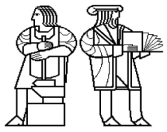

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AVIAN INFLUENZA PRE-PANDEMIC PROCUREMENT: RECOMMENDATIONS FOR THE US FEDERAL GOVERNMENT

Final Report – ESD.10

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January 2007

Avian Influenza
Pre-Pandemic Procurement
Recommendations for the US Federal Government

> "I am sure that what any of us do, we will be criticized either for doing too much or for doing too little…. If an epidemic does not occur, we will be glad. If it does, then I hope we can say… that we have done everything and made every preparation possible to do the best job within the limits of available scientific knowledge and administrative procedure."
>
> **US Surgeon General Leroy Burney, Meeting of the Association of State and Territorial Health Officers**
> **August 28, 1957**

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Fall 2006

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Committee Charge

Medical advances in the past century have dramatically increased our ability to contain and prevent disease outbreaks. Concurrently, however, increased globalization and rapid population growth mean that diseases can transmit faster and to more people than ever before.

Many experts view avian influenza (AI) as the most likely cause of a human pandemic in the near future. Few studies have focused on analyzing US technology procurement policies from a holistic perspective integrating technological, economic, and social analyses. This type of analysis is critical in designing effective, comprehensive policies to limit the potential impact of an AI pandemic.

The objectives of this study are therefore to (1) determine what technologies are available to address an AI pandemic and (2) to determine what policies are already adopted or should be adopted to effectively procure these technologies. By understanding these issues, we hope to allow policymakers to make more informed decisions regarding pre-pandemic preparations. Questions we will address include the following:

1) What technologies are important to procure in order to reduce the impact of pandemic influenza?

2) What has impacted the availability of these technologies?

3) What policies should the US adopt or implement to ensure the availability of the critical technologies needed to reduce the effect of pandemic influenza?

    a) What challenges face the adoption or implementation of these policies?

Executive Summary

Many experts fear that an influenza pandemic will occur in the near future. There is currently much debate about how the US should best prepare. Previous US responses give only minimal guidance as the last major influenza pandemic occurred nearly a century ago—before flu viruses had ever been isolated.

An influenza pandemic could spread quickly, and working estimates are that 30% of the US population will be infected - although the virulence of the virus will greatly affect mortality rates amongst those infected (HHS, 2005). Comprehensive pre-pandemic planning is needed, and in October 2005, the Bush Administration launched the National Strategy for Pandemic Influenza Preparedness and Response. A cornerstone of this strategy is government procurement of resources that will be needed in the event of a pandemic influenza outbreak. For example, $1.76 billion, out of the $7.1 billion that the President requested for the National Strategy will be "spent on increasing vaccine production." (Agnuwobi, 2006). A wide range of state and federal government agencies, as well as private industries, are engaged in efforts to limit the impact of an avian influenza pandemic on the US.

In this report, we survey the technologies available for surveillance, diagnosis, containment, treatment, and prevention of an AI pandemic in humans. We focus our analysis on those technologies that the US government might need to procure prior to or during a pandemic. We perform a comparative market analysis and reach conclusions about which technologies the government needs to procure. Finally, we discuss the challenges the government may encounter in procuring adequate supplies prior to an AI pandemic.

In conducting our research, we were guided by the following four framing questions:

1) What technologies are important to procure in order to reduce the impact of pandemic influenza?

2) What has impacted the availability of these technologies?

3) What policies should the US adopt or implement to ensure the availability of the critical technologies needed to reduce the effect of pandemic influenza?

    a) What challenges face the adoption or implementation of these policies?

Upon the emergence of a pandemic virus, immediate demand surges can be expected. Anticipating shortages, governments have already begun to stockpile key technologies such as antivirals and facemasks. However, even with adequate funds for purchasing supplies, market conditions will render some technologies unavailable without other government interventions. Government procurement can improve the supply of technologies needed for pandemic response.

The markets for the technologies relevant to avian influenza vary significantly in terms of their competitiveness, cost to entry, regulatory environment, and degree of excess manufacturing

capacity, among other factors. The ability of the government to procure supplies of technologies, and the urgency for doing so, depends heavily on the market conditions for each technology. Our analysis matches each technology with specific procurement policy options and considers the various stakeholders involved in procurement. In the various phases of the pandemic, different technologies will be most relevant. In addition, technologies are used in a range of different contexts.

In order to consider these technologies holistically in the context of the evolution of a global pandemic, the committee developed a technology map framework to guide our analysis. Technologies were mapped onto the framework using two dimensions: pandemic phases and types of action. We considered seven pandemic phases spanning from limited animal outbreaks to major human outbreaks; the types of action were detection, observation, containment, treatment and prevention.

Critical technologies that the government might want to procure prior to a pandemic were derived from an extensive literature review and from feedback provided by experts throughout the field of pandemic preparedness. After analyzing the role and specific strengths of each, the committee placed each technology on the map. The technology map allowed us to understand the various interdependencies between technologies and the relative importance of these technologies in each phase.

In looking holistically at the set of technologies, we observed that technologies targeted at containment, treatment and prevention are, in general, unlikely to be adequately supplied by the market in the event of a pandemic. Government pre-pandemic preparations are especially important for these technologies including vaccines, antiviral drugs, facemasks, and ventilators.

In contrast, we found that technologies for diagnosis and observation will likely be provided by the market in adequate supply. In addition, we found that procurement of these technologies is less relevant to pre-pandemic preparedness as they have only minimal roles in emergency response.

In light of our analysis, we make five recommendations.

> **Recommendation 1:** Government should limit research and development support for technologies that are adequately provided through market forces.

We recommend that the government focus research and development funding on those technologies that are not supported fully by the market. Research and development funding is most critical when conditions do not exist for the competitive production and development of technologies in the market. There are many demands on the funding that has been made available for pandemic influenza, and this recommendation calls for careful prioritization of this funding.

Conditions for competitive production and development of diagnostic tests are in place. There appears to be no shortage in the supply of these tests and production could be significantly

increased if demand were to increase. However, for technologies such as vaccines and antivirals, there is a clear need for government support of R&D efforts.

We suggest that this recommendation could be implemented through a formal mechanism that allows scientists, economists, public health officials, and health care providers to work together to establish research priorities with respect to influenza preparedness.

> **Recommendation 2:** Government must stockpile critical technologies that are available.

The timeframe governing the emergence of a pandemic is highly uncertain. As a result, private companies have little incentive to significantly increase production before a pandemic emerges. Even in those industries that have significant production capabilities, such as facemasks and ventilators, there will be a delay between the pandemic emerging and any significant increases in production. Therefore, it is critical that the government stockpile the supplies that are likely to be needed immediately upon the outbreak of a pandemic. Stockpiling targets for technologies such as ventilators should be reexamined in light of our analysis.

> **Recommendation 3:** The US government should actively provide markets for critical technologies where a market does not currently exist.

For pandemic vaccines as well as new antivirals government should actively participate in the creation of markets for critical technologies both by supporting their production and through demand stimulation. Potential policies include advance purchase agreements and the creation of award systems for prototype vaccine development. These policies could give companies the confidence to invest in what would otherwise be a risky investment. In addition, expanding current seasonal flu vaccine programs could provide immediate demand incentives to expand capacity or improve manufacturing efficiency.

Setting an appropriate timeline that ensures the government receives products while they could still be of use is essential. However, a timeline that is too rigid could reduce willingness on behalf of pharmaceutical companies to commit to development. In order to achieve their desired end, these agreements must adequately balance the need for rapid production with reasonable consideration of possible delays.

