filling will add several steps to the deployment process in a time of likely unstable conditions thereby increasing the risk of error or delay. Finally, as the outbreak containment stockpile must be held in filled doses, holding the essential populations portion in bulk would require two parallel stockpiles to be managed with different structures, deployment strategies, requirements, and vendors.
- **Politically attractive.** Recipient countries understand these non-costs tradeoffs and have voiced that they consider a filled strategy most attractive. As a result they are less likely to see a bulk strategy as a viable solution to provide them with timely access to H5N1 vaccine in the case of an outbreak³⁶.

Substantiating this view, the majority of existing country-specific H5N1 stockpiles and other global vaccine stockpiles are held in filled or filled-equivalent form. Those countries that have chosen to hold bulk H5N1 vaccine stockpiles stated that guaranteed access to filling capacity and the ability to pre-deploy their stockpiles were the major factors in their

decisions³⁷. Those assurances, however, would not exist for the H5N1 global stockpile under consideration.

c) Placing the stockpile in one-to-three strategic locations would balance country preferences and complexity concerns.

Various stockpile configurations were tested for this analysis, including regional, sub-regional, manufacturer-based, and centralized / semi-centralized. Example distribution networks were analyzed from a set of 25 cities, chosen based on their ability to fulfill various stockpile criteria (for a full list of the cities examined, see Appendix III). Modeling showed little cost difference between the different configurations that were tested. This was largely due to the relatively small portion of overall costs attributable to storage and transportation (less than 10% of the total of a two-replenishment stockpile) and the fact that costs tended to be offsetting (e.g., having more location decreases transportation cost, but increases storage and management costs)³⁸.

The main tension is between the preferences of recipient countries and the need to reduce stockpile complexity. In particular, recipient countries stated a preference for a regional stockpile configuration (i.e., a portion of the stockpile held in each WHO region – see Figure 5 above). However, adding locations to the stockpile configuration increases the difficulty of managing the stockpile in both the inter-pandemic period and upon an outbreak. Reducing complexity is most critical for outbreak containment, favoring the placement of the entire containment stockpile in a single site. For the essential populations component of the stockpile, selecting a limited number of sites (i.e., up to three) that are attractive to the maximum numbers of recipient countries, provides the best balance.

d) Locations considered for stockpile placement should have superior logistical infrastructure, top tier cargo airports, and small populations.

Over 100 locations were initially considered for the placement of the stockpile with detailed modeling conducted on a prioritized set of 25 countries. These locations included logistical hubs, WHO regional office locations, locations recommended by recipient country representatives, locations that have been chosen for other similar stockpiles, and cities near manufacturing sites (for a complete list of locations considered, see Appendix III).

As with the stockpile configuration, the specific location selection has a minimal impact on total cost. This is due to the overall small portion of cost in storage and transportation and the fact that costs tended to be offsetting (e.g., countries with low storage costs tend to have increased transportation costs).

Therefore, selection of locations should be driven by the non-cost criteria:

- **Response time:** Modeling showed that stockpile response time was highly sensitive to the logistical capabilities of the host cities. This is especially true of the cargo capabilities of the cities' airports, with smaller airports adding days or weeks to the deployment time. This pointed to host cities needing to have world class logistical infrastructures and cargo airports.
- **Supply certainty:** Supply certainty risks can be mitigated by placing the stockpile in countries with small populations, with existing H5N1 stockpiles, and in cities with major logistical hubs (i.e., have world-class cargo airports).

- **Political attractiveness:** Recipient country representatives in interviews tended to prefer that the stockpile be placed in the cities where their WHO regional office was located³⁹ or in other major cities within their region. The WHO regional offices are in countries with large populations (i.e., New Delhi, Manila, Washington, Cairo) and/or in cities with inadequate logistical capabilities and air cargo facilities (i.e., Brazzaville)⁴⁰, so other regionally strategic cities were considered. In particular, cities that have been selected for other aid hubs or stockpiles were considered good proxies for regionally attractive locations.

Figure 7 shows an evaluation of the potential stockpile host cities based on the criteria above. This comparison leads to the prioritization of countries with characteristics similar to Singapore, Dubai, and Panama City. Though a full site selection process will need to be conducted with a complete assessment of factors such as facility availability, host country preferences, and pricing, cities with these characteristics should be favored.

Figure 7: Example of Cities’ Ratings in Key Placement Considerations^{41,42,43,44,45}

City	Logistics capability	Air cargo rank	Storage Cost (Cold)	Supply Certainty	Aid Hub	WHO Regional Office
Singapore		9	\$80	High		
Dubai		18	\$76	High	WFP, UNICEF	
Panama City		n/a	\$46	High	WFP, UNICEF	
Hong Kong		2	\$97	Low		
Copenhagen		48	\$133	Medium	UNICEF	EURO
Geneva		n/a	\$133	High		WHO
Kuala Lumpur		31	\$74	Medium	WFP	
Shanghai		8	\$97	Low	UNICEF	
Accra		n/a	\$63	Medium	WFP	
Bangkok		19	\$74	Medium		
New Delhi		41	\$108	Low		SEARO
Manila		39	\$70	Medium		WPRO
Cairo		n/a	\$63	Medium		EMRO

	Top Tier
	Lowest Tier

e) Holding ancillary supplies (e.g., syringes, PPE) with the vaccine will increase the likelihood of success without raising costs.

The purchase, storage, and deployment of ancillary supplies is estimated to represent less than 10% of the total stockpile cost, assuming a 2-replenishment stockpile (for a complete list of the supplies included along with their physical specifications, see Figure 4 above). This is largely driven by the fact that all ancillary supplies are in regular use and the assumption that

they will be able to be “sold back” to UNICEF or individual nations at cost prior to expiry. This will allow ancillary supplies to be stockpiled with no, or very little, replenishment cost. Because ancillary supplies do not require cold storage – ambient storage, less than 25°C is assumed⁴⁶ – the storage costs are also low despite their large volume⁴⁷. Given these factors, it is not surprising that various storage strategies for the ancillary supplies showed little difference in cost⁴⁸.

Since cost differences are minimal and vaccine cannot be delivered without these ancillary supplies, the dominant criteria for ancillary supplies placement becomes risk mitigation (i.e., ensuring that the vaccine can be properly delivered when needed). Outbreak response experts universally agreed that the execution risk can be best minimized by placing the ancillary supplies with the vaccine and delivering them together.

7. Stockpile replenishment options

7.1. Considerations around replenishment of stockpile vaccine

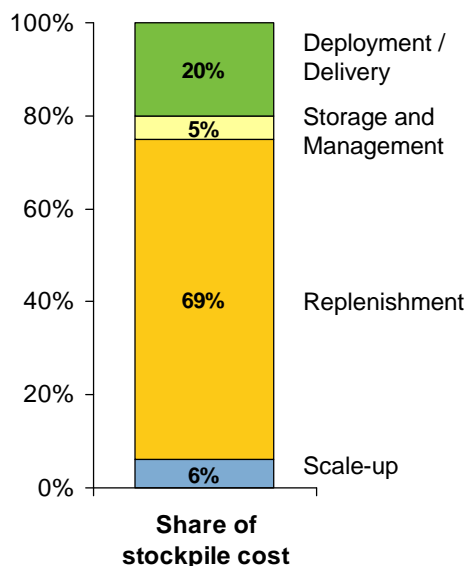
Given that vaccine that will be held in the H5N1 vaccine stockpile will have a limited shelf life, it will be necessary to replenish the vaccine if the stockpile is to be maintained beyond the 3 year expected shelf life of the donated vaccine (with ongoing testing potentially extending that time). Currently, manufacturers have not committed to donate vaccine for stockpile replenishment, so this vaccine may have to be purchased by the stockpile.

The need to replenish vaccine creates a complex set of decisions due to three factors:

- **Vaccine replenishment will be very costly relative to other stockpile costs, so decisions around replenishment will drive the funding need.** To put this cost in context, each full replenishment cycle of 150 million doses of vaccine would cost \$450 million in nominal terms (in nominal terms without accounting for inflation)⁴⁹. The average replenishment cycle would cost \$360 million (as adjuvant has a longer shelf-life and would not need to be replenished as often). When compared to the approximately \$60 million required to pay for all ancillary supplies for the life of the stockpile and \$7 million per year for stockpile storage and transportation, it is clear that the replenishment cost will need to be carefully managed. As seen in Figure 8, replenishment accounts for approximately 70% of the total costs for a stockpile with 2 replenishment cycles.
- **The number of replenishment cycles required is not possible to predict upfront.** This is driven by two uncertainties related to the stockpile:
 - **The vaccine replenishment interval is not known and may vary significantly.** As discussed earlier, the information on the likely shelf life of H5N1 vaccines is incomplete and inconclusive. This means that the funding requirement for the H5N1 vaccine stockpile cannot be definitively determined going into its creation. Further, the shelf life of the vaccine could vary for each replenishment cycle as evidence has shown that vaccine stability can vary with changes in the virus, manufacturer, production method, and form.
 - **The length of time needed to maintain the stockpile is uncertain.** The next influenza pandemic could occur next year or twenty years from now. That

uncertainty makes it difficult to know how long to maintain stockpile commitments and raises the risk of donor fatigue if the pandemic does not occur for many years. In addition, new vaccine technologies could emerge that would eliminate the need to stockpile H5N1 vaccine or public health concerns could shift away from pandemic influenza.

