Ensuring Vaccine Supply for the Next Pandemic Flu: Will the World Be Ready?

Pandemic influenza has periodically occurred over the past several centuries, with the Great Influenza Pandemic of 1918-19 the deadliest on record. That pandemic killed an estimated 40-100 million people, primarily young relatively healthy adults, with a mortality rate of about 2.5% in the United States. Other major flu epidemics occurred in 1957-1958 and 1968-1969 and caused an estimated one to two million and 700,000 deaths respectively.

In particular, viruses that originate in non-humans (especially animals) and spread to humans have been on the rise. Near eradication of viruses such as polio has been possible, in part, because humans are the disease’s only host. However, viruses that can transmit between humans and non-humans make control more difficult as many non-human hosts may be asymptomatic but their human host counterparts may not have such immunity. Modern development—especially the increasing disruption of ecosystems—coupled with the globalization of transit, commerce, and information has effectively turned the threat of pandemic flu into a global problem. Since 2000, two such viruses—the highly pathogenic H5N1 avian flu virus and the fast-spreading but relatively mild H1N1 swine flu—have raised fears of another pandemic flu that could have major public health and economic consequences.

Recent experiences with both H5N1 and H1N1 have shown that the global institutions to deal with this impending risk have proven to be insufficient for the task. With both viruses there were significant problems with the development, production and distribution of flu vaccines. (Recognizing that a wide range of public health measures need to be taken to respond to an influenza pandemic, for teaching purposes, this case focuses on vaccines as one key element of a comprehensive response.) Global challenges to stemming a modern day pandemic include rapid development, sufficient production, and equitable as well as timely access to pandemic influenza vaccines. In addition to these factors, there are definite unknowns if a new virus appears. These include severity levels, transmission ease, human immunity and drug vulnerability.

Given both the known and unknown challenges, how can the international community most effectively prepare for the next pandemic? What needs to happen at the international level so that vaccines are rapidly developed, produced in sufficient quantity, and reach those who are at greatest risk when the next pandemic hits? In particular,
what medium-term changes in policies and institutional arrangements in the international arena need to take place so that vaccines may be used more effectively to manage this impending threat?

**Background**

Flu viruses circulate constantly, but when a new virus is detected, it significantly increases the risk of a pandemic for several reasons: populations or sub-populations (e.g. children) may not have any immunity to the virus, it is unknown how severe the virus is and how rapidly it will spread, it is unknown how well existing drugs will work to treat infected people, and a new vaccine must be developed to prevent infection. Since 2000, two viruses – avian flu H5N1 and swine flu H1N1 – have caused particular concern.

In 1997 the H5N1 influenza virus emerged in Hong Kong; it is a highly pathogenic virus that is transmitted from birds to humans and is extremely deadly. The virus can decimate poultry stocks, and cause illness and death in wild bird populations. In humans H5N1 has demonstrated an extremely high mortality rate of about 60% among confirmed cases.1 H5N1 in birds has been detected in 63 countries, while infection in humans has been confirmed in 15 countries.2 Starting in 1999 through 2012 a total of 682 human cases have been confirmed, of which 366 have died.3 In 2004, the first suspected H5N1 case of human-to-human transmission occurred.4 (The most common form of transmission affecting humans is still predominantly from animal to human.)

In April 2009, the H1N1 swine flu virus was detected in Mexico and by the end of the year the World Health Organization (WHO) had declared it to be the first flu pandemic since 1969.5 Within eight months of detection H1N1 had rapidly spread world-wide, reaching 212 countries & territories.6 While precise mortality rates are not available due to the difficulty of collecting reliable data, death rates linked to H1N1 were far lower than those related to H5N1. For example, in the U.S., the Centers for Disease Control estimated the overall death rate for H1N1 in 2009 to be 0.97 per 100,000 persons (about 0.001%).7 In some cases, H1N1 mortality rates appeared to be lower even than the regular seasonal flu. By the time the WHO officially declared the epidemic to have passed in August 2010, over 15,000 people had died from H1N1, as confirmed by laboratory tests – the actual number of deaths is likely to be much higher but uncounted.8 (Many more people died from the mild H1N1 than from the more severe H5N1 because many more people became infected with H1N1 due to its ease of transmission. See Exhibit 1 for cumulative number of reported H5N1 cases and number of daily H1N1 cases during the first two months of the epidemic.)