In the case of awards for vaccine development, vaccine manufacturers would be encouraged to develop prototype vaccines based on strains similar to the one likely to cause a pandemic. The manufacturers would carry out clinical trials on these vaccines and receive regulatory approval. Then once a pandemic emerged the companies could submit applications to regulatory agencies considering the new vaccines simply ‘variants’ of their previous products rather than entirely new vaccines (requiring the same rigorous clinical studies and approval processes).

Finally, it may be possible to increase pandemic vaccine supply indirectly by expanding current seasonal flu vaccine programs. The expansion of seasonal flu vaccine programs would provide a guaranteed market for manufacturers of seasonal vaccines, and encourage near term

capacity expansion or improved yields within existing plants. Additional capacity created through this process could then be used to produce greater quantities of pandemic vaccines if a pandemic emerges. A primary challenge to this approach is that it would require increased buy-in from citizens in order to be successful. If the government is not able to successfully encourage demand increases for seasonal influenza vaccines, it will have wasted valuable resources. In addition, it will be difficult for the government to predict in advance the potential capacity expansion that might result from increasing the demand for influenza vaccines, so it is likely that this policy is best used as a complement to other policies for increasing demand.

> **Recommendation 4:** The US Government should institute emergency fast-track approval and liability protection for vaccine and antiviral manufacturers.

Development of a vaccine targeted at pandemic AI cannot commence until the pandemic virus strain has been isolated, and development alone is likely to take on the order of six months. Thus, it will be necessary to use fast-track approval for a new vaccine in order to provide for production and distribution that is as rapid as possible after the onset of the pandemic. In addition, the importance of vaccines in limiting the loss of lives during a pandemic warrants liability protection for manufacturers. Similar treatment is also necessary for new antiviral drugs. Current reliance on one antiviral drug leaves antiviral resistance as a large vulnerability. Alternative antiviral drugs should be considered for fast track approval by the FDA.

The public's safety should be the dominant consideration in the implementation of this recommendation. A balance must be struck between protecting pharmaceutical companies from unforeseeable problems with new drugs and encouraging strict adherence to quality manufacturing practices. Liability protection should not exempt companies from damages due to reckless development strategies or unsafe manufacturing environments.

> **Recommendation 5:** The government should provide incentives for manufacturers to increase domestic manufacturing capacity of critical technologies.

If pandemic influenza reaches the US, it will probably already have affected other parts of the world. Pandemic emergencies abroad will likely lead to international supply chain disruptions. Foreign manufacturing facilities may not fulfill contracts if the country in which they are based experiences a pandemic crisis. Without domestic manufacturing capacity, the US cannot ensure adequate supplies of vaccines, antiviral drugs, and other crucial AI technologies.

Increasing domestic manufacturing capacity requires that the government provide economic incentives to manufacturers of critical technologies. These incentives should encourage both domestic and foreign manufacturers to expand or build plants in the US. Incentives should also address production time. For example, advance purchase agreements might take into account manufacturing time by having the government pay more to vaccine companies if they produce vaccines faster. Alternatively, the government could directly subsidize manufacturing expansion, or provide tax incentives to entice foreign firms to build plants in the US.

Another advantage of domestic manufacturing capacity is increased government scrutiny and response. For example, British vaccine manufacturer Chiron discovered contamination in several influenza vaccine batches in 2004. The US government stopped importation of Chiron's vaccines, leaving the US with only half its expected supply (Pearson, 2004). Had this problem occurred in a US facility, the FDA may have been able to respond quickly and work with the manufacturer to resolve the problem, thereby preventing the supply disruption.

Government policy already addresses this recommendation to some degree. The government recently gave $1 billion to five vaccine manufacturers to install domestic vaccine plants that use new, efficient cell-based production methods. Additionally, the government has negotiated with Roche to increase its antiviral production capacity on US soil over the next several years.

Introduction

Since 2003, widespread outbreaks of a lethal avian influenza (AI) in poultry have generated significant concern about the threat of a global influenza pandemic. The disease has impacted bird populations across much of Asia and has expanded rapidly into both Europe and Africa. While the disease has been blamed for only 154 human deaths thus far (WHO, Nov 2006), experts fear that the virus may evolve to become readily transmissible between humans, causing a human influenza pandemic. This report is concerned with the response of the United States to the current pandemic threat.

This report addresses procurement policy options that the United States could implement prior to the emergence of a pandemic virus. The report will assess how these policies fit into the broader framework of addressing AI and recommends policies the US Government should enact to effectively limit the impact of an AI pandemic. Specific questions this report addresses are the following:

1) What technologies are important to procure in order to reduce the impact of pandemic influenza?

2) What has impacted the availability of these technologies?

3) What policies should the US adopt or implement to ensure the availability of the critical technologies needed to reduce the effect of pandemic influenza?

    a) What challenges face the adoption or implementation of these policies?

This report represents the first comprehensive look at pre-pandemic procurement policy options known to the authors. The majority of previous work has focused on individual technologies or single policy options in narrow organizational contexts. In this report the authors study a wide range of technologies and their interdependencies, and develop a framework for analyzing policy options for these technologies that will be useful in other pandemics. In addition, we compare the market and policy conditions facing each technology, and assess where government procurement might be the most effective in terms of limiting the impact of the virus on humans. Previous reports that have attempted a broader view of pre-pandemic procurement have rarely conducted such comparative analyses of different technologies and their markets.

Given that human infection with avian influenza has already occurred, this report focuses on procurement of technologies that are important to limiting the impacts of the virus once it develops the ability to spread efficiently among humans. The analysis matches each technology with specific procurement policy options and considers the various stakeholders involved in procurement. We have adopted a broad definition of procurement that covers the range of policies spanning between short-term stockpiling of existing products and longer term research and development into new technologies. This definition has given us the freedom to include many of the interactions between procurement and other types of policy instruments.

Scope of this report

This report examines the technology and policy solutions necessary to prevent mass loss of human life from an AI pandemic. It addresses the technology and policy responses pertinent to the United States, and it is primarily concerned with the potential economic and health impacts on the human population.

The AI problem is global and it must be tackled through international co-operation. Therefore this report is global in its reach. Our recommendations, however, deal with the US response to such a pandemic because this report is aimed towards US policymakers. Accordingly, we have not made recommendations for other governments, international organizations, or private entities. This report is intended for policy makers but will be useful to those with little or no technical expertise in the technologies being examined.

Background

Influenza has ravaged human and animal populations throughout history. Increasing population density, the growth of mega-farms, and increasing global connectedness due to industrialization, however, have amplified the risks of influenza infections leading to pandemics. This was best exemplified by the 1918 "Spanish Flu" pandemic, which killed over 20 million people worldwide and caused illness in 20% to 40% of the world population (HHS, 2004). Experts believe that the 1918 pandemic originated from birds (CDC, Jan 2006). The H5N1 strain of avian influenza is the latest in a list of possible influenza pandemic threats, and its history is explored in this section.

US Procurement: Previous Influenza Outbreaks

In developing preparedness policy for avian influenza, it is instructive to review the effectiveness of government responses to past outbreaks of virulent forms of influenza. Four notable outbreaks of influenza have occurred in the US in the past century, and government response varied significantly among them: the "Spanish Flu" of 1918, the "Asian Flu" of 1957-58, the "Hong Kong Flu" of 1968-69, and the "Swine Flu" scare of 1976.

Although there had been sporadic flu outbreaks in the US prior to the 20th century, none were on a large enough scale to warrant government intervention. The first serious flu pandemic affecting the US was the Spanish Flu of 1918. It first surfaced at an army base in Kansas and rapidly spread among US military personnel as troops contacted each other in packed troop transports and at bases. Despite warnings by military medical personnel, President Woodrow Wilson ordered deployment of troops to Europe to fight in World War I, further increasing the number of victims. As doctors, scientists, and lab technicians were drafted into the military to help fight the flu, civilian medical services were left debilitated. Influenza quickly swept across the globe killing 675,000 Americans (~0.5% of the population) between September 1918 and June 1919 (Garrett, 2005) and an estimated 20 to 50 million people worldwide (CDC, Jan 2006). Eventually, after many waves, the virus mutated towards a less lethal form, ending the pandemic without an effective intervention by medical science (Knobler, Mack, Mahmoud, Lemon, 2005).