Figure 8: Cost profile for a 2-replenishment, filled dose stockpile (life of 9 years)



- **Establishing a stockpile of 150 million doses at a single point in time will not occur without some purchase of vaccine or changes to the manufacturer pledges and WHO's requirements.**

Formal pledges of intentions to donate 110 million doses of H5N1 vaccine to the stockpile have been received: GlaxoSmithKline⁵⁰ for 50 million doses and Sanofi Pasteur⁵¹ for 60 million doses. Though no other formal pledges have been made, several manufacturers have expressed a willingness to donate vaccine. In theory, such donations would make it possible to establish the H5N1 vaccine stockpile without any upfront purchase of vaccine. However, there are several challenges associated with using only donated vaccine to establish the stockpile.

WHO does not ordinarily accept vaccines into a stockpile unless those vaccines have been licensed by a national regulatory agency, and prequalified by WHO. At the moment, only one H5N1 vaccine has been licensed – GSK's Prepandrix by EMEA⁵² – and none have been prequalified. Given expected timelines for licensure and prequalification, it is expected that the earliest that vaccine would be available from any manufacturer would be late-2009 and will vary by manufacturer. Further impacting the timeline, both GSK and Sanofi Pasteur have stated that their donations will be made over a period of three years^{53,54}.

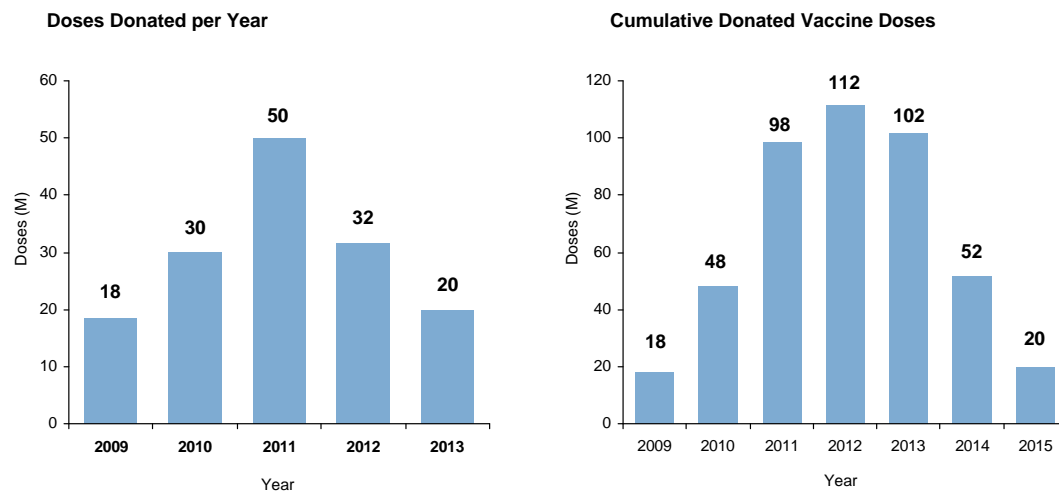
To understand the impact of these factors on the creation of the H5N1 vaccine stockpile, donations were modeled over time. For modeling purposes, it was assumed that manufacturers' donation will be made over three years, starting at the time of the

manufacturers' expected prequalification of H5N1 vaccine at the donating facility⁵⁵. For those manufacturers who have indicated an interest in pledging, but have not yet suggested a number of doses, it was assumed that they would donate enough vaccine to complete the 150 million dose stockpile and that those donations would be in proportion to their share of the current seasonal influenza vaccine market⁵⁶. Using these assumptions, the projected donation schedule shown in the left chart in Figure 9 was obtained. When product expiry is factored into this view (see right chart), donations alone would not result in a stockpile that reaches 150 million doses at any point in time.

In order for the H5N1 vaccine stockpile to have 150 million doses at one point in time, one of the following actions would have to occur:

- 1) WHO accepts unlicensed vaccine and /or vaccine that is not prequalified;
- 2) The donation schedules are revised;
- 3) Vaccine is purchased to supplement manufactures' donations

Figure 9: Potential Vaccine Donation Schedule Based on Expected Licensure of Donated Vaccines



Based on these considerations, the global community must make a set of complex decisions around replenishment including: Whether to purchase any additional vaccine up-front? Whether to fund additional replenishment cycles beyond the expiration or use of donated vaccine? Whether to pursue innovative financing mechanisms to mitigate the risks associated with the funding uncertainty?

7.2. Stockpile replenishment options

This study evaluated three major replenishment options, but recognizes that variants may exist on each option. Clear tradeoffs exist across the options that need to be weighed in finalizing the decision. Unless otherwise noted, it is assumed that these options will employ the logistical design discussed above (filled doses held in 1 – 3 strategic locations).

Option 1: “Pay-as-you-go” physical stockpile

In this option, the donated vaccine would be accepted, but funding would not be committed for additional replenishment. Following expiration of the stockpile (approximately three years after donation), the international community would need to re-evaluate whether to continue stockpiling and raise additional necessary funds. In order for the stockpile to be fully constituted with 150 million doses, WHO would need to relax its requirement that donated vaccine be licensed and prequalified and/or manufacturers would need to agree to change their planned donation schedules.

Estimated costs for Option 1: See Column 1 in Figure 10

- The required cost is \$85 million in nominal value, \$70 million in present value⁵⁷, primarily comprised of ancillary supplies, transportation, and storage / management (which could be further reduced if those services are donated)

Figure 10: Estimated replenishment option cost breakdown

Cost Components	Option 1: “Pay-as-you-go”	Option 2: Committed Replenishment 1 Cycle	Option 2: 2 Cycles	Option 3: Virtual Stockpile
Scale-up:				
▪ Donated Vaccine (not included in cost components)	\$450M	\$450M	\$450M	\$450M
▪ Materials & Transport.	\$60M	\$60M	\$60M	\$50M
Ongoing:				
▪ Replenishment	\$0M	\$260M	\$760M	\$0M
▪ Storage & Mgmt.	\$25M	\$40M	\$60M	\$20M
Total Nominal Cost	\$85M	\$360M	\$880M	\$70M
Total Present Value Cost	\$70M	\$280M	\$610M	\$65M
Total Present Value Cost (w/ innovative mechanisms)	\$70M	\$240M	\$520M	\$65M

Applicable financing mechanisms for Option 1:

- The available financing mechanisms for this option are fairly simple – funds will need to be provided upfront in the form of cash or donated services to pay for ancillary supplies and transportation (which comprise the majority of the cost)
- The storage and management cost (\$25 million) could be raised over time

Advantages of Option 1:

- This option allows the world community to make use of the donations offered by the manufacturers with minimal upfront commitment of funding. This may be especially attractive given the current economic environment.
- The lack of committed funding provides flexibility for the global community to regularly assess the continued priority and structure of the H5N1 vaccine stockpile.

- This option allows the stockpile to be configured according to the logistical design described above (filled doses in 1 – 3 strategic locations).

Disadvantages of Option 1:

- This option only provides for the existence of a stockpile for approximately 3 years if held in filled doses (with testing potentially extending that time). When the donated vaccine expires, additional funding would need to be raised to purchase replenishment vaccine (without a guarantee upfront that those funds would be available).
- The manufacturers and WHO would have to compromise on their proposed donation schedules and requirements for vaccine donation in order for a stockpile of 150 million doses to be constituted. Alternatively, the stockpile would never be comprised of 150 million doses at a single point in time.
- This option does not favor the use of innovative financing mechanisms, which would require longer funding commitments.

Option 2: “Committed replenishment” physical stockpile

In this option, the global community would commit to pay for some number of replenishment cycles and all other associated stockpile costs (e.g., storage, management, transportation). This could theoretically be any number of cycles (with each costing an average of \$360 million⁵⁸) – we examine below commitments of one or two replenishment cycles, which would guarantee the stockpile’s existence for approximately five or nine years.

A choice would exist for the first replenishment cycle: the purchased vaccine could either be used to replace donated expiring vaccine or some portion of the vaccine could be purchased up-front to configure an initial stockpile of 150 million doses, which would not be possible from donated vaccine alone. It is assumed here, that the purchased vaccine is used to replace donated expiring vaccine⁵⁹. It is assumed that for one replenishment cycle, replenishment adjuvant is not purchased (resulting in a five year stockpile life). For two replenishment cycles, one round of replenishment adjuvant is purchased⁶⁰.

Estimated costs for Option 2: See Columns 2 and 3 in Figure 10

- The estimated nominal cost of one replenishment cycle is \$360 million, \$280 million in present value, comprised of the upfront purchase of ancillary materials and transportation, on-going storage costs, and one cycle of antigen replenishment.
- The estimated nominal cost of two replenishment cycles is \$880 million, \$610 million in present value, comprised of the upfront purchase of ancillary materials and transportation, on-going storage costs, one cycle of adjuvant replenishment, and two cycles of antigen replenishment.
- Use of the innovative financing mechanisms discussed below could reduce the cost of this option to \$240 million for one cycle and \$520 million for two cycles if all funding is raised upfront.