H5N1 is highly pathogenic but has low transmissibility between humans, while H1N1 is essentially the opposite.4 A virus that combined the worst traits of the two—highly pathogenic and transmissible—would have enormous public health and economic consequences. A senior economist from the World Bank 2005 estimated that a pandemic could cause $800 billion in economic losses worldwide.9

**Challenges: Virus Mutation and Transmission Control**

There are two ways in which either virus could mutate to become either more highly transmissible or highly pathogenic: if H5N1 infects a human who is simultaneously infected with another flu virus that is easily transmissible, genetic reassortment between the two viruses could occur and produce a mutated virus that is both highly pathogenic and highly transmissible. Alternately, the H5N1 virus itself could mutate (without combining genetic material from another flu virus), and begin to become more easily transmissible; in this case, transmission would increase but probably not as quickly as if reassortment occurred. Similarly, reassortment or mutation of H1N1 could render the virus much more dangerous. It is not known when such a pathogenic and transmissible strain might emerge. Regular monitoring of influenza virus samples from infected persons or animals is currently carried out to manage this risk.

Several traits of the influenza virus make it particularly difficult to control:

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• Reservoir: The virus has a diverse reservoir in multiple species of animals including birds (both domesticated poultry and wild), pigs, tigers and leopards, domestic cats and dogs, and wild civets. This trait makes controlling the spread of the virus much more difficult than if the reservoir was limited to one species (as with malaria and mosquitoes). In most animals, it seems the virus causes illness and death, which makes tracking the virus feasible; however, recently asymptomatic ducks have been found to carry and shed the H5N1 virus, making detection even more difficult.10

• Spread: The migration of wild birds, trade in poultry and pigs, and international travel of humans may all contribute to the global spread of influenza viruses. Thus, the spread of the virus is contingent on both natural (e.g. bird migration) and human factors (e.g. travel, trade).

• Treatment: Thus far the only treatment expected to be effective for pandemic influenza is the antiviral drug oseltamivir (brand name Tamiflu). It is widely patented and therefore quite costly in many countries; to be most effective it should be given within 48 hours of symptoms appearing. Zanamivir may also be effective but is likely to be less so than oseltamivir. (H5N1 has demonstrated resistance to the two other drugs often used to treat flu, amantidine and rimantadine.11) Hence, oseltamivir is widely considered the drug of choice. However, even oseltamivir is only partially effective, and widespread use of the drug to treat other variants of influenza in Japan have raised concerns about its safety profile. Furthermore, there have been shortages as many countries simultaneously tried to stockpile the drug; many developing countries are unable to stockpile large volumes, as estimated costs for a treatment course range from $2.50 to $20.12 There is also a shortage of production capacity and the drugs have a limited shelf-life of three years, making continuous investment in maintaining a stockpile necessary and costly. Finally, some resistance to oseltamivir has already observed. Therefore, widespread access to an effective vaccine can be considered the best tool to help control an outbreak.

Challenges: Vaccine Access

Several characteristics of flu vaccines make fast, equitable access difficult to achieve:

Time Lags

In general, flu vaccines take four to six months (possibly reduced to three with newer technology) to produce and must be re-invented each year based on experts’ predictions of which influenza virus strains will be prominent in the coming flu season. Annual global vaccine production capacity estimates range from a likely 2.5 to an optimistic 7.7 billion doses which implies between 1.5 to 4 years to meet global demand at two doses per person.13,14 This production capacity is an increase from just 500 million doses/year a few years ago; part of the increase in production capacity has been spurred by the fear of pandemic flu.

Several H5N1 vaccines for humans have now been developed, but it is uncertain whether they will provide protection to the specific mutation that may cause rapid transmission; an effective vaccine can only be developed after such a virus is identified (i.e. after rapid spread has begun). A vaccine against H1N1 was developed and made available about five months after the initial outbreak was identified in Mexico. However, high public demand combined with

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b In this context reservoir refers to “the reservoir for a disease is the site where the infectious agent survives. For example, humans are the reservoir for the measles virus because it does not infect other organisms. Animals often serve as reservoirs for diseases that infect humans. The major reservoir for Yersinia pestis, the bacteria that causes plague, is wild rodents. There are also nonliving reservoirs. Soil is the reservoir for many pathogenic fungi as well as some pathogenic bacteria such as Clostridium tetani, which causes tetanus.” NIH, Understanding Emerging and Re-emerging Infectious Diseases, Teachers’ Guide, http://science.education.nih.gov/supplements/nih1/diseases/guide/understanding1.htm, accessed January 2013.

unexpectedly low vaccine yield (which relies on the growth of viruses in hen eggs) led to supply shortages and delays.\textsuperscript{14}