No preparations for an influenza outbreak had been made prior to the 1918 outbreak as scientific understanding of viruses did not exist. However, many of the actions taken once the pandemic emerged have relevance today.[1] These actions included reducing the size and number of public gatherings, staggering work schedules, isolating uninfected towns, isolating patients, and closing schools to decrease person-to-person contact. People also began wearing facemasks in public (Barry, 2004). The Red Cross alone contributed $575,000 (Crosby, 1976) to aid the 1918 pandemic response; this is equivalent in 2006 dollars to what the Federal Government is contributing to the current crisis. No reliable estimates have been made of the cost to the government of the 1918 pandemic. However, the ongoing First World War competed for both money and resources.

[1] Discussion of the interventions taken falls outside the scope of this report but Crosby (1976) provides an excellent account of the actions taken in the US to deal with the devastating pandemic.

Scientific understanding of viruses grew significantly during the interwar period. The influenza virus was finally isolated in 1933 (Garrett, 2005). In 1944 the first vaccine trials were conducted, and by June 1, 1945, 3 million doses had been administered to US Army personnel. The Army pioneered mass vaccinations within its ranks to prevent losses such as those seen in 1918 (Woodward, 1994). This was the first example of the use of mass procurement as a policy to limit the spread of influenza in the US.

In 1957, a flu strain originating in China reached the US The disease proved most lethal in the old and young populations; US flu deaths were estimated at 80,000 (Potter, 2001). A slightly milder strain, Hong Kong flu, subsequently killed 34,000 people in the US during the 1968-69 flu season (NAIAD, 2006). The total cost of these pandemics was ~$40 billion in 2006 dollars (Strikas, Wallace & Myers, 2002). Surprisingly, "In both 1957 and 1968, the first wave of the impending pandemic was detected some months before it struck the United States." (Silverstein, 1981, p.20) Although public health officials monitored the situation and urged the mass production of vaccines, companies were hesitant to increase production following several years of low demand prior to the pandemic (Silverstein, 1981). Unfortunately, according to Silverstein, "the time did not seem socially ripe for such large-scale government involvement" (p.21) and Congress was concerned about bypassing the private health care system lest they be accused of "socialized medicine." Silverstein also notes that the vaccines that were produced were distributed in a highly inequitable manner with large geographic variations in availability and rumors of corporations buying large stocks. The challenges observed during the 1957 pandemic highlight the importance of cooperation between the public and private sectors in pandemic response.

The government responded swiftly to next influenza pandemic scare in 1976, known as the Swine Flu outbreak. Following the death of Army Private David Lewis in 1976, medical determined that the soldier had been infected with influenza that had mutated from pigs[2]. Fearing a repeat of the 1918 flu pandemic, President Ford announced on national television that he was appropriating $135 million ($478 million in 2006 dollars) to produce enough vaccine to inoculate every American (Garrett, 2005). Given the short production window mandated by the government, producers insisted on liability protection. To ensure the production of an adequate supply of vaccines, the government granted manufacturers this protection (Silverstein, 1981). Ultimately, Swine flu never caused a pandemic. However, the vaccine had deleterious side effects, in some cases causing Guillian-Barré Syndrome (GBS). GBS is a paralytic nerve disease, akin to Polio, that can lead to death (Silverstein, 1981). Over 4 million Americans had been vaccinated before the program was halted. Twenty-five people died from the side effects of the vaccine and thousands of compensation claims were filed against the government. The government ended up paying damages of $90 million to those harmed by the vaccine (Garrett, 2005). The Swine Flu response was perceived as an appalling failure. The rapid increase in vaccine production and subsequent side effects illustrate the tradeoffs involved in the provision of liability protection to vaccine manufacturers.

[2] Swine are thought to be key in aiding the transmission of influenza from birds to humans. The 1918 strain also mutated from Swine.

The Emergence of a New Pandemic Threat

The first recorded case of H5N1 in humans occurred in 1997 in Hong Kong (FAO, 2006). As of November 29, 2006 154 people have died worldwide from H5N1 (WHO, Nov 2006), and the Food and Agriculture Organization of the United Nations (FAO) estimates that 220 million birds have been culled in Asia alone to control the disease (FAO, 2006). As shown in Table 1 confirmed human cases of AI have been reported in Asia and the Middle East, and animal cases have been reported in Asia, the Middle East, Africa, Europe, and the US (WHO, Feb 2006). Figure 1 shows the United States Agency for International Development's (USAID) predicted level of risk faced by countries throughout the world to H5N1. The virus is endemic in China and several other countries in Southeast Asia. In addition, the Western Hemisphere faces a pandemic risk.

Country	2003		2004		2005		2006		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Azerbaijan	0	0	0	0	0	0	8	5	**8**	**5**
Cambodia	0	0	0	0	4	4	2	2	**6**	**6**
China	1	1	0	0	8	5	12	8	**21**	**14**
Djibouti	0	0	0	0	0	0	1	0	**1**	**0**
Egypt	0	0	0	0	0	0	15	7	**15**	**7**
Indonesia	0	0	0	0	19	12	55	45	**74**	**57**
Iraq	0	0	0	0	0	0	3	2	**3**	**2**
Thailand	0	0	17	12	5	2	3	3	**25**	**17**
Turkey	0	0	0	0	0	0	12	4	**12**	**4**
Viet Nam	3	3	29	20	61	19	0	0	**93**	**42**
Total	**4**	**4**	**46**	**32**	**97**	**42**	**111**	**76**	**258**	**154**

Table 1: Confirmed human cases of avian influenza as of November 29, 2006 (WHO, Nov 2006) [3]

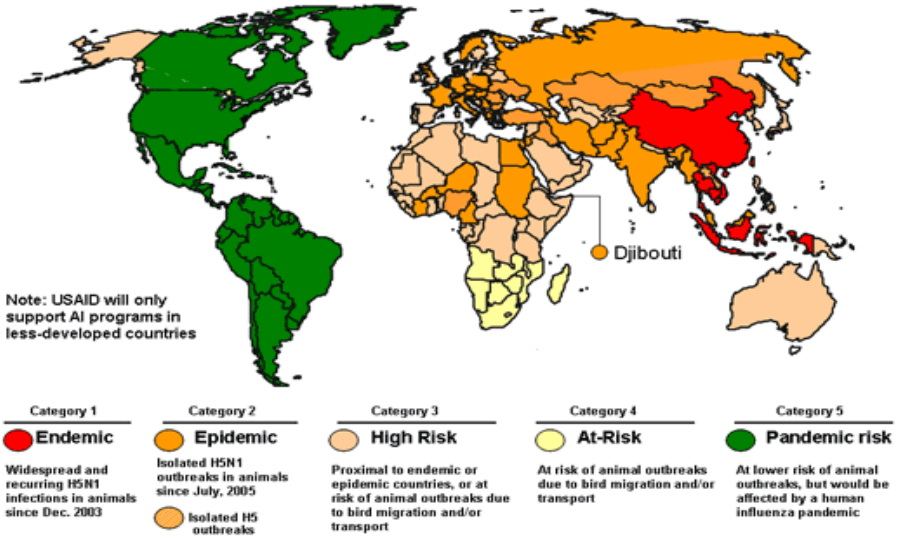


Figure 1: Global risk map for avian influenza (USAID, 2006)

[3] Total number of cases includes number of deaths. WHO reports only laboratory-confirmed cases

Given the pandemic virus has yet to emerge in humans, agencies are only able to loosely predict the likely impact of the disease.