Applicable financing mechanisms for Option 2:

- In addition to the financing mechanisms discussed for Option 1, this option enables two innovative financing mechanisms not viable with the other replenishment options:

A. Product Warranty: The first mechanism is designed to address the uncertainty in the stockpile replenishment costs. In this case, the stockpile could contract with

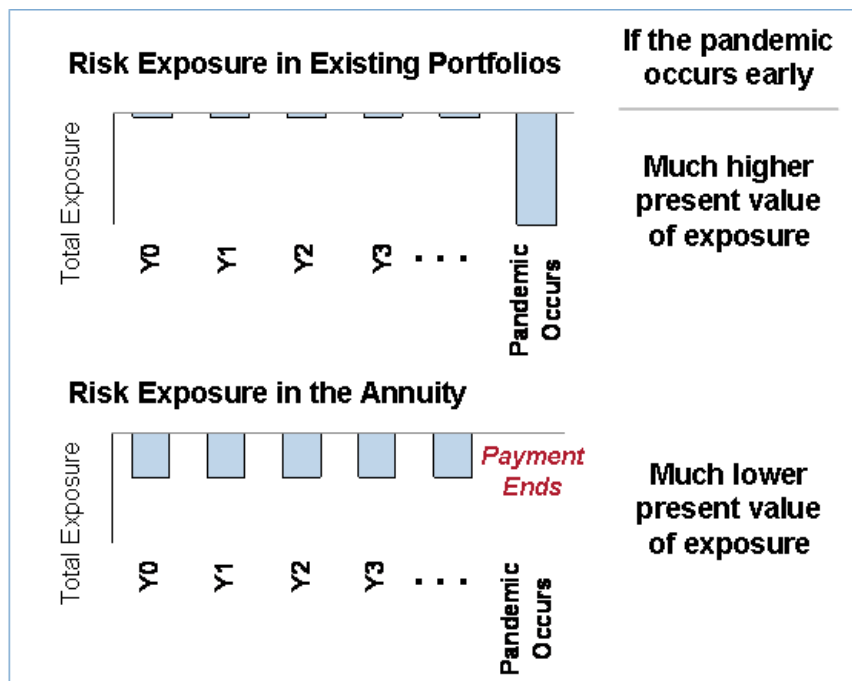
manufacturers to provide a “product warranty” on their vaccine. Under these warranties, the stockpile would pay an upfront or annual fee in return for a guarantee that the vaccine provided would maintain its immunogenicity within agreed parameters. If the vaccine proves to have a shorter than expected shelf life, the manufacturer would provide replacement vaccine. If it has a longer than expected shelf life, the manufacturer would benefit by not having to replace the vaccine. This mechanism has the advantage of transferring the uncertainty of vaccine replenishment timing to the manufacturers, who are best positioned to manage that uncertainty. It also enables funding to be committed to maintain a stockpile for a fixed period of time rather than for a number of replenishment cycles with unknown length.

Discussions with traditional insurers and capital markets experts revealed little interest in taking on this risk due to a lack of technical expertise in vaccine shelf life issues. Initial discussions with manufacturers revealed theoretical interest in this mechanism assuming certain, reasonable stipulations are met regarding the storage and maintenance of the vaccine. If this mechanism is pursued, the community should seek to gain as much knowledge as possible regarding H5N1 vaccine shelf life so as to ensure its ability to reach mutually agreeable terms for sharing the shelf life risk with the manufacturers.

B. Pandemic Annuity: The second innovative mechanism is designed to address the uncertainty of costs driven by the unknown timing of the pandemic. This mechanism involves the purchase of a “pandemic annuity” from a single or a consortium of reinsurers. Under the annuity, the stockpile would make an upfront payment to an insurer in exchange for a guaranteed stream of fixed payments for a set period of time (e.g., 10 years) or until the stockpile is fully deployed. This mechanism transfers the uncertainty of the pandemic timing to the insurer and guarantees that the stockpile will have funding for a fixed period of time.

A further benefit of this mechanism is that it provides a financial hedge to the reinsurers and may, therefore, lower the stockpile maintenance cost. By virtue of their life insurance business, reinsurers carry a high level of exposure to a global pandemic. This exposure is such that reinsurers have commissioned multiple studies to examine the potential impact of a pandemic on their finances, with estimates rising as high as \$133 billion in losses for a severe pandemic^{61,62}. In an effort to hedge against their exposure to the pandemic and other catastrophic mortality events, some reinsurers have issued catastrophe bonds^{63,64,65}. While these bonds pay high premiums to their holders, in the case of a catastrophic mortality event, a portion of the premium of the bond is forfeited and can be used to pay life insurance claims. A pandemic annuity would provide a similar hedge to reinsurers (see Figure 11). The value of this hedge combined with other factors could result in a present value reduction in stockpile funding requirements of 15 – 30%.

Figure 11: Hedge Value of Pandemic Annuity to Reinsurers



Advantages of Option 2:

- Ensures that stockpile will exist beyond the expiry of the donated vaccine
- Enables a stockpile to be configured with the full 150 million doses at one point in time
- Allows the stockpile to minimize funding uncertainties and potentially decrease the total funding need through the use of innovative financing mechanisms.
- Allows the stockpile to be configured according to the logistical design described above (filled doses in 1 – 3 strategic locations).

Disadvantages of Option 2:

- The cost of this option is considerable. Given the current financial environment, \$250 to \$600 million in present day funding may not be available and innovative financing mechanisms may not be feasible.
- It is possible that over the time of the committed funding window, global public health priorities could shift or breakthroughs in vaccine technology could change the inherent nature of vaccine stockpiling, creating a reprioritization of global health needs away from the H5N1 vaccine stockpile.

Option 3: Virtual stockpile

In this option, manufacturers would hold vaccine in their regular inventory to be delivered to the recipient countries at the time of need, rather than donating physical vaccine. As the vaccine would be held as part of manufacturers’ rolling inventory (i.e., sold before it expires), it would not need to be replenished. This “virtual” stockpile model is similar to the stockpiles that WHO and UNICEF currently hold for yellow fever and meningitis^{66,67}.

Unfortunately, this option is not feasible today as H5N1 vaccine would need to be in regular, routine use on a large scale. Manufacturers, therefore, do not have the ability to “roll the stock” to another user before it expires.

Estimated costs for Option 3: See Column 4 in Figure 10

- As there is no need to replenish vaccine in this option, the estimated cost is only \$70 million in nominal value and \$65 million in present value over a ten year period, comprised of ancillary supplies and storage / management (which could be further reduced if those supplies or services are donated).
- The annual cost to extend this design would be small (less than \$5 million per year). As most of the cost of this option is in the purchase of ancillary supplies, there is little difference between the nominal and present value cost.

Applicable financing mechanisms for Option 3:

- The available financing mechanisms for this option are fairly simple – funds would need to be provided upfront in the form of cash or donated services to pay for ancillary supplies and transportation (which comprise the majority of the cost).
- Funds for the storage of ancillary supplies and any other management costs could be raised over time.

Advantages of Option 3:

- Because the vaccine in this option would be held as part of manufacturers’ rolling stocks, this option has no specified timeline, end date, or replenishment cost.
- This option may be easily adapted as new technologies or stockpiling requirements emerge.

Disadvantages of Option 3:

- A virtual stockpile is only viable if H5N1 vaccine is in regular use, which is not a reality today. In addition, manufacturers have stated that this option is not necessarily consistent with their intent to donate vaccine to the H5N1 vaccine stockpile.
- Because vaccine is held with the manufacturers in this option, it does not allow the use of the physical logistical design described above.
- The major H5N1 vaccine manufacturers are almost exclusively located in developed countries with large populations⁶⁸. Access to the H5N1 vaccine stockpile would be subject to the risk of export restrictions at the time it is most needed with the consequent risk that it may fail to be delivered to the recipient countries when needed.
- Holding the vaccine at multiple manufacturer sites would increase the complexity of deploying the stockpile and potentially add to the eventual deployment time.
- This strategy may need to be pursued in bulk form due to potential differences in vaccine presentation / packaging from other demand sources (precluding the ability to roll stock). Holding in bulk form would extend the stockpile response time, adding a minimum of 20 days to the delivery time. In addition, filling capacity may not be immediately available for the H5N1 vaccine stockpile as host countries’ demands may take precedence, further delaying the deployment of the vaccine.
- Recipient countries largely recognize these risks and may not see this strategy as a viable solution to provide them with timely access to H5N1 vaccine.