**Vaccine Production, Access, and Virus-Sharing**

Furthermore, access to vaccines remains a highly contentious global political issue. Very few developing countries produce influenza vaccine, but low- and middle-income countries comprise 85% of the world’s population. Developing countries were disproportionately affected by H5N1 and heavily affected by H1N1. However, vaccine production capacity resides largely in the high-income countries. Industrialized countries in which vaccine manufacturers exist may limit export in the case of a pandemic; the Australian government ordered its vaccine producer CSL to do precisely that during the H1N1 pandemic.\textsuperscript{15} CSL was able to deliver only a fraction of the doses it had been contracted to produce by the U.S. Government due to the Australian policy.\textsuperscript{16} In another instance, a former Deputy Commissioner for Medical and Scientific Affairs at the U.S. Food and Drug Administration testified before a Senate subcommittee that, “In Canada, where GlaxoSmithKline maintains one of its two flu vaccine production facilities, the company had to assure the Canadian government that the Canadian population would be served first from that facility before any other countries that rely on that manufacturing site—including the United States—received fulfillment of their H1N1 vaccine orders.”\textsuperscript{17}

With the inevitable time lags involved in vaccine development and production, a central question arises regarding which countries will get what quantities of vaccine and when. Furthermore, since the poorest countries are unlikely to be able to afford the vaccine, who will pay? If developing countries are unable to access sufficient quantities of vaccine in a timely manner, it is not only their populations that will be affected; rather, several consequences of global magnitude may occur: the virus will continue to spread with an increased risk of further mutation; the economic impact – particularly on the emerging markets – will affect all economies; and developing countries may be unwilling to share the virus samples and information required to generate protective vaccines for global use. Recognizing this risk, producers and donor governments committed approximately 200 million doses of H1N1 vaccine to 95 developing countries through the WHO. This quantity would cover roughly 2\% of the population in those countries, with health workers, children and pregnant women getting first priority.\textsuperscript{18} However, by late January 2010, only 2 of the 95 countries had received any.\textsuperscript{19} Close to the end of the pandemic in August 2010, 65 countries had received 60.5 million donated vaccine doses.\textsuperscript{20}

In early 2007, Indonesia, the country hardest hit by H5N1, announced it would stop sharing its virus samples with the WHO.\textsuperscript{21} By the end of 2006, WHO reported Indonesia had both the highest number of reported cases (42) and deaths (37) from H5N1. (By 2012 Indonesia had had 31\% of the total global confirmed cases, and 44\% of the total global deaths from H5N1.)\textsuperscript{4,22} The government argued that pharmaceutical companies would profit handsomely from the vaccines produced based on Indonesian virus samples, but Indonesians were not likely to get access to such vaccines. Commenting to a *Time Magazine* reporter at the time, the Health Minister of Indonesia said, “The current unfair access to vaccines worsens the global inequality between the rich and the poor, between the North and the South—and I think that is more dangerous than a pandemic.”\textsuperscript{23} In refusing to share its samples, the country broke with a half-century of precedent in international influenza virus-sharing and generated considerable controversy; however, they also won widespread political support from other developing countries with similar concerns.\textsuperscript{24} Several months later, Indonesia announced that it would resume sharing samples with the WHO. This incident sparked ongoing efforts to reform the international system for virus-sharing and related benefit-sharing.

The international scientific community uses virus samples for multiple purposes, including tracking the spread of the virus; tracking its susceptibility to antiviral drugs and the possible development of resistance; developing vaccines; and testing the accuracy of diagnostic tests. Since the virus mutates constantly, samples of viruses from

\textsuperscript{4} Calculations by casewriter based on data from the World Health Organization. From 2003 – August 2012, Indonesia had 191 confirmed cases out of 608 worldwide and 159 deaths out of 359 worldwide. For cumulative cases from 2003-2012 as reported by country see WHO, [http://www.who.int/influenza/human_animal_interface/EN_GIP_20120810CumulativeNumberH5N1cases.pdf](http://www.who.int/influenza/human_animal_interface/EN_GIP_20120810CumulativeNumberH5N1cases.pdf), accessed January 2013.
affected patients are a key resource. However, sovereign states may refuse to share the virus samples collected on their territory, as Indonesia did in 2007.

**Vaccine Production: A Lucrative but Risky Business**

In the 1990s, many pharmaceutical companies were withdrawing from the vaccine business because of low-margins and high-risk; this led to insufficient production capacity and shortages of vaccines, even in high-income countries. By the first decade of the 21st century, however, many companies were interested again in vaccines because they had proven to be more profitable than in the past. The fear of pandemic flu has contributed to this perception, as have changes in national recommendations to include more target populations such as children. One forecast predicted that the seasonal influenza vaccine market would grow to $4.7 billion by the 2021/2022 flu season. In 2009, the industry was highly concentrated with six global firms. Analysts had initially predicted that GlaxoSmithKline, Sanofi-Aventis and Novartis would report revenue increases respectively of $3.6 billion, $1.1 billion and $750 million due to the sales of H1N1 vaccines. Sanofi-Aventis had previously referred to 2009 as a record year for anti-flu vaccine sales with a net profit increase of 11%.