Figure 2 illustrates the estimates developed by the US Department of Health and Human Services (HHS) based on data from past pandemics. They assume that outbreaks will occur nationwide simultaneously or near-simultaneously.

Characteristic	Moderate (1958/68-like)	Severe (1918-like)
Illness	90 million (30%)	90 million (30%)
Outpatient medical care	45 million (50%)	45 million (50%)
Hospitalization	865,000	9,900,000
ICU care	128,750	1,485,000
Mechanical ventilation	64,875	742,500
Deaths	209,000	1,903,000

Figure 2: HHS estimates of various pandemic influenza scenarios (HHS, 2005)

The potential economic costs of an influenza pandemic are high: a 2006 Asian Development Bank study predicts that an AI pandemic in livestock would lead to economic recession costing Asia US $297 billion per year (2006). For this reason, some Asian countries have been known to withhold information on H5N1 outbreaks when they occur, so as to prevent negative economic consequences (Elegant, 2004).

H5N1 has resulted in near 100% mortality rates in birds after onset of severe symptoms. Although it can infect all birds, domesticated birds such as chickens seem especially vulnerable while wild birds have been observed to carry H5N1 without signs of harm (WHO, Feb 2006). According to the Centers for Disease Control (CDC), strain H5N1 has not been observed in the US, but other strains of avian influenza have (Aug 2006).

Given the virulence observed in poultry populations, H5N1 is of particular concern as it satisfies all the characteristics of a pandemic strain except the ability to transmit between humans (WHO, Feb 2006). Influenza viruses are worrisome because of their ability to change over time to forms readily transmitted among humans. To date, only very limited human to human transmission of H5N1 has been observed (OSHA, 2006). Most human infections have occurred through contact with infected poultry.

US Response to Current Threat

Fear of a global pandemic has prompted governments and private industry alike to devote resources to the design and implementation of pandemic mitigation strategies. In December 2005, the US Congress appropriated $3.8 billion as the first installment of a $7.1 billion request by President Bush for emergency funding for the National Strategy for Pandemic Influenza, published in November 2005 (Gellin, 2006). As shown in Figure 3, a majority of the funding has been directed toward efforts at procuring vaccines and antiviral drugs.

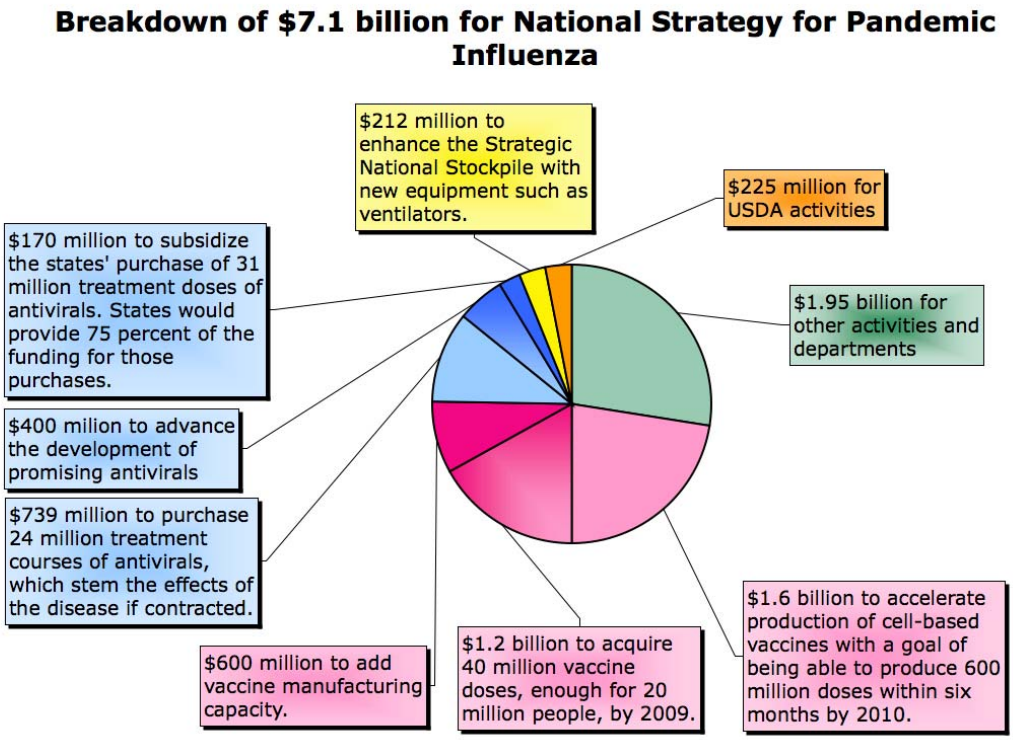


Figure 3: Breakdown of emergency funding requested by President Bush in November 2005[4]

The National Strategy for Pandemic Influenza states its purpose as "(1) stopping, slowing or otherwise limiting the spread of a pandemic to the United States; (2) limiting the domestic spread of a pandemic, and mitigating disease, suffering and death; and (3) sustaining infrastructure and mitigating impact to the economy and the functioning of society." (HSC, 2005)

In order to accomplish these goals the government is focusing on three key areas (HSC, 2005):

- "Preparedness and Communication: Activities that should be undertaken before a pandemic to ensure preparedness, and the communication of roles and responsibilities to all levels of government, segments of society and individuals.

- Surveillance and Detection: Domestic and international systems that provide continuous 'situational awareness,' to ensure the earliest warning possible to protect the population.

- Response and Containment: Actions to limit the spread of the outbreak and to mitigate the health, social and economic impacts of a pandemic."

These three areas are translated into a National Strategic Implementation Plan that distributes specific responsibilities among many different government agencies. **Error! Reference source not found.** shows the diversity of government agencies responsible for pandemic preparedness. [5] Furthermore, every state has a local implementation plan.

[4] Graphic by authors, data sources: (All Things Considered, 2005) and (USDA, 2006)

Beyond this, the government has also provided advice for individuals, schools, businesses, communities and health care providers to try and enable all channels to be prepared. For example, the Massachusetts Institute of Technology has a comprehensive plan to deal with pandemic influenza. Specific efforts include stockpiling facemasks, encouraging use of seasonal flu vaccines, and promoting hygiene, as well as preparing for supply chain disruptions. (Friscino, D, Interview with authors, Nov 2006)

[5] Organizational Chart (United States Government Manual, 2006) with annotations by authors