Figure 12: Summary of design option tradeoffs

	Option 1: "Pay-as-you-go"	Option 2: Committed Replenishment	Option 3: Virtual Stockpile
Present Value Funding Need	\$70M	1 Cycle: \$280M 2 Cycles: \$610M	\$65M
Time Period Covered	~3 years	1 Cycle: 5 years 2 Cycles: 9 years	Timeframe Undefined (Indefinite if continuous rolling stock)
Feasibility	<ul style="list-style-type: none"> Requires future funding to pay for replenishment 	<ul style="list-style-type: none"> Requires significant committed funding 	<ul style="list-style-type: none"> Not feasible unless there is regular inter-pandemic production and use of vaccine
Deployment Timing	10 days	10 days	10 - 30+ days (Outbreak containment held in filled doses)
Supply Certainty	<p>High</p> <ul style="list-style-type: none"> Locations chosen to minimize nationalization and disruption risk 	<p>High</p> <ul style="list-style-type: none"> Locations chosen to minimize nationalization and disruption risk 	<p>Low</p> <ul style="list-style-type: none"> High pop., developed countries Filling capacity may not be available when needed

8. Stockpile deployment options

Throughout our consultations, there was clear consensus that measures should be taken in advance to ensure that funds are in place for deployment and delivery (given the size and immediacy of the requirement). However, there was considerable debate as to whether the global community or the countries themselves should fund these activities.

One argument is that deployment and delivery is a critical element of any vaccination strategy and assistance should be provided by the global community in advance to maximize the likelihood that vaccine ultimately makes it into the targeted arms. Given the size and immediacy of the funding need at the time of a pandemic, countries may not be prepared to fund these activities on their own. If required in year 10, the cost to deploy and deliver 150 million doses of vaccine to potential recipient countries is estimated to be over \$300 million in nominal terms and \$170 million in present value terms⁶⁹. As Figure 8 above shows, this is the second largest component of the stockpile cost and may come suddenly. Those in support of funding assistance for deployment and delivery, further argue that all countries (not just those covered by the H5N1 vaccine stockpile) will benefit from the timely deployment and use of the stockpile – the stockpile will help delay, or even prevent, a global pandemic and dampen the level of economic disruption and political upheaval that a pandemic could trigger.

The counter-argument is that individual countries' interests will be aligned with the funding need at the time of deployment and they should therefore fund these activities – there will be strong interest by countries in ensuring that they receive and deliver their share of the stockpile to protect their populations. While the total funding burden is \$300 million in nominal terms, the average cost per country is only \$2 million, a relatively small cost for countries to cover at the time of an emergency. In addition, approximately 95% of the cost is

driven by delivery with the country itself, with human resources accounting for the majority of that cost.

A hybrid argument is that the countries covered by the stockpile represent a mix of income levels, and assistance should only be provided to those least likely to be able to self-finance. For example, GAVI-eligible countries represent approximately half (\$150 million in year 10 nominal terms, \$80 million in present value) of the cost of deploying and delivering the H5N1 vaccine stockpile. Support could be provided to these countries by GAVI itself or other donors.

Regardless of whether the global community or the countries themselves fund the deployment and delivery, a set of financing mechanism options exist:

Cash financing: In the traditional, cash financing option, funds would be reserved upfront or guarantees would be made to ensure that funds are available when needed.

Deployment insurance: The uncertainty associated with the timing of the pandemic suggests the potential use of an insurance mechanism to manage the risk. Financing experts and insurers discussed the possibility of a “deployment insurance” policy that would provide funding for deployment and delivery costs at the time of distribution. This policy would transfer the timing risk to the insurer in exchange for upfront or ongoing payments and guarantee that funding is available when needed. However, given that this policy would add to an insurers’ already substantial pandemic influenza risk profile (see discussion of “pandemic annuity” above), it is unclear whether insurers would be willing to provide this product at favorable terms.

Guaranteed line of credit: An alternative option is the establishment of a guaranteed line of credit that can be drawn upon when required to pay for deployment and delivery costs. This line of credit could be held for a small annual cost (to compensate the financier for the loss of liquidity associated with holding the line of credit) and then drawn upon when needed. If it is backed by developed country governments with strong credit, the interest rate associated with the line could be negotiated in advance and is likely to be attractive. However, there are several complexities with this mechanism. First, clear agreement would need to occur upfront around repayment of the debt (i.e., which party and at what terms). Second, the potential financial havoc from a public health event of the magnitude that would result in stockpile deployment could increase the counterparty risk associated with the guaranteed line of credit (i.e., the creditor being unable to provide the credit when needed). Third, the current financial environment may make this mechanism less viable.

9. Next steps

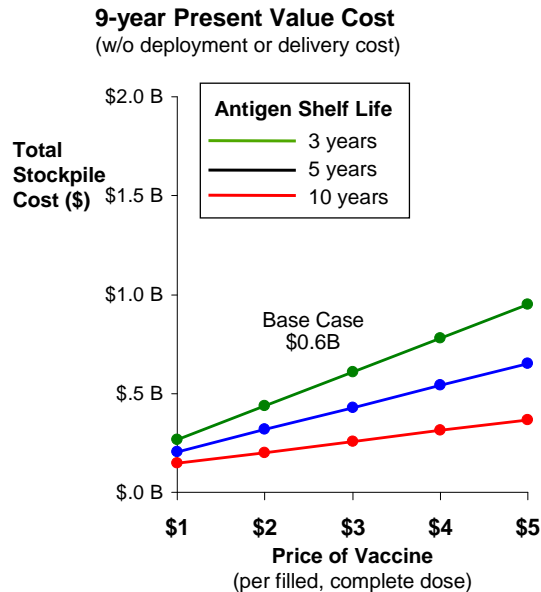
This work was intended to advance the global agenda around H5N1 vaccine stockpiling. Based on the proposed design options, it is recommended that several activities be undertaken to complete the design and creation of the H5N1 vaccine stockpile.

- **Test the critical cost assumptions**

The short-term and long-term cost estimates rely on two critical assumptions: (1) Price - Vaccine price of \$3 per complete dose and a 50 / 50 price split between antigen and adjuvant; (2) Shelf-life - Three year shelf life for filled antigen, five years

for bulk antigen, and five years for adjuvant (filled or bulk). These assumptions should continue to be tested as the expected funding needs for the H5N1 vaccine stockpile are highly sensitive to these assumptions (see Figure 13).

Figure 13: Stockpile Cost Sensitivity to Vaccine Price and Shelf Life



In addition, this effort was completed prior to the most dramatic effects of the global financial crisis. That event is likely to have had an impact on some of the assumptions used in this work (e.g., inflation and discount rates) and the attractiveness of some of the financing options discussed. These options should be reevaluated within the context of the current economic environment.

- Decide on the logistics and replenishment design of the stockpile**
 The global community needs to consider the options presented in this document and determine which of these best fit the needs for an appropriate international response to H5N1 outbreaks or pandemic. This needs to be combined with perspectives on available funding and additional potential donations of vaccine, materials, and/or services.
- Finalize detailed logistics (e.g., site selection) and build stockpile**
 Once the stockpile design has been determined, the remaining detailed elements of the logistical design should be finalized. Among these are: selection of specific locations (i.e., countries and facilities) for the stockpile; determination of how much vaccine will be held in each location; and development of detailed plans to stock product and deploy and deliver it when needed.

WHO will also need to finalize the vaccine donations and donation terms with the suppliers. This will include defining the delivery timing, vaccine form and presentation, liability waivers, and other vaccine specific requirements.

- Finalize financing mechanisms and raise funding**

The selection of the specific financing mechanisms should be evaluated within the context of the logistics and replenishment options pursued. As described, it may be possible to use a range of innovative financing mechanisms to decrease the funding requirement of the stockpile, manage risks, and make the funding schedule most attractive to donors. To determine the attractiveness of these options and finalize the selection, public health financing, capital markets, and insurance experts should be consulted.

In addition, the required funds to establish the stockpile will need to be raised. This should be conducted as a continuous process, working with potential donor countries, foundations, and other organizations and should begin as part of a broad-based communication effort.