At the same time, vaccine production is commercially risky, for several reasons: First, predictions of demand are volatile and difficult to ascertain, particularly in a fast-moving pandemic: for example, initial panic regarding H1N1 in the U.S. and many other countries led to high demand estimates, which were subsequently sharply revised downwards as people chose not to get vaccinated when the H1N1 virus proved to be much less lethal than originally feared. In response, some governments sought to re-negotiate vaccine orders with companies; one analyst estimated that vaccine “returns” from France, Germany, U.K. and Spain could reduce producers’ revenue by 15% by January 2010, France, for example, had immunized only 5 million out of 62 million French citizens and had sought to cancel a little more than half of its initial 94 million dose order from various vaccine manufacturers. These orders had led to lucrative gains for the pharmaceutical industry. France, for example, had spent over $1.25 billion.

In response, at least one vaccine manufacturer implied that countries that reneged on their purchase commitments would not be at the front of the line for supply the next time a pandemic hits. Daniel Vasella, Novartis CEO, told the French news agency, AFP, “The same governments that exerted a lot of pressure on the industry...to deliver vaccines very quickly were the same governments that then said 'we don't want any more what we ordered', once they saw they ordered too much.... the next time that there will be a pandemic—and there will be another one—the governments who have been reliable partners will be treated preferentially.”

Furthermore, seasonal flu vaccine, in general, cannot be used beyond one season.

**WHO as Global Pandemic Arbiter**

The emergence of H1N1 initially caused great alarm. WHO, which is mandated to issue assessments of global pandemics, declared H1N1 to be the first flu pandemic in 40 years due to its rapid spread to multiple regions of the globe. In June 2009, WHO Director Margaret Chan stated to the press,

“No previous pandemic has been detected so early or watched so closely, in real-time, right at the very beginning. But it also creates a demand for advice and reassurance in the midst of limited data and considerable scientific uncertainty.

...Although the pandemic appears to have moderate severity in comparatively well-off countries, it is prudent to anticipate a bleaker picture as the virus spreads to areas with limited resources, poor health care, and a high prevalence of underlying medical problems... In the previous century, this spread has typically taken around 6 to 9 months, even during times when most international travel was by ship or rail...

...WHO has been in close dialogue with influenza vaccine manufacturers... [soon] full capacity will be available....” (See Exhibit 2 for the complete statement.)
On August 2010, Dr. Chan released another statement declaring the end of the pandemic but cautioned that future health security could not be taken for granted based on past experiences:

“As I said, pandemics are unpredictable and prone to deliver surprises. No two pandemics are ever alike. This pandemic has turned out to be much more fortunate than what we feared a little over a year ago. This time around, we have been aided by pure good luck. The virus did not mutate during the pandemic to a more lethal form. Widespread resistance to oseltamivir did not develop. The vaccine proved to be a good match with circulating viruses and showed an excellent safety profile. Thanks to extensive preparedness and support from the international community, even countries with very weak health systems were able to detect cases and report them promptly. Had things gone wrong in any of these areas, we would be in a very different situation today.”

Some actors criticized WHO for ‘over-hyping’ the pandemic and creating a false sense of alarm. Governments initially had asked industry to produce at maximum levels—which also implied some replacement of seasonal flu vaccine production as capacity was taken up with H1N1 vaccines—but, high-income governments subsequently sought to renegotiate their vaccine purchase commitments after a lackluster public willingness to get vaccinated.

Political finger-pointing was widespread. A former German parliament member complained, “WHO advised us falsely. They raised a false alarm.” The Social Health and Family Affairs Committee of the Council of Europe commissioned a special report on the handling of the H1N1 pandemic. Referring to WHO, the rapporteur wrote, ‘the Assembly regrets that WHO has not moved swiftly to revise or re-evaluate its position on the pandemic and the real health risks involved, despite the overwhelming evidence that the seriousness of the pandemic was vastly overrated by WHO at the outset.”

Ultimately the rapporteur faulted the handling of the epidemic from several different perspectives concluding:

“…the main concerns regarding the current H1N1 influenza include the proportionality of the response given to the public health threat of H1N1, the transparency of relevant decision-making processes, including the possibility of undue influence by the pharmaceutical industry, and the way in which the pandemic, and the use of precautionary principle, was communicated to member states’ governments and to the European public at large, also by the media.”

The rapporteur was also critical of the pharmaceutical industry’s role and influence. The rapporteur noted, “Suspicion of undue influence and pressure put on national authorities by the pharmaceutical industry has been reinforced by other factors, such as the character of contractual arrangements concluded between governments and pharmaceutical groups… [The rapporteur] encourages greater cooperation between national governments in order for them to be able to take coherent and strong stands when negotiating with large pharmaceutical groups in the future.”