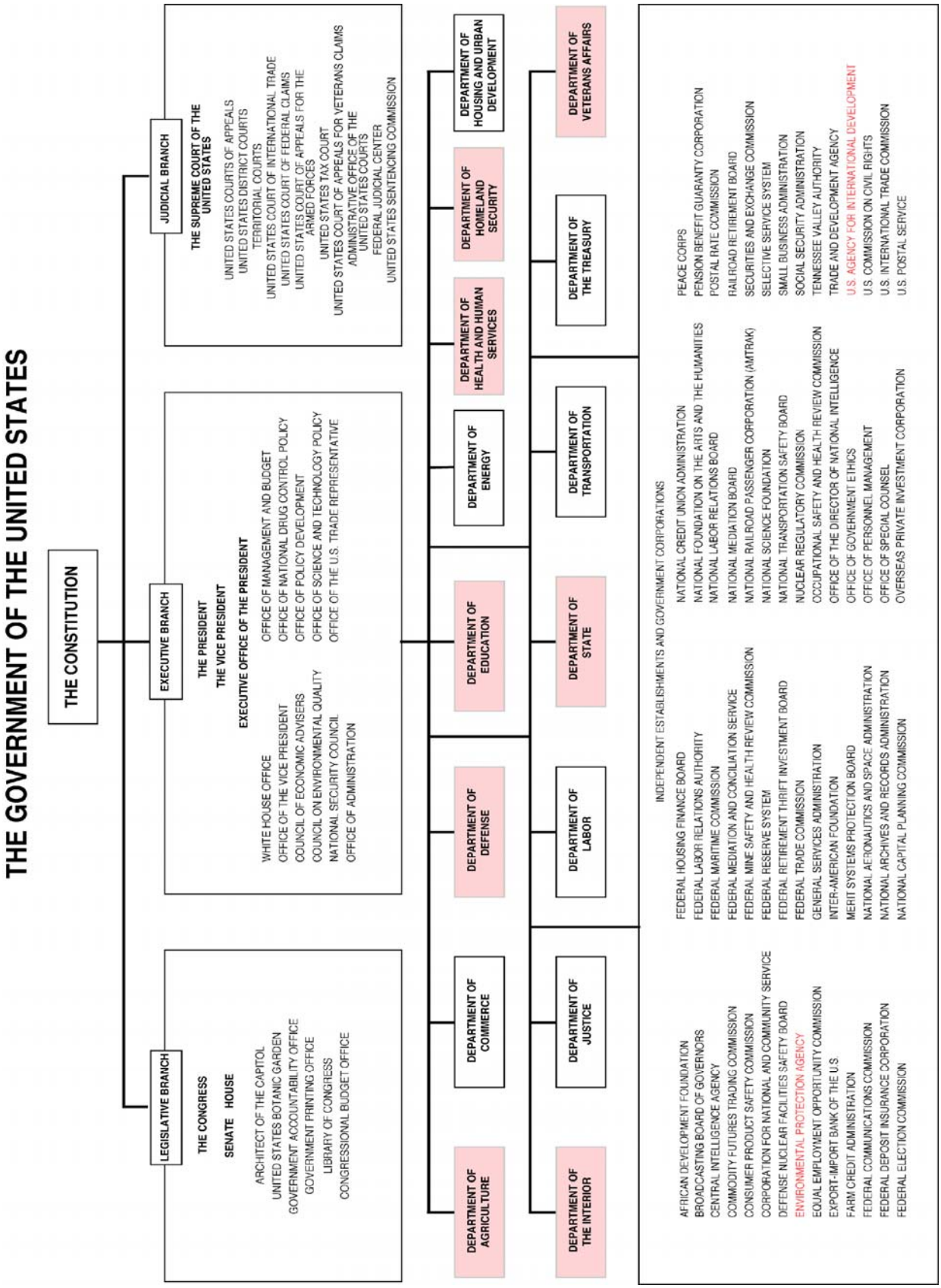


Figure 4: Federal responsibilities for avian influenza on organizational chart

Avian Flu Technologies

A wide range of state and federal government agencies, and private industries, are engaged in efforts to limit the impact of an avian influenza pandemic on the US. In the various phases of the pandemic, different technologies will be most relevant. However, it is important to consider these technologies in the context of the evolution of a global pandemic. Stepping back to consider a holistic view of the set of technologies as part of a greater system, the committee developed a technology mapping framework.

Technology Map Framework

The technology map illustrated in Figure 5 allowed us to understand the various interdependencies between technologies and the relative importance of these technologies in each phase.

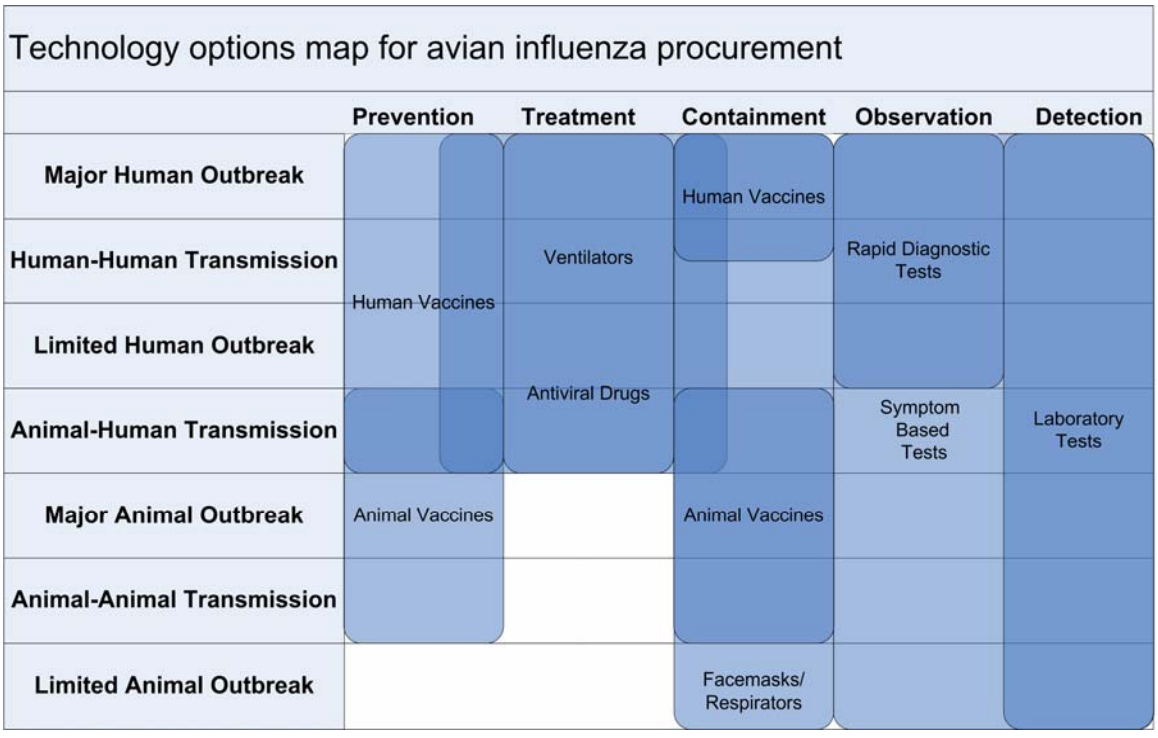


Figure 5: Avian influenza technology options map

The vertical axis on the technology map consists of seven phases of a pandemic. These phases are: limited animal outbreaks, animal-animal transmission, major animal outbreaks, animal-human transmission, limited human outbreaks, human-human transmission, and major human outbreaks. We are using these phases as a rough indication of the development of a pandemic and acknowledge that transitions from one phase to another will not be straightforward and clear.

In addition, it is important to note that different geographical regions are likely to experience each individual phase of a pandemic at different times. Geographically dispersed organizations should be prepared to react to different phases of the pandemic concurrently. In addition, the unpredictable nature of the evolution of influenza viruses makes it likely that the pandemic will not follow each phase in a neat linear order. Widespread human-human transmission certainly could occur before widespread animal-human transmission. However, the occurrence of each phase makes the next phase moving up the vertical axis more likely.

The horizontal axis represents six different types of actions that can be taken during each phase of an emerging pandemic including detection, observation, containment, treatment, and prevention. Detection refers to those actions that initially identify an emergent virus and can be used to determine which phase of the pandemic the disease is currently in. Our use of detection refers to actions that consider entire populations on a local or regional scale. Observation refers to actions that determine whether or not the disease has infected individuals and how those individuals are reacting to the disease. Containment actions are those that seek to limit the spread or escalation of the disease once it has been observed in individual patients or patient populations. Treatment refers to actions aimed at reacting to infection and helping individuals recover from the disease. Finally, prevention encompasses those actions taken in order to either prevent the disease from reaching later phases or preventing future pandemics from emerging. This definition of prevention takes into account that the virus has already emerged, and thus preventing the disease altogether is no longer possible.