Appendix I: Contributing Organizations

WHO (HQ and Regional Offices)

WHO Strategic Advisory Group for Immunization (SAGE)

Bill & Melinda Gates foundation

Potential Recipient Country Consultations

- Iran
- Mexico
- India
- Indonesia
- Nigeria
- Vietnam
- Thailand
- Kazakhstan

Regulators / Testing Agencies

- European Medicines Agency (EMA)
- Australian Therapeutic Goods Administration (TGA)
- British National Institute of Biological Standards and Controls (NIBSC)

Other Experts

- RTI International
- Imperial College
- CIDRAP
- UNICEF Supply Division
- World Food Program

Current National Stockpile Holders

- United States
- Australia
- Japan
- Switzerland
- Finland
- United Kingdom
- France

Ancillary Supplies Manufacturers

- Pa-Hu
- Morningside
- MEDECO
- Terumo
- Gerson & Co.
- Blow Kings
- HMD Healthcare

Vaccine Manufacturers

- Sanofi Pasteur
- GlaxoSmithKline
- Novartis
- Baxter
- CSL
- Omnivest
- Green Cross
- Korean CDC
- Microbix
- MedImmune
- Taiwan CDC
- Bio Farma
- Butantan
- Sinovac
- IVAC
- VACSERA
- Serum Institute
- Biological E
- BIRMEX
- IFMPA
- DCVMN

Logistics Providers

- Panalpina
- Armstrong & Assoc.
- FedEx
- UPS
- LifeConEx
- Americold
- D&D Distribution
- Sentry Logistics
- MBX Logistics
- DHL / Exel
- Menlo Logistics
- BAX Global
- Loginex Int'l
- Expeditors Int'l
- Schenker Int'l
- United Airlines Cargo
- Int'l Air Svc.
- DHL-Panama

Financing Experts

- GAVI
- Asia Development Bank
- Center for Global Development
- World Bank
- Resources for the Future
- Swiss Re
- Insurance Information Institute
- MBA Actuaries
- Guy Carpenter
- Oliver Wyman Financial Services
- Lion's Head Global Partners

Appendix II: Key stockpile characteristics

A. Characteristics of Vaccine and Supplies to be Stockpiled

The H5N1 vaccine stockpile is expected to hold both vaccine and ancillary supplies needed to deliver that vaccine. Given that the scope of the ancillary materials were not defined by SAGE, a broad interpretation was taken as to what could be included as part of the stockpile. The list of ancillary products is based on interviews with EPI and immunization campaign experts at WHO as well as pandemic preparedness experts more broadly. Product specifications were provided either directly by the manufacturers or through UNICEF Supply Division. In all cases, product characteristics have been aggregated to create weighted average dimensions, units per pallet, weight, etc. This was done to protect individual manufacturers' product specifications.

All told, the H5N1 vaccine stockpile will comprise nearly 11,000 pallets of vaccine and supplies – hundreds of times as many pallets as are held by the other WHO stockpiles. Its footprint would be ~3,200 square meters or ~55 meters by 55 meters. Transporting the stockpile will require nearly 200 cargo flights, employing approximately 10% of the global fleet of cargo aircraft⁷⁰. Full details on the storage requirements of the stockpile are provided in Appendix II Figure 1.

Appendix II, Figure 1: Storage requirements of stockpiled products

Storage Requirements: Vaccine (2 - 8° C)

Product	Doses per Pallet	Total Pallets	Footprint (M ²) ¹
H5N1 Vaccine	82,000	1,835	918

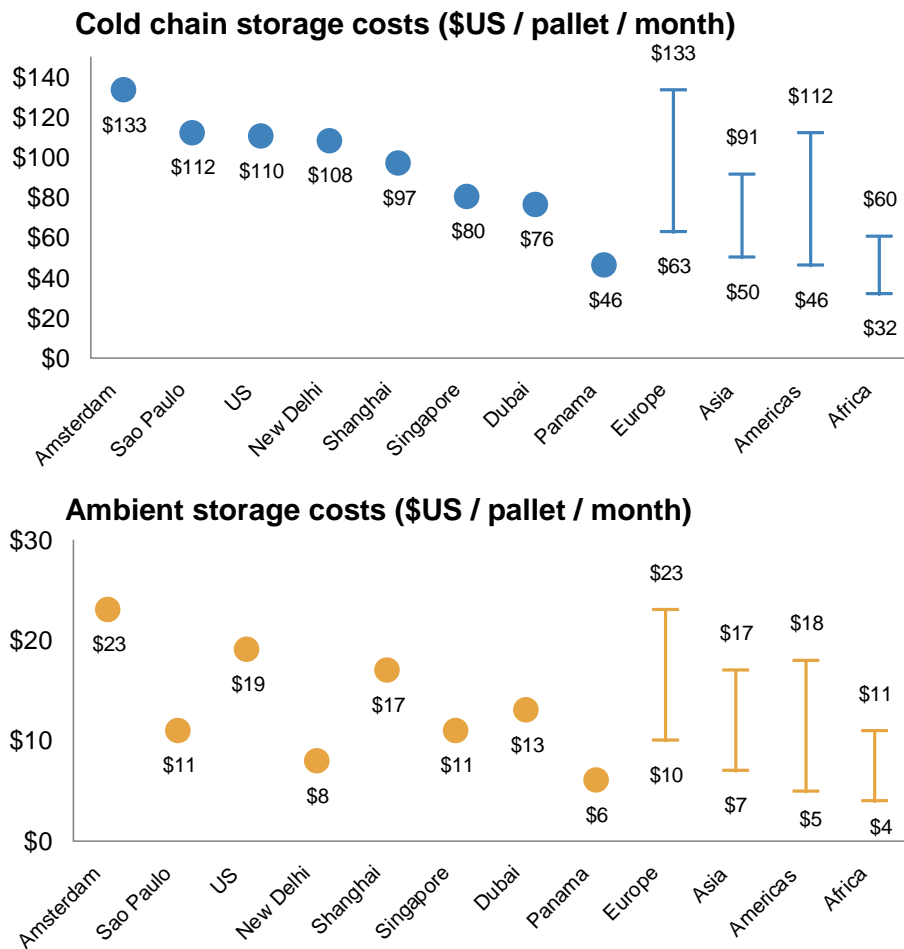
Storage Requirements: Materials (<25° C)

Product	Required per dose	Total Req. (M)	Units per Pallet	Total Pallets	Footprint (M ²) ¹
Ice packs ²	1 / 1,250	0.12	4,800	25	8
Case shippers	Varies	0.001	12	84	21
Syringe	1.1 / 1	165	42,900	3,846	962
Mixing syringe	1 / 10	15	27,190	552	138
Safety boxes	1 / 100	1.5	1,515	990	248
Masks	1 / 20	7.5	27,346	274	69
Gloves	2 / 1	300	360,000	833	208
Alcohol Swabs	1 / 1	150	105,495	1,422	355
Band Aid	1 / 1	150	2,057,143	73	18
Cotton	1 / 1	150	507,357	296	74
Paper	1 / 1	150	200,000	750	188
Total Materials				9,137	2,290

The cost of storing the vaccine and ancillary materials is shown in Appendix II Figure 2 below. The cost estimates shown here as dots are actual estimates given by logistics providers for specific locations (in the cases where multiple quotes were received for a location, the results were averaged). These costs assume storage of the entire stockpile in one location. In cases where the stockpile is stored in multiple locations, a scale curve based on interviews with service providers was applied. The impact of this scale curve is such that by moving from 1 to 4 locations, the price of storage increases by ~25%. These costs are also assumed to be for “inactive” stock, providing a slight discount on typical prices. It should be noted, however, that these were preliminary estimates and are not meant to represent formal bids.

For locations where detailed cost estimates were not received (shown by the lines below), prices were based on modeling of cost components (land, labor, capital, and utilities) and extrapolation from the pricing in known locations. These ranges were then tested with and confirmed by service providers.

Appendix II, Figure 2: Cold and ambient storage costs by city



B. Transportation Requirements and Options

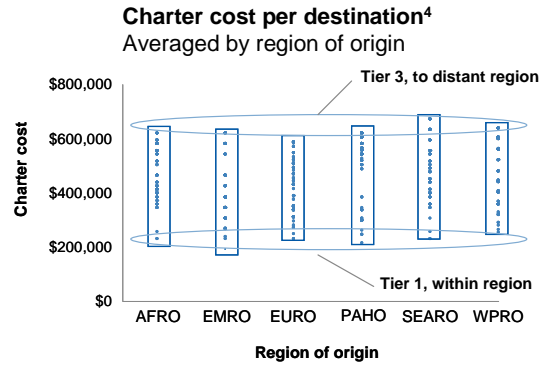
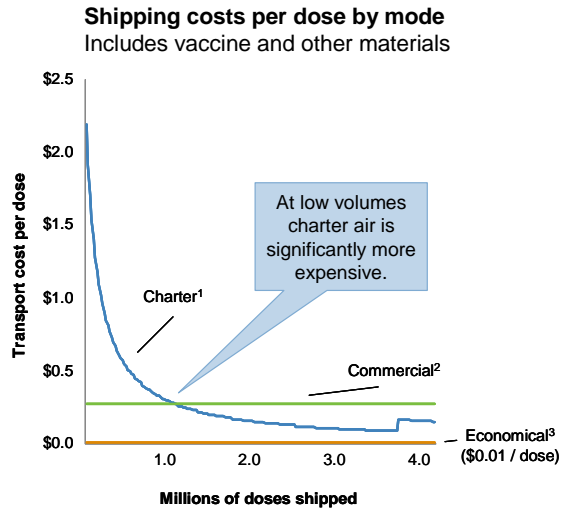
The transport of stockpiled vaccine and ancillary supplies was estimated for product shipment to the stockpile and subsequent shipment to recipient countries at the time of an outbreak. For the purposes of this analysis, it was assumed that the transport of vaccine to the stockpile occurred via commercial air while the ancillary materials were supplied via the “most economical mode” – typically sea freight or rail. For the deployment of the stockpile to recipient countries, a mix of charter, commercial, and “belly cargo” capacity, incorporating the most reasonable deployment time and cost efficient mode was used. The key considerations for each mode are included in Appendix II Figure 3 below.