The WHO Director General had proposed an external review of the global response to the H1N1 epidemic in January 2010 in the context of the International Health Relations (IHR) 2005. (The IHR assists the international community in preventing and responding to immediate public health risks that threaten the world and may travel across borders. The H1N1 pandemic was the first Public Health Emergency of International Concern to occur since the release of the 2005 IHR.) Dr. Chan addressed the Committee in September 2010 during the opening intervention of the IHR committee summarizing some of her thoughts on the pandemic while also inviting full inquiry into WHO’s actions. She told the committee that, “We are grateful for moderate impact. Had the virus turned more lethal, we would be under scrutiny for having failed to protect large numbers of people. Vaccine supplies would have been too little, too late, with large parts of the developing world left almost unprotected.” Dr. Chan reminded members that H1N1 preparations had taken place based on the assumption that its impact and severity would be

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similar to that of H5N1 and that “a new disease is, by definition, poorly understood as it emerges. Decisions with far-reaching consequences need to be made quickly.” Moreover, the modern technological advances ushered in a new level of examination that “WHO and many countries were unprepared for… [this] new form of scrutiny: electronic scrutiny by the public, including through social media. Today, people draw their own instant information from a wide range of sources. They make their own decisions about which advice to follow. The public health community must urgently adapt to this reality.” She acknowledged the distribution of donated vaccines had been slow but she also defended WHO’s independence from the pharmaceutical industry, by closing her remarks with “I can assure you: never for one moment did I see a single shred of evidence that pharmaceutical interests, as opposed to public health concerns, influenced any decisions or advice provided to WHO by its scientific advisers. Never did I see a shred of evidence that financial profits for industry, as opposed to epidemiological and virological data, influenced WHO decisions.” (See Exhibit 3 for the complete remarks.)

At the same time that WHO was in the midst of the review of its handling of the H1N1 pandemic, it had been in negotiations to create an influenza agreement among its member states. Negotiations had begun during the H5N1 outbreak when Indonesia had initially refused to share virus samples with WHO. In April of 2011, a formal agreement, the Pandemic Influenza Preparedness (PIP) framework was reached which identified “principles, norms, governance mechanisms and oversight arrangements that all members of WHO’s global influenza surveillance and response system (GISRS) and other allied nations [were] expected to comply with.” Part of the framework principles included, “sovereignty over biological resources, virus and benefit sharing on an equal footing, and financing mechanisms for equitable access to benefits.” PIP’s purpose was to address the global equity of vaccine distribution and also strengthen pandemic influenza surveillance. One commentator remarked, “The framework reinforces a global norm but does not alter the status quo.” The agreement was not legally binding but did make it easier for member states to share viruses and genetic sequence data. Among the most important benefits of PIP were “increased transparency of virus transfers” and a change in mindset that made access valued as an exchange thus requiring industry “to pay half of GISRS’ annual operating costs and provide benefits under the second standard material transfer agreement (e.g. vaccine donations). These contributions give industry access to PIP biological materials in exchange for assisting developing countries.”

Some called PIP a milestone because it “represent[ed] the first international agreement on influenza virus and benefit sharing.” However, some found PIP lacking arguing that the “agreement has not sufficiently engaged with, or found appropriate solutions to, the current market-based structural hurdles that prevent equitable access to vaccine, namely limited overall global production capacity, the prevalence of APAs [advance purchase agreements] and the need for more private sector investment.” In addition, some argued that while the PIP agreement was a sign of progress it did not go far enough as it only “reinforces a global norm but does not alter it.” For example, the lack of any legal binding language coupled with “the absence of even ‘soft’ norms encouraging developed countries to make specific equity enhancing contributions to developing countries, such as donating portions of purchased vaccines” was considered not far-reaching enough in its expectations. Specifically PIP “failed to tackle adequately the embedded structure inequalities, namely, the existing market-based political economy surrounding the influenza vaccine production and procurement.”

In addition to PIP, the WHO also updated the Global Action Plan (GAP) for Influenza Vaccines in July 2011. Initially spearheaded by WHO in 2006 with public health, academic experts, vaccine manufactures and funders, GAP’s purpose was to increase influenza vaccine production capacity. Short term goals for GAP included creating enough vaccine to protect two billion people within six months of a vaccine becoming available for a declared pandemic. Longer term goals included making possible the immunization of the entire world’s population (6.7 billion people). Based on the lessons learned from both the H1N1 and H5N1 outbreaks, GAP II focused on “addressing the access, affordability and effective deployment of pandemic vaccines by countries that have limited or no such access.” A particular focus of GAP II was to increase production capacity in developing countries through a WHO sponsored technology transfer as well as with financial support of approximately $395 million for the program. In 2010 WHO had identified 25 country participants from both the developed and developing world and by the end of
2012, WHO had awarded 14 grants to establish in-country manufacturing capacity for influenza vaccine. Moreover, WHO estimated in 2010 seasonal influenza vaccine global production capacity had almost doubled to one billion doses per year since 2006. However, as of 2009-2010, 80% of influenza seasonal vaccine doses were produced by seven large manufacturers based in Australia, Canada, China, Japan, Russia, the U.S., and western Europe.