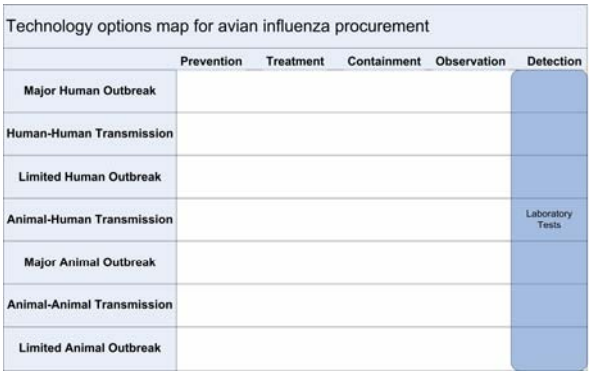
The technologies included on the map were derived from an extensive literature review and from feedback provided by experts throughout the field of pandemic preparedness. The committee placed each technology on the map only after a consensus was reached concerning its most suitable place. In the sections that follow we briefly discuss all of the technologies and explain their specific placements on the map.

Diagnosis of Influenza

A range of methods can be used to diagnose influenza in patients. The most rudimentary of these involves diagnosing patients based on their presenting symptoms. While this is likely to be used during a pandemic, it is relevant to procurement policy, and hence is not discussed here. The methods differ in the amount of time required, the sophistication of the lab facilities needed, and their sensitivity. Gavin and Thompson (2003) have classified the tests into four broad categories based on how the virus is detected: serology, virus culture, nucleic acid, and antigen.

Laboratory Tests

Serology, the measurement and characterization of antibodies and other immunological substances in body fluids, is primarily used for epidemiological or research purposes. Serology requires samples to be collected over two to four weeks, extensive laboratory facilities, and trained personnel. (Gavin & Thomson, 2003). These requirements limit its applicability for use with patients in a pandemic situation.



Laboratory culturing of viruses is often referred to as the "gold standard" of diagnostic tests. The tests are critical in monitoring circulating influenza strains due to their ability to determine exact virus subtypes with high accuracy. Detection by virus cultures requires less time than serology, with results typically available within 4-5 days. However, similar to serology, the tests require extensive laboratory facilities and trained clinicians. This limits the applicability of this technique in pandemic emergencies. Laboratory tests have been sped up by the use of rapid culture techniques. These new processes give results in 1-3 days after inoculation, making it faster but at the cost of lower accuracy than the conventional method (Gavin & Thomson, 2003).

Even faster than serology and the culturing of viruses is the detection of viral nucleic acid by such methods as polymerase chain reactions and the use of gene arrays[6]. The processes have a 1-2 day delay before results are available. Microarrays offer the promise of rapid and accurate detection and subtyping of respiratory viruses, including influenza, in individual patients or as part of large scale-surveillance (Gavin & Thomson, 2003). However, the methods still require extensive laboratory equipment and trained technicians.

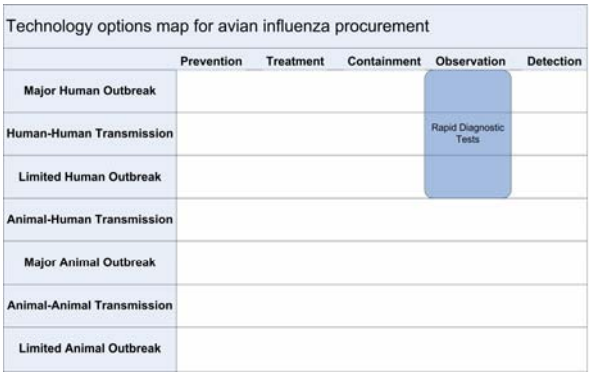
The final method used to diagnose influenza is to detect virus antigens. Several methods exist to detect virus antigens. One method, Direct Fluorescent Antibody staining (DFA), involves

[6] Polymerase chain reaction methods use primers - nucleic acid strands or related molecules that serve as starting points for DNA replication ("Primer", 2006) - to detect and sub-type influenza viruses. DNA microarrays use labeled DNA or RNA sequence to detect the presence of a complementary sequence by hybridization with a nucleic acid sample. ("Reverse transcription", 2006).

tagging antibodies with fluorescent compounds. The antibodies glow under UV light and can therefore be detected when they attach to a certain virus. This test is typically offered as a "same-day" test as it takes about 24 hours to perform. The use of enzyme immunoassays and optical immunoassays are similar methods. Rapid enzyme immunoassays use enzymes to label the antibodies instead of fluorescent compounds. Optical immunoassays label antibodies by detecting their reflection of light (Harbeck, Teague, Crossen, Maul & Childers, 1993).

The long timeframes, expensive laboratory facilities, and highly trained technicians required by the diagnosis methods discussed above limit their practically in a pandemic emergency. For these reasons, these technologies are more appropriately used as detection mechanisms to follow the diseases evolution on a large scale. They would not be helpful in identifying H5N1 in individual patients as a guide to treatment options. On our map, these techniques can be found in the detection column with applicability to all phases of a pandemic.

Rapid Diagnostic Tests



Several rapid diagnostic tests which are also based on the detection of virus antigens are currently on the market. These tests are all designed as single-use and are designed to detect influenza virus within 30 minutes of inoculation time. However, these tests are somewhat expensive for widespread use in a pandemic emergency.[7]

Although the tests have been proven to detect H5N1, no rapid flu test currently on the market can differentiate it from other subtypes. In addition, a negative result using a rapid test does not rule out avian flu entirely. This fact led Singer (2005) to conclude that rapid tests are important for determining appropriate antiviral drugs, for isolating patients, and for informing health authorities but that *surveillance* of H5N1 using rapid tests is "never acceptable." Weinberg and Walker (2005) reached similar conclusions after evaluating three rapid immunoassay diagnostic kits, claiming the low sensitivities made them useful only as "screening tools" (p 367).

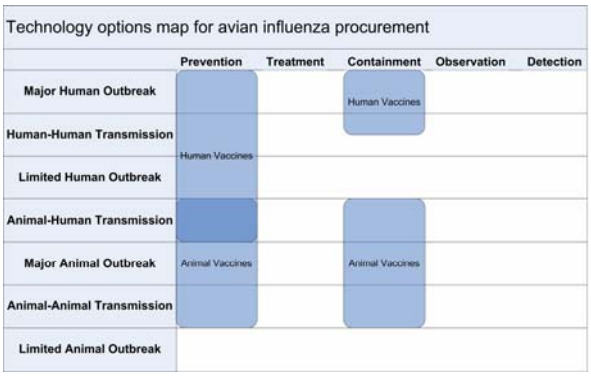
Government-funded research has led to the development of a new rapid test based on gene arrays, representing an important advance in this technology. Two products developed by a team at University of Colorado at Boulder and CDC, MChip and its predecessor FluChip can rapidly identify multiple H5N1 subtypes. MChip represents a significant advance from FluChip in that it is based on a single gene segment (the "M" segment) that mutates much less frequently than the HA and NA segments. This implies that the test would need to be updated less frequently as the virus evolves (Pellerin, 2006).

Rapid diagnostic tests eliminate many of the challenges facing the more traditional diagnosis methods. These tests could be used on a wide enough scale to be useful as

[7] $429 for 25 Quick Vue tests (from http://www.cliawave.com)

observation/diagnosis tools for individual patients. The results of these tests will be available in a short enough timeframe to inform treatment decisions. On the technology map, rapid diagnostic tests are located in the observation column spanning from animal-human transmission through major human outbreaks. The use of these tests on animals is restricted due to their expense.