Appendix II, Figure 3: Key shipping considerations

Mode	Key considerations	Implications
Charter	<ul style="list-style-type: none"> ▪ LTL (less-than-load) pricing ▪ Prices will be higher in pandemic ▪ Wide variance in capacity by plane 	<ul style="list-style-type: none"> ▪ Assume at least one plane per destination <ul style="list-style-type: none"> – However, assume commercial country receives <10 pallets ▪ Assume 50% premium for essential populations ▪ Assume DC-10 (480 m³) for all shipments
Commercial	<ul style="list-style-type: none"> ▪ Greater-actual-dimensional pricing (GAD) makes shipping ancillary supplies more expensive ▪ Pricing and access varies by type of carrier: <ul style="list-style-type: none"> – Integrators (e.g. FedEx) – Cargo airlines (e.g. Polar) – Belly cargo (e.g. United) 	<ul style="list-style-type: none"> ▪ Assume minimum pallet weight of 200kg ▪ Assume integrator service if >10 pallets ▪ Assume belly cargo if <=10 pallets
Economical (ground / sea)	<ul style="list-style-type: none"> ▪ Ship time requires active packaging to maintain cold chain 	<ul style="list-style-type: none"> ▪ Assume vaccine ships in 40' refrigerated container

In terms of transportation pricing, sets of representative point-pair pricing from a number of potential transportation providers were used. As price is heavily influenced by both the distance of the trip and the tier of the destination airport (because of the ability to fill a return flight), it was important to understand specific point-to-point costing and then extrapolate that on a broader basis. The results of this extrapolation are seen on the right side of Appendix II Figure 4. The left side of this figure shows the nature of commercial and charter pricing. Given that charter price is constant per flight, the economics of chartering aircraft can be attractive once the aircraft reaches more than ~50% capacity.

Appendix II, Figure 4: Pricing by transportation mode



Transport time

- Charter air: <1 day
- Commercial air: 1 – 5 days
- Economical: 3 days – 6 weeks

Appendix III: Candidate stockpile locations

Starting from a base of 100 potential stockpile locations, the list was narrowed to the 25 locations shown in Appendix III Figure 5. The narrowing was based on cities' ranking in the various evaluation criteria shown here (including logistic capabilities, airport cargo ranking, storage costs, supply certainty, city's selection for other stockpiles, and if it is a WHO regional office location) as well as a desire to model a range of different stockpile configurations. This led to some cities being eliminated simply because they were "logistically redundant" with other cities already included in the final set (e.g., Paris and Frankfurt were considered interchangeable from a modeling perspective). On the other hand, some cities were added to enable a broader set of regional scenarios (e.g., Warsaw) and still others in order to approximate manufacturer locations (e.g., Newark).

The sources used for the city rankings are:

- **Logistic capability:** World Bank LPI Index⁷¹ ranking of 1 – 10 = full ball; 11 – 25 = $\frac{3}{4}$ ball; 26 – 50 = $\frac{1}{2}$ ball; 51 – 75 = $\frac{1}{4}$ ball; >75 = empty ball
- **Air cargo rank:** Global air cargo ranking of city's airport from Air Cargo World⁷²
- **Storage cost (cold):** Cold storage cost per pallet per month. Derived from quotes from storage providers or extrapolation as described in Appendix II.
- **Supply certainty:** Based only on population of country where city is located; 2007 populations < 10 million = High; 10 million – 60 = Medium; >60 million = Low

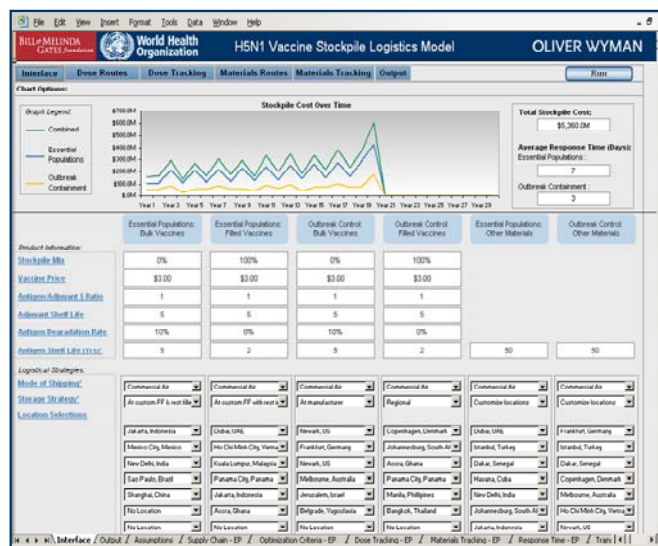
Appendix III, Figure 5: Evaluation of Candidate Cities

City	Logistics capability	Air cargo rank	Storage Cost (Cold)	Supply Certainty	Aid Hub	WHO Regional Office
Singapore		9	\$80	High		
Dubai		18	\$76	High	WFP, UNICEF	
Panama City		n/a	\$46	High	WFP, UNICEF	
Geneva		n/a	\$133	High		WHO
Frankfurt		6	\$132	Low		
Hong Kong		2	\$97	Low		
Copenhagen		48	\$133	High	UNICEF	EURO
Newark, USA		21	\$110	Low		
Tokyo		4, 23	\$173	Low		
Bangkok		19	\$74	Low		
Kuala Lumpur		31	\$74	Medium	WFP	
New Delhi		41	\$108	Low		SEARO
Shanghai		8	\$97	Low	UNICEF	
Warsaw		n/a	\$114	Medium		
Manila		39	\$70	Low		WPRO
Jakarta		50	\$74	Low		
Istanbul		n/a	\$114	Low		
Jerusalem		n/a	\$76	High		
Sao Paulo		36	\$111	Low		
Ho Chi Minh City		n/a	\$74	Low		
Moscow		n/a	\$114	Low		
Tehran		n/a	\$74	Low		
Accra		n/a	\$63	Medium	WFP	
Cairo		n/a	\$63	Low		EMRO
Havana	n/a	n/a	\$80	Medium		

Appendix IV: Cost and logistics model methodology

To model the costs and service times of the stockpile design options and scenarios, we built an interactive logistics and cost model. This model allows easy creation of design options and scenarios, sensitivity testing, and cost / service time breakdowns. The key features and output of the model are listed in Appendix IV Figure 6. This screen shot also shows a portion of the model interface, where all scenarios and sensitivities can be tested.

Appendix IV, Figure 6: Logistics and cost model overview



Key model features

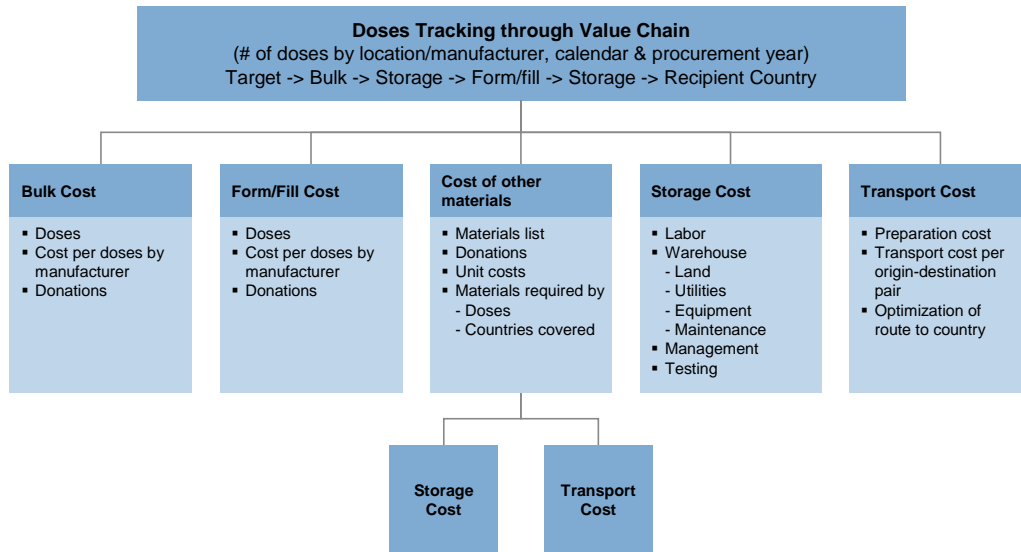
- One-click analysis of a set of pre-defined scenarios
- Ability to test user-defined custom strategies by varying key inputs:
 - Price
 - Form
 - Shelf life & degradation
 - Placement
 - Year of pandemic
 - Number of doses
- Ability to model impact of multiple outbreaks, larger dose sizes, vaccination upon expiry, and routine delivery

Key model outputs

- Costs
- Service time
- Doses delivered to country

The model track vaccine doses and stockpile costs through every step of the supply chain from the manufacturer to form / fill (if applicable) to storage to country based on the data described in the other appendices. It does this on an individual manufacturer basis so as to capture any subtle impact resulting from differences in product configurations and production locations. The model allows scenario building and sensitivity testing related to the timing of vaccine deployment, vaccine shelf life, adjuvant / antigen cost split, portion of the stockpile held in bulk or filled doses, locations where vaccine is to be deployed, number of “controlled” outbreaks, stockpile size, and use of vaccine upon expiry. For any of these scenarios the model returns the estimated total cost of the stockpile by year, min / max / average service time by stockpile location, and doses delivered to each country. Appendix IV Figure 7 shows the analytical methodology that drives the model.