What Steps Need to Be Taken?

The possibility of another flu pandemic is very real. Effectively combating another pandemic will involve addressing many global governance issues within the traditional health sphere as well as other spheres. What issues must be considered to ensure that the world is better equipped to deal with a future pandemic, in particular with regard to vaccine supply? In thinking about possible solutions consider the major governance gaps that occurred around vaccine supply with the H1N1 and H5N1 outbreaks. What kinds of international institutional arrangements are needed to ensure more equitable, efficient and effective deployment of vaccines to combat a future pandemic?

What needs to be done, who needs to do it, and how can any new measures or arrangements be implemented?

When proposing feasible solutions to this complex challenge, it is important to balance and prioritize many different factors. Consider, for example, the large degree of inherent uncertainty and the related problems of risk, risk-sharing and risk mitigation; keep in mind the difficult questions of cost and cost sharing, especially when those with the most need may have the least resources; finally, pay attention to the biggest political issues and obstacles—domestic as well as international.

- **“What”** refers to the policy interventions. These could be financing, vaccine development, vaccine production, risk mitigation, disease surveillance, campaigning/advocacy, and other tasks that you may identify. Identify and highlight those “what” options that seem most important to improving recent performance of the global health system.

- **“Who”** refers to actors that have a key role to play in implementing the identified options. Actors may include high-income country governments, low-/middle-income (developing) country governments, the World Health Organization, other parts of the UN system, regional bodies, the pharmaceutical industry, the science community, philanthropists, non-governmental organizations/civil society groups, journalists, etc. An analysis should identify actors seen as most essential to carrying out the key identified “what” tasks and take into consideration actors’ motivations, incentives and constraints.

- **“How”** refers to the institutional aspects, in particular to the governance arrangements that need to be in place so that the various key actors identified will actually do what they are supposed to do in implementing the chosen technical options. New governance arrangements may be needed at all scales. For this case, focus on the most important global governance arrangements, taking national and local arrangements largely for granted. How can the various actors work together to achieve a stronger global response with respect to flu vaccines? What are the norms, formal and informal rules, decision-making procedures and incentives that would be necessary?
### Exhibit 1  
Timelines of H5N1 and H1N1

#### H5N1 Cumulative Number of Confirmed Human Cases and Deaths as Reported to WHO (1997 – 2012)

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#### H1N1 Cases Timeline of Laboratory Confirmed Cases and Deaths as Reported to WHO (April 2009 – May 27, 2009)

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Note: Figures unavailable for May 24, 2009.

**Source:** Exhibit created by casewriter based on data from the World Health Organization,  
http://www.who.int/influenza/H5N1_avian_influenza_update_20121217.pdf,  
http://www.who.int/influenza/human_animal_interface/EN_GIP_20121217CumulativeNumberH5N1cases.pdf,  
Exhibit 2  Statement to the Press Announcing Influenza Pandemic by Margaret Chan

World now at the start of 2009 influenza pandemic

Statement to the press by WHO Director-General Dr. Margaret Chan
11 June 2009

Ladies and gentlemen,
In late April, WHO announced the emergence of a novel influenza A virus.
This particular H1N1 strain has not circulated previously in humans. The virus is entirely new.
The virus is contagious, spreading easily from one person to another, and from one country to another. As of today, nearly 30,000 confirmed cases have been reported in 74 countries.
This is only part of the picture. With few exceptions, countries with large numbers of cases are those with good surveillance and testing procedures in place.
Spread in several countries can no longer be traced to clearly-defined chains of human-to-human transmission. Further spread is considered inevitable.
I have conferred with leading influenza experts, virologists, and public health officials. In line with procedures set out in the International Health Regulations, I have sought guidance and advice from an Emergency Committee established for this purpose.
On the basis of available evidence, and these expert assessments of the evidence, the scientific criteria for an influenza pandemic have been met.
I have therefore decided to raise the level of influenza pandemic alert from phase 5 to phase 6.
The world is now at the start of the 2009 influenza pandemic.