Vaccination



Vaccination has traditionally been used to produce immunity against viruses. When they work, they are excellent in preventing disease, and diseases such as Polio have been virtually eradicated due to vaccines.

The goal of vaccination, particularly in the event of a potential pandemic, is to produce an immune response with the lowest quantity of antigen possible, and avoiding the need for additional rounds of injection. The principle driving creation of a vaccine for AI is the generation of antibodies directed against hemagglutinin (HA), the surface protein that binds to the cells of infected individuals. Successful vaccine development requires that researchers identify and recreate the subtypes of two of the virus's surface proteins HA and neuraminidase (NA) (Hood, 2006). These two proteins are responsible for the strength and transmissibility of the virus.

Vaccines could be a powerful tool to limit the spread of a pandemic and could also be used to prevent the resurgence of the virus. Therefore, vaccines are located in the containment and prevention columns of the technology map.

Animal Vaccination

Vaccine technology for animals tends to be similar to the technologies for human vaccines, discussed in the next section, though it is subject to far less standardization (Capua & Marangon, 2006). Historically, animal vaccination efforts have not focused on AI because infection with AI viruses tends to occur less frequently than other viruses against which the agricultural sector tends to vaccinate. The recent outbreaks, however, have provided momentum for the development of AI vaccines for poultry. The first vaccines became available in 2004.

China began a program of vaccinating commercial poultry in 2004, and as of mid-2005 had not seen any additional outbreaks in these birds (Webster & Hulse 2005). Thailand has begun investigating vaccination of backyard poultry and free-range ducks, and Vietnam began testing poultry vaccines in 2005. Webster and Hulse note that animal vaccines currently raise two primary concerns. First, agricultural vaccines vary in quality: there are "good" and "bad" agricultural vaccines. Good vaccines will provide protection from disease symptoms and reduce virus load in the individual below what is necessary for transmission. Bad vaccines might limit the appearance of disease symptoms but not excretion, and thus, transmission, of

the virus. Second, animal vaccines may promote mutation of the virus, maintaining the risk of infection in the vaccinated species or in others. With this in mind, Webster and Hulse (2005) note that culling has remained the preferred option for controlling the virus for many health professionals. In addition, they note that the resurgence of AI in Indonesian poultry and pigs and in live poultry markets in China suggests that vaccines of insufficient quality may have been used to some extent in these countries.

Human Vaccination

While vaccination has been an important part of the strategy to control animal outbreaks, there is no commercially available AI vaccine for humans. Research efforts, however, have been ongoing. Monto (2006) notes a number of the challenges pertaining to vaccine development in the specific context of avian flu. One is the ability to gauge the extent to which a particular vaccine produces a sufficient antibody response to guarantee immunity. Monto (2006) notes that vaccine research on other types of avian influenza has not resulted in sufficient antibody response, suggesting that multiple doses and the use of adjuvants[8] would be required. Further, evaluating the meaning of response to tested avian flu vaccines has been difficult in practice, requiring additional testing. Similarly, Luke and Subbarao (2006) note that despite the advances made since the first appearance of H5N1 AI viruses in 1997, many gaps remain in the understanding of immune response to AI. Table 2 summarizes our current state of knowledge on pandemic influenza vaccine development.

What we know from experience with human influenza viruses	What we don't know
Antibodies against the HA (and to a lesser extent NA) are critical for protection.	Which avian influenza virus will cross species barrier to cause a pandemic
Systemic immune response is strain specific.	Importance of antigenic drift among avian influenza viruses
Mucosal immune response provides broader cross-protection.	Immunogenicity of HA of avian viruses in humans (unknown or poor)
Cellular immunity is needed for viral clearance.	
Vaccine strain must closely match the circulating strain.	

Table 2: Current knowledge on pandemic influenza vaccines development (Luke & Subbarao, 2006)

Methods of vaccine production have changed little over time. Many vaccines are still manufactured by replication of inactivated virus strains in poultry eggs. However, this process is both time and labor-intensive, requiring millions of eggs and several months lead time for vaccine development. As a result, the pandemic threat has generated increased interest in the development of cell-based vaccine production technologies, which promise much greater yield. (Ulmer, Valley, Rappouldi, 2006)

The majority of recent research has focused on the further development of reverse genetics for vaccine production. In particular, research involving plasmid-based reverse genetics has shown promising results. With reverse genetics, researchers splice genes from both a harmless strain of the virus with strong reproductive potential and the HA and NA genes from the virulent strain, though the dangerous part of these genes is removed. These pieces of DNA are called plasmids, and these plasmids can then be entered into animal cells in order to generate the seed virus (Hood, 2006).

[8] Adjuvants are agents which modify the effect of other agents while having few if any direct effects when given by themselves. In this sense, they are very roughly analogous with chemical catalysts. ("Adjuvant", 2006)

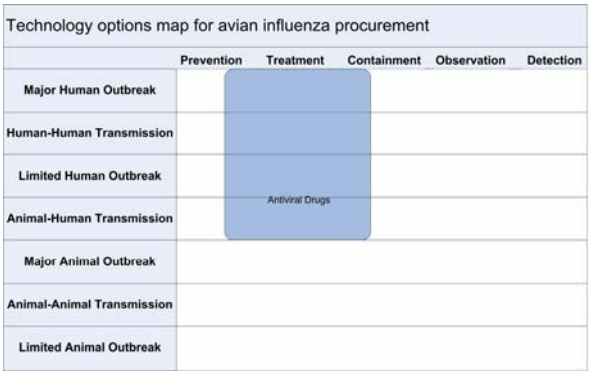
In addition, research conducted by the National Institute of Allergy and Infectious Diseases (NIAID) has focused on live attenuated cold-adapted influenza virus vaccines used in concert with plasmid-based reverse genetics. Cold-adapted vaccines are created from a virus modified to replicate efficiently only at low temperatures. The use of live rather than inactivated viruses has advantages for populations that have not yet been exposed to the virus, including the generation of higher levels of antibody and also cellular and mucosal immunity, which could ultimately protect against a number of different strains (Schultz-Cherry & McCullers, 2006). In addition, attenuated vaccines generate rapid immunity, generally within 10 days of inoculation. The goal of this research program is the development of test vaccines based on existing strains of the AI virus (Luke & Subbarao, 2006).

One concern with using an attenuated AI vaccine is the possibility that the vaccine virus could reassort with an influenza virus in circulation, resulting in a novel influenza subtype that could spread among the population. Luke and Subbarao (2006) caution that this risk must be considered by public health officials in deciding to introduce an attenuated vaccine for public use.

While currently it is impossible to know which specific variant of AI will lead to a pandemic, identification of this virus at the start of the pandemic will provide information for the course of vaccine development. Depending on how the virus has evolved vaccines made from other variants of AI may or may not be effective in generating immunity, and vaccine development would then commence with identification of the novel virus. Vaccine creation would then require manipulation of the pandemic virus for vaccine production, in order to reduce pathogenicity and improve reproductive yield.

Monto (2006) emphasizes the importance of strategy in maximizing the benefits of vaccine use in addressing an AI pandemic. For example, while it is possible that use of genetic material from viruses similar to the pandemic virus could be stockpiled and combined with material from the pandemic virus in vaccine use, this genetic material might be used more effectively in vaccines for use before the onset of a pandemic. Although AI has continued to evolve, it is possible that a vaccine that does not exactly match it could provide some protection, or reduce the dose of a matching vaccine that is developed after a pandemic begins.