Appendix IV, Figure 7: Logistic and cost model structure



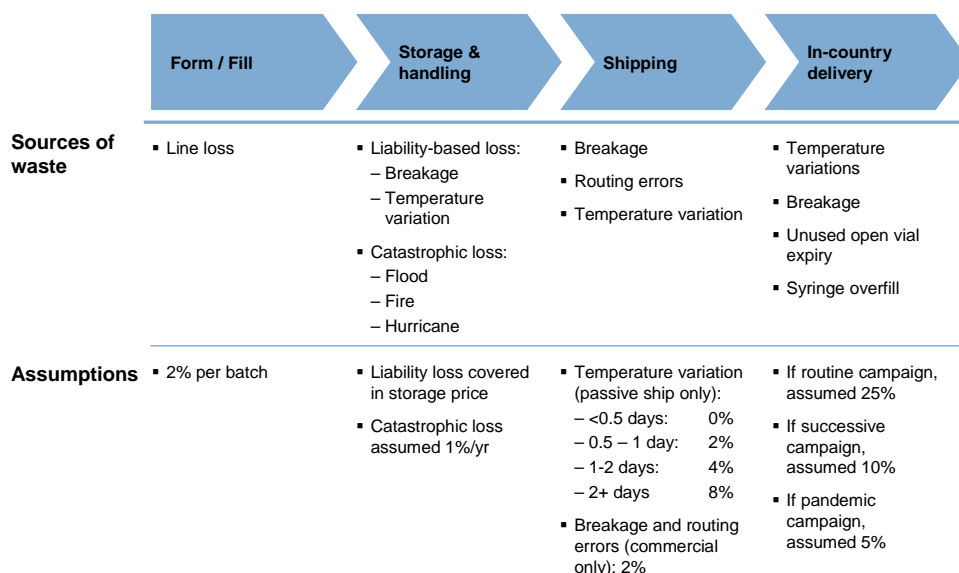
Appendix V: Other cost components

A. Wastage

Wastage can occur at several places in the stockpile supply chain and can be driven by the decisions that are made in the stockpile design. For example, deploying vaccine via commercial air over complex routings (e.g., from South America to Africa) can take several days. Though the cold boxes used to transport the vaccine are expected to keep vaccine within the target temperature range for 3+ days, the chance of container failure rises exponentially with each passing day⁷³. Further breakage, temperature variation, or catastrophic events could result in lost doses that need to be replaced at a cost to the stockpile.

Wastage assumptions were built on a supply chain step-basis (see Appendix V Figure 8) driven by interviews with experts in vaccine logistics and in-country operations.

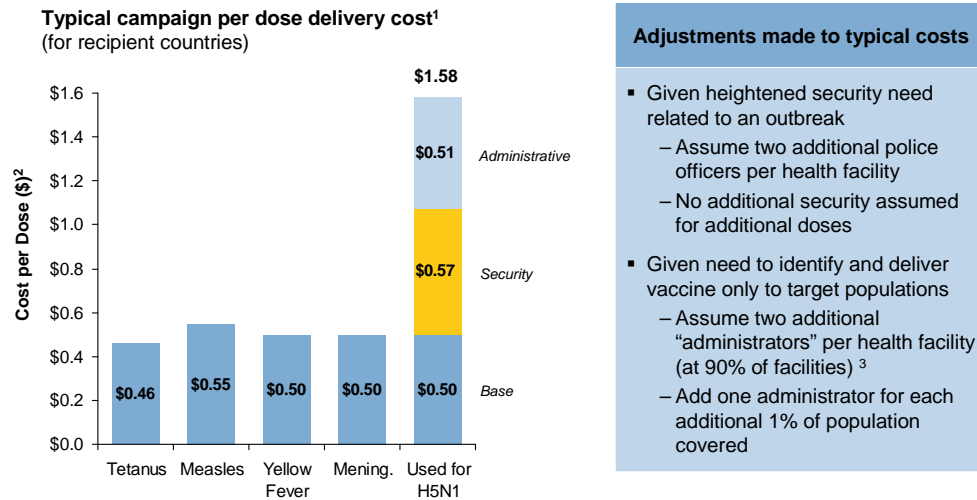
Appendix V, Figure 8: Vaccine wastage assumptions



B. In-country Delivery

In-country delivery costs were estimated using the Global Immunization Vision and Strategy (GIVS) costing model⁷⁴, which approximates different programmatic costs on a per country basis. The model was tailored to calculate estimated costs for H5N1 vaccine campaigns, then modified to reflect the special circumstances that are likely to exist when the H5N1 vaccine is deployed. The actual assumptions used are provided in Appendix V Figure 9

Appendix V, Figure 9: In-country vaccination campaign cost breakdown



C. Management and Testing Costs

A hypothetical management structure for the H5N1 vaccine stockpile was also developed and tailored to each stockpile design option (e.g., complex bulk options require more management than simple filled dose options). The data used to build the management structure is not publicly available.

Similarly, confidential data from regulators and testing agencies was used for vaccine testing and associated costs.

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- ¹ Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. "Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis." Lancet. December 23, 2006. 368(9554):2211-8
- ² World Health Assembly Resolution WHA 60.28. May, 2007.
- ³ WHO/IVB/06.13 and WHO/CDS/EPR/GIP/2006.1
- ⁴ Ferguson, et. Al.. "Strategies for Mitigating an Influenza Pandemic." Nature. July 27, 2006. pp. 448 – 452.
- ⁵ Anderson, Roy M. "Planning for Pandemics of Infectious Diseases." The Bridge. National Academy of Engineering. Fall 2006.
- ⁶ Ensuring Global Access: H5N1 Stockpile meeting. June 19, 2008. Seattle, USA. Hosted by the Bill & Melinda Gates foundation.
- ⁷ Capital cities used as a proxy for countries preferred logistical hub. Analysis did not extend to distribution beyond the delivery to each countries' capital city.
- ⁸ Derived from interviews with functional experts in each supply chain step: manufacturers, contract form / fillers, air cargo expeditors, warehouse / supply chain managers, cargo transporters, and emergency response expert. For full list of contributing organizations, see Appendix I.
- ⁹ Based on specific, individual product specifications for example products received from vaccine and ancillary supplies manufactures and the expected composition of the stockpile. Footprint assumes metric pallets two high for vaccine, four high for ancillary supplies
- ¹⁰ See Appendix I for full list of contributing organizations. The goal was to speak with a representative set of countries on this issue. Many views likely exist outside of those expressed here.
- ¹¹ "Yellow fever in Brazil." WHO Epidemic and Pandemic Alert and Response. February 5, 2008. Supplemented through interviews with members of WHO ARO who coordinated deliveries of yellow fever vaccine from the global emergency stockpile.
- ¹² "Spreading Panic." Flight International. April 22, 2003.
- ¹³ "Global SARS Trade Warning." The Cargo Letter. Issue 388.
- ¹⁴ For list of logistical service providers interviewed for this effort, see Appendix I.
- ¹⁵ RFI respondents included: DHL/Exel, FedEx, UPS, Menlo Logistics, and Sentry Logistics
- ¹⁶ Ferguson, Neil. Fraser, Christophe. Cauchemez, Simon. Burke, Don. Cummings, Derrick. Parmanto, Bambang. Schwartz, Ben. "Use of Vaccination During Pandemic Containment." Prepared for U.S. National Institute of Health MIDAS program and shared with SAGE in November 2007.
- ¹⁷ Based on a minimum time to fill the vaccine of 21 days and deployment time of 3 days.
- ¹⁸ Holding bulk vaccine also decreases storage and vaccine transportation costs as bulk vaccine requires substantially less space than filled vaccine. These cost savings, however, are small in comparison to the savings achieved through longer replenishment cycles (approximately 15% of the total bulk vs. filled dose savings).
- ¹⁹ Assumes three weeks to some level of seroconversion after delivery of first vaccine dose.
- ²⁰ The first purchase of H5N1 vaccine was made by US Department of Health and Human Services in September 2004 from Sanofi Pasteur. US Department of Health and Human Services Press Release. "HHS Orders Avian Flu Vaccine Doses As Preventive Measure." September 21, 2004.
- ²¹ Derived from interviews with current H5N1 vaccine stockpile holders, manufacturers, and other experts. See Appendix I for complete list of contributing organizations.
- ²² Three of the major manufacturers of H5N1 vaccine utilize novel adjuvants, each with the potential to be able to be stored separate from the antigen. Corporate press releases and trial data.
- ²³ Derived from interviews with current H5N1 vaccine stockpile holders, manufacturers, and other experts. See Appendix I for complete list of contributing organizations.
- ²⁴ GlaxoSmithKline press release. "Switzerland to Purchase GSK's H5N1 Vaccine for Pre-pandemic Use." October 18, 2006.
- ²⁵ Swissinfo.ch. "Swiss Announce Stockpile of Bird Flu Vaccine." October 18, 2006.
- ²⁶ UK National Health Service press release. "Bird Flu – Health Officials Finally Propose Big Rise in Antiviral Drugs for Pandemic." February 6, 2007.
- ²⁷ Baxter press release. "Baxter Receives Vaccines Contract from UK's NHS." February 24, 2006.
- ²⁸ "Flu-drug Stockpiles are Doubled as Britain Gets Ready for a Pandemic" Times Online. November 23, 2007.
- ²⁹ US Department of Health and Human Services Press Release. "HHS Orders Avian Flu Vaccine Doses As Preventive Measure." September 21, 2004.
- ³⁰ Range represents high and low quotes provided by manufacturers under various procurement scenarios and volumes. For a complete list of manufacturers consulted for this effort, see Appendix I.