We are in the earliest days of the pandemic. The virus is spreading under a close and careful watch.
No previous pandemic has been detected so early or watched so closely, in real-time, right at the very beginning. The world can now reap the benefits of investments, over the last five years, in pandemic preparedness.
We have a head start. This places us in a strong position. But it also creates a demand for advice and reassurance in the midst of limited data and considerable scientific uncertainty.
Thanks to close monitoring, thorough investigations, and frank reporting from countries, we have some early snapshots depicting spread of the virus and the range of illness it can cause.
We know, too, that this early, patchy picture can change very quickly. The virus writes the rules and this one, like all influenza viruses, can change the rules, without rhyme or reason, at any time.
Globally, we have good reason to believe that this pandemic, at least in its early days, will be of moderate severity. As we know from experience, severity can vary, depending on many factors, from one country to another.
On present evidence, the overwhelming majority of patients experience mild symptoms and make a rapid and full recovery, often in the absence of any form of medical treatment.
Worldwide, the number of deaths is small. Each and every one of these deaths is tragic, and we have to brace ourselves to see more. However, we do not expect to see a sudden and dramatic jump in the number of severe or fatal infections.
We know that the novel H1N1 virus preferentially infects younger people. In nearly all areas with large and sustained outbreaks, the majority of cases have occurred in people under the age of 25 years.
In some of these countries, around 2% of cases have developed severe illness, often with very rapid progression to life-threatening pneumonia.
Most cases of severe and fatal infections have been in adults between the ages of 30 and 50 years. This pattern is significantly different from that seen during epidemics of seasonal influenza, when most deaths occur in frail elderly people.

Many, though not all, severe cases have occurred in people with underlying chronic conditions. Based on limited, preliminary data, conditions most frequently seen include respiratory diseases, notably asthma, cardiovascular disease, diabetes, autoimmune disorders, and obesity.

At the same time, it is important to note that around one third to half of the severe and fatal infections are occurring in previously healthy young and middle-aged people.

Without question, pregnant women are at increased risk of complications. This heightened risk takes on added importance for a virus, like this one, that preferentially infects younger age groups.

Finally, and perhaps of greatest concern, we do not know how this virus will behave under conditions typically found in the developing world. To date, the vast majority of cases have been detected and investigated in comparatively well-off countries.

Let me underscore two of many reasons for this concern. First, more than 99% of maternal deaths, which are a marker of poor quality care during pregnancy and childbirth, occurs in the developing world.

Second, around 85% of the burden of chronic diseases is concentrated in low- and middle-income countries.

Although the pandemic appears to have moderate severity in comparatively well-off countries, it is prudent to anticipate a bleaker picture as the virus spreads to areas with limited resources, poor health care, and a high prevalence of underlying medical problems.

Ladies and gentlemen,

A characteristic feature of pandemics is their rapid spread to all parts of the world. In the previous century, this spread has typically taken around 6 to 9 months, even during times when most international travel was by ship or rail.

Countries should prepare to see cases, or the further spread of cases, in the near future. Countries where outbreaks appear to have peaked should prepare for a second wave of infection.

Guidance on specific protective and precautionary measures has been sent to ministries of health in all countries. Countries with no or only a few cases should remain vigilant.

Countries with widespread transmission should focus on the appropriate management of patients. The testing and investigation of patients should be limited, as such measures are resource intensive and can very quickly strain capacities.

WHO has been in close dialogue with influenza vaccine manufacturers. I understand that production of vaccines for seasonal influenza will be completed soon, and that full capacity will be available to ensure the largest possible supply of pandemic vaccine in the months to come.

Pending the availability of vaccines, several non-pharmaceutical interventions can confer some protection.

WHO continues to recommend no restrictions on travel and no border closures.

Influenza pandemics, whether moderate or severe, are remarkable events because of the almost universal susceptibility of the world’s population to infection.

We are all in this together, and we will all get through this, together.

Thank you.

External review of WHO’s response to the H1N1 influenza pandemic

Dr. Margaret Chan
Director-General of the World Health Organization

Opening intervention at the International Health Regulations Review Committee
Geneva, Switzerland
28 September 2010

Dr. Fineberg, distinguished members of the Review Committee, ladies and gentlemen,

I and my staff are at your disposal. These staff represent the diversity of expertise involved in the response. We will do our best to answer your questions faithfully and factually.

We kept extensive records, and these are also at your disposal. Among other things, these documents will allow you to see, in the context of a rapidly evolving situation, what data were available and considered when key decisions were made.

As you know, this has been the most carefully watched and scrutinized pandemic in history. Understandably, the response of countries and WHO is also under scrutiny. To some, response measures now look excessive compared with the moderate impact of the pandemic.

We are grateful for the moderate impact. Had the virus turned more lethal, we would be under scrutiny for having failed to protect large numbers of people. Vaccine supplies would have been too little, too late, with large parts of the developing world left almost entirely unprotected.