³¹ This is the weighted average global inflation rate projected for the next 5 years. International Monetary Fund. World Economic and Financial Database. April 2008 Edition.

³² Based on a range of estimates provided by manufacturers under various procurement scenarios and volumes. For a complete list of manufacturers consulted for this effort, see Appendix I.

³³ Twenty additional days assumes filling by the donating manufacturers at their world class filling facilities. It further assumes immediate access to that filling capacity and best possible testing and approval times. Storage at filling facilities with less available filling capacity, delays in accessing filling capacity, or delays in testing and approval could add substantially to the time to deliver a bulk stockpile.

³⁴ Based on interviews with manufacturers, corporate websites, and press releases. Though many countries have manufacturers with some filling capacity, most of these have very low capacity and would, therefore, not be viable options for the filling of the H5N1 vaccine stockpile. Further, any form / filler would have to receive technology transfers and certifications to be able to fill the vaccine held in the stockpile. Finally, most form / fillers do not have the ability to fill emulsions as may be required for the vaccines with novel adjuvants.

³⁵ In interviews, manufacturers maintained that their strong preference would be to avoid doing technology transfers and certifications to contract fillers for the H5N1 vaccine stockpile, citing as part of that, the high cost and level of effort associated with establishing and maintaining these agreements.

³⁶ In interviews with recipient country representatives, all representatives requested that at least a portion of the stockpile be held in filled form (esp. for frontline health workers).

³⁷ Pre-deployment is defined as filling doses when epidemiological evidence suggests that the likelihood of an influenza pandemic has increased (but prior to actual sustained human-to-human transmission). It is considered unlikely that WHO would be able to pre-deploy the H5N1 vaccine stockpile because of the signal it would send regarding the likelihood of a potential pandemic.

³⁸ For a more complete explanation of the logistical analysis that drives this conclusion, see Appendix II.

³⁹ Among recipient country representatives interviewed, 75% stated a preference for stockpile placement in the same city as their WHO regional office.

⁴⁰ WHO regional offices are located in New Delhi, India; Manila, the Philippines; Washington DC, USA; Copenhagen, Denmark; Brazzaville, Congo; and Cairo, Egypt. See Appendix III for a full assessment of potential stockpile locations.

⁴¹ Logistics capability based on World Bank LPI Index: Arvis, Jean-Francois. Mustra, Monica Alina. Panzer, John. Ojala, Lauri. Naula, Tapio. "Connecting to Compete: Trade Logistics in the Global Economy." The International Bank for Reconstruction and Development / World Bank. 2007.

⁴² Air cargo rank based on annual tonnage from: "Top 50 Airports." *Air Cargo World*. July, 2008.

⁴³ Storage cost is the cold storage cost per pallet per month. For full description of methodology and sources see Appendix II.

⁴⁴ Supply certainty based on total population. For full explanation of methodology, see Appendix III.

⁴⁵ Aid hub and WHO regional office locations from WFP, UNICEF, WHO interviews and websites.

⁴⁶ Based on interviews with and product specifications received from ancillary supplies manufacturers.

⁴⁷ Ambient storage costs were typically quoted at 1/5th to 1/8th of those for cold storage on a per pallet basis. See Appendix II for detailed ambient / cold storage comparisons.

⁴⁸ Options examined for the storage of ancillary supplies included storage with manufacturers, at UNICEF aid hubs, at other aid hubs or stockpile locations (e.g., World Food Program), and with the vaccine.

⁴⁹ This estimate is provided for comparison purposes only. In reality, the expected longer shelf life of adjuvant and fact that it can be held separate from the antigen means that antigen and adjuvant will have separate replenishment cycles thus reducing the cost of each "round" of replenishment. For example, over the course of 5 rounds of filled dose antigen replenishment, only 3 rounds of adjuvant replenishment would be expected. That would yield an average cost per antigen replenishment cycle of \$360 million.

⁵⁰ Company press release. "GlaxoSmithKline to make unprecedented vaccine donation to WHO pandemic flu stockpile." June 13, 2007.

⁵¹ Company press release. "Sanofi Pasteur to donate 60 million doses of H5N1 vaccine to WHO over 3 years for its influenza vaccine global stockpile." June 16, 2008.

⁵² Company press release. "First pre-pandemic vaccine approved to help protect against pandemic influenza." May 19, 2008.

⁵³ Company press release. "GlaxoSmithKline to make unprecedented vaccine donation to WHO pandemic flu stockpile." June 13, 2007.

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- ⁵⁴ Company press release. “Sanofi Pasteur to donate 60 million doses of H5N1 vaccine to WHO over 3 years for its influenza vaccine global stockpile.” June 16, 2008.
- ⁵⁵ Based on interviews with each of the manufacturers, conducted between May and September of 2008. For complete list of manufacturers interviewed, see Appendix I.
- ⁵⁶ Market shares determined based on influenza vaccine capacity analysis performed from July – August 2008. Results to be published in Spring 2009.
- ⁵⁷ Assumes a discount rate of 6%. Based on expert interviews regarding other, similar financing programs.
- ⁵⁸ The expected longer shelf life of adjuvant and fact that it can be held separate from the antigen means that antigen and adjuvant will have separate replenishment cycles thus reducing the cost of each “round” of replenishment. For example, over the course of 5 rounds of filled dose antigen replenishment, only 3 rounds of adjuvant replenishment would be expected. That would yield an average cost per antigen replenishment cycle of \$360 million.
- ⁵⁹ If vaccine is purchased upfront, antigen and adjuvant will have to be purchased. Doing this would increase the cost of the first replenishment cycle from \$260M to \$430M.
- ⁶⁰ For the first replenishment cycle, this would result in one year of antigen shelf life with no adjuvant to use with it. For the second replenishment cycle, there would be one year of adjuvant shelf life with no antigen to use with it.
- ⁶¹ Toole, Jim. Potential Impact of Pandemic Influenza on the US Life Insurance Industry. MBA Actuaries. May 2007.
- ⁶² Weisbart, Steven. “Moderate Avian Flu Pandemic Similar to 1957 and 1968 Outbreaks Could Cost U.S. Life Insurers \$31B in Additional Claims – Severe Pandemic Could Generate \$133B in New Claims.” Insurance Information Institute Press Release. January 17, 2006.
- ⁶³ Insurance Information Institute. The Topic: Reinsurance. December 2008.
- ⁶⁴ Lewis, Michael. “In Nature’s Casino.” The New York Times. August 26, 2007.
- ⁶⁵ “Munich Re Sets Up \$1.5 Billion Pandemic Risk Cat Bond Facility.” Insurance Journal. February 21, 2008.
- ⁶⁶ GAVI Yellow Fever Vaccine Stockpile Interim Annual Progress Report. July 2004.
- ⁶⁷ International Coordinating Group (ICG) on Vaccine Provision for Epidemic Meningitis Control. Report of the ninth meeting. December 15 – 16, 2003.
- ⁶⁸ Manufacturing facilities for the major potential H5N1 vaccine manufacturers (GSK, Sanofi, Novartis, CSL, and Baxter) are located in Germany, France, the UK, Italy, the Czech Republic, Canada, Australia, and the USA. Corporate websites and publications.
- ⁶⁹ In-country delivery costs estimated through the use of the Global Immunization Vision and Strategy (GIVS) model with special provisions made for the additional administrative and security costs associated with administering vaccine during a pandemic. A full explanation of the methodology is provided in Appendix V.
- ⁷⁰ “A Review of Trends in the Airline and Commercial Jet Aircraft Industries.” The Airline Monitor. July, 2008.
- ⁷¹ Logistics capability based on World Bank LPI Index: Arvis, Jean-Francois. Mustra, Monica Alina. Panzer, John. Ojala, Lauri. Naula, Tapio. “Connecting to Compete: Trade Logistics in the Global Economy.” The International Bank for Reconstruction and Development / World Bank. 2007.
- ⁷² Air cargo rank based on annual tonnage from: “Top 50 Airports.” Air Cargo World. July, 2008.
- ⁷³ Based on interviews with manufacturers of cold storage containers and review of product specifications.
- ⁷⁴ Wolfson LJ, Gasse F, Lee-Martin SP, Lydon P, Magan A, Tibouti A, Johns B, Hutubessy R, Salama P, Okwo-Bele JM. Estimating the costs of achieving the WHO-UNICEF Global Immunization Vision and Strategy, 2006-2015. Bull World Health Organ. 2008 Jan;86(1):27-39.