I am, of course, alert to all perceptions of how this Organization performs, in all areas.

For the pandemic, WHO has received some praise and support from early assessments published in the medical and scientific literature, in addition to support and feedback from our Member States.

WHO has also received some criticism.

Large sums of money were invested in commodities that were not used, sometimes because the public saw no need for them or questioned their safety. The definition of a pandemic and the pandemic phases have been questioned. The clinical value of oseltamivir has been questioned. Conflicts of interest and their influence on decisions have become an issue.

But between criticism and praise is a solid middle ground.

It is in your hands to determine what worked well, and what went wrong, especially as this pandemic was the first major test of the revised International Health Regulations. It is in your hands to advise us on necessary changes in the way we coordinate the response to public health emergencies of international concern.

This review is being conducted very rigorously and taken very seriously. We trust your expertise, and thank your Chairman for his diligence.

Ladies and gentlemen,

The world was better prepared for a pandemic than at any time in history. But it was prepared for a different kind of event than what actually occurred.

Experts widely assumed that H5N1 would cause the next pandemic, and its severity was almost taken for granted. Changes in the H5N1 situation frequently made the headlines. Pandemic became a hugely frightening word in the minds of the public and the media.

This was the mind-frame when the new H1N1 virus emerged.
The phased approach to pandemic alert was introduced by WHO in 1999. The intention was to allow WHO to gradually increase the level of preparedness and alert without inciting undue public alarm. In reality, it had the opposite effect. It dramatized the steps leading to the declaration of the pandemic and increased the build up of anxiety.

I personally do not believe that WHO exaggerated the threat. When I announced the move to phase 6, I reminded the world that the number of deaths worldwide was small and that we did not expect to see a sudden and dramatic increase in this number. I stressed that the overwhelming majority of patients recovered fully without any medical care.

Managing the discrepancy between what was expected and what actually happened was problematic. Attempts to dial down preparedness plans to suit a less severe event were problematic. No one could answer, with certainty, a fundamental question. Is it safe to do so? Are we sure? Do we dare?

Though much early evidence pointed to a moderate, if not mild impact, most health officials decided to err on the side of caution.

A new disease is, by definition, poorly understood as it emerges. Decisions with far-reaching consequences need to be made quickly in an atmosphere of considerable scientific uncertainty. Flexibility to adapt to emerging information is critical.

In this regard, the phased approach to the declaration of a pandemic was rigid and confining. In communicating the level of alarm, authorities need to be able to move down as well as up.

The finite capacity and long production times of vaccine manufacturing reduced the flexibility of the response. Some countries placed large orders before data were available to support evidence-based projections of need, including the number of doses.

The public health community faced many difficult communication challenges.

We did not anticipate that large numbers of people would decide not to be vaccinated.

WHO and many countries were unprepared for a new form of scrutiny: electronic scrutiny by the public, including through social media. Today, people draw their own instant information from a wide range of sources. They make their own decisions about which advice to follow.

The public health community must urgently adapt to this reality.

As the pandemic progressed, we had great difficulty explaining why the number of laboratory-confirmed deaths, reported on our website, was not a reliable measure of the pandemic’s impact.

Many journalists and bloggers compared the number of these deaths with estimated excess deaths during seasonal epidemics, either for a country or worldwide. This led to the familiar conclusion that the pandemic was even milder than normal influenza, and supported the perception that vaccination was unnecessary.

I believe some things worked well. The International Health Regulations brought a clear set of obligations, channels of communication and coordination, and mutual accountability.

The IHR also introduced a series of checks and balances designed to ensure that no one, myself included, had unfettered power. In my view, the Emergency Committee, with both experts and affected states represented, functioned well as a balanced and inclusive advisory body.

I believe the early distribution of stockpiles of oseltamivir to developing countries was useful. In many cases, health officials could announce confirmation of the first cases together with the reassuring message that medicines were in hand to manage cases.

We did less well with the distribution of donated vaccines. They arrived, but much slower than was hoped.

I have a final remark. I was deeply involved in the discussions that led WHO to announce phase changes.
I can assure you: never for one moment did I see a single shred of evidence that pharmaceutical interests, as opposed to public health concerns, influenced any decisions or advice provided to WHO by its scientific advisers.

Never did I see a shred of evidence that financial profits for industry, as opposed to epidemiological and virological data, influenced WHO decisions.

As I said, I, my staff, and our records are at your disposal.

Endnotes


Vaccine Supply


54 Jeffrey Partridge, et. al., “Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009-2010 and comparison with previous estimates and global action plan targets,” Vaccine, 28 (2010) 4709-4712.


59 Jeffrey Partridge, et. al., “Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009-2010 and comparison with previous estimates and global action plan targets,” Vaccine, 28 (2010) 4709-4712.