Antiviral Drugs



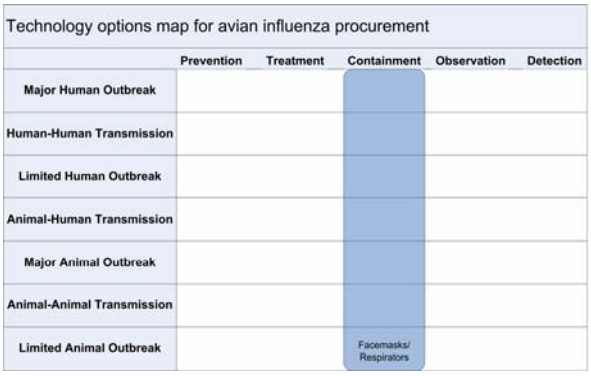
In the absence of a vaccine for AI, antiviral drugs could be used for containment of human avian flu outbreaks and reduction of overall medical and economic costs. These drugs work either by preventing the release of viruses from cells (M2 channel inhibitors) or preventing viral replication within cells (NA inhibitors). Democratis, Pareek and Stephenson (2006) note that use of M2 channel inhibitors for treatment of influenza is limited because of their toxicity and problems with drug resistance. According to CDC, two M2 channel inhibitors used for

treatment of influenza, amantadine and rimantadine, have not been effective in treating human cases of avian influenza in Asia. CDC suggests that two NA inhibitors, Tamiflu (oseltamivir) and Relenza (zanamivir) may work to treat avian flu, but further study on their effectiveness is needed. NA inhibitors work by binding to the active site on the viral NA, inhibiting viral replication and the virus's ability to spread. Because pandemic AI is likely to be a systemic infection, Tamiflu is considered the antiviral drug most likely to be effective in treating avian flu, because, unlike other existing antivirals, it can be absorbed throughout the system. However, Relenza, with which absorption is limited to the respiratory tract, could play an important role in prevention, because infection is likely to occur via that route (Democratis et al, 2006).

One company, BioCryst, has seen promising results with an injectable antiviral drug called Peramivir for treating both seasonal and avian influenza.[9] BioCryst (2006) also notes that the drug was given fast-track status for approval by the FDA in 2005. Testing is also expected to take place in Vietnam and Thailand (Roos, Oct 2006). If the drug proves to be successful, one important implication is the possibility that the drug can be manufactured more quickly relative to other antivirals. BioCryst's chairman recently suggested that one Swiss manufacturer could produce one metric ton of the drug within a month, which he suggested could treat about 8 million people (Roos, Oct 2006). In addition, Democratis et al (2006) noted that Peramivir has shown some potential to inhibit viral strains that have shown resistance to Tamiflu and Relenza.

Antiviral drugs will be most effective in treating individuals who have already contracted the disease. However, since antivirals slow the replication of influenza viruses they may also be helpful in containing the disease and in prevention. Therefore, antivirals cover all of the treatment column and stretch into both the prevention and containment columns on the technology map.

Facemasks



Facemasks could limit the extent of transmission of AI by providing a physical barrier against transmission, though they are typically viewed as a last resort strategy (IOM, 2006). Facemasks come in two forms: respirators, which are fitted masks designed to protect the user from inhalation of contaminants; and medical masks, which are unfitted masks designed to protect the user against potentially infectious body fluids. Because respirators protect against inhalation risks, they are believed to be more effective than medical masks in protecting against airborne transmission of disease. The most common type of disposable respirators are

[9] Peramivir was found to improve survival of mice and ferrets infected with AI, and clinical testing in humans has found that high blood levels of the drug can be given in humans without causing any adverse effects (BioCryst, 2006).

N95 filtering facepiece respirators, which are so named because they exhibit a 95% efficiency in filtering out particles greater than 0.3 microns in diameter[10].

A recent Institute of Medicine (IOM) study (2006) assessed the potential for the development of disposable N95 respirators in healthcare settings. In addition, the study assessed the current state of knowledge on the need for reusable facemasks for healthcare providers and the public. The report was motivated by the likelihood that in a near-term pandemic, disposable respirator and facemask supplies would likely be insufficient.

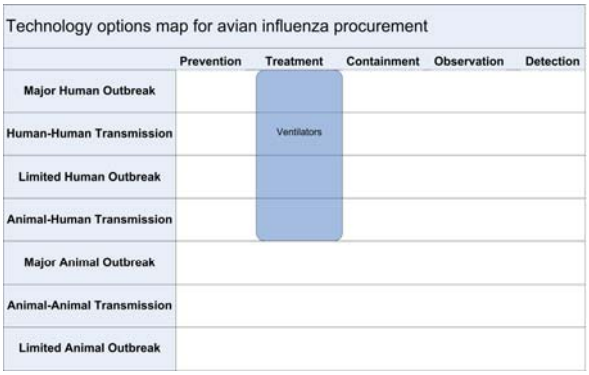
The IOM committee was unable to identify modifications to facemask or respirator manufacturing that would make them suitable for reuse. The committee was also unable to assess the effectiveness of woven cloth masks that have been used in Asia during AI outbreaks, and notes that while there is not sufficient information to recommend or discourage their use; they are unlikely to provide the same level of protection as medical masks or respirators. In addition, the committee warns that use of such devices might provide a false sense of security and encourage less caution in preventing exposure in those wearing them.

Overall, the IOM committee recommended that HHS pursue further research on transmission of infectious diseases in general, and, more specifically, on the epidemiological aspects of novel influenza strains and the design and development of reusable respirators and medical masks. This would include research on new materials that might further enhance effectiveness, including innovations targeted at the cloth face masks that are prevalent in Asia. In addition, the committee notes that an important aspect such research is the development of decontamination techniques that would not cause harm to users of the mask and would retain the mask's integrity and performance. Finally, the committee noted that regardless of the quality of respirators and facemasks, their effectiveness depends on proper usage - particularly mask fit and need for hand hygiene after handling the mask - and that public health education should stress this point.

Facemasks are best used as a tool for containment of the virus. While they have no relevance in the early phases of the pandemic before humans can contract the diseases, they are still likely to be requested by those working around animals as a precaution. For this reason, we have placed facemasks under the containment spanning all of the pandemic phases.

[10] Further information on N95 disposable respirators can be found at http://www.health.state.mn.us/divs/idepc/dtopics/infectioncontrol/ppe/comp/n95.html

Ventilators



Ventilators will be an important technology for treatment of some patients with AI. Mechanical ventilation can be used to support life in patients suffering from acute respiratory failure by moving air into and out of their lungs until they regain the ability to breathe independently. A ventilator takes oxygen and air from a building supply or tank, pressurizes the gas and blends it to the desired oxygen level, and ultimately delivers it to the patient. A respiratory therapist determines the appropriate magnitude, rate, and duration of flow.

The FDA classifies ventilators into three groups: hospital, transport, and home-use. Hospital units offer many monitoring features and cost $15,000 to $35,000 each. Transport (or portable) ventilator units cost between $5,000 and $12,000 per unit. They offer full ventilation capabilities but fewer monitoring features than hospital ventilators. Home-use ventilators cost several hundred dollars, and offer the least monitoring features (Kurtzweil, 1999).

Experts expect a shortage of mechanical ventilators if a human AI pandemic hits. In March 2006, there were 105,000 ventilators in the country, and HHS estimates a need of between 64,875 and 742,500 in varying pandemic scenarios (as shown in Figure 2 pg 12). Currently, 100,000 ventilators are used during regular flu seasons. The Strategic National Stockpile holds 4,000 to 5,000 portable ventilators (McNeil, 2006).

As a critical piece of hospital equipment, in the event of a pandemic, ventilators will be used solely for the treatment of individuals with the disease. Ventilators are found in the treatment column of the technology map.

Analysis of Procurement Strategies

The markets for the technologies relevant to avian influenza vary significantly in terms of their competitiveness, cost to entry, regulatory environment, and excess capacity in the industry, among other factors. However, several themes can be highlighted to understand market efficiencies and the barriers to pandemic preparedness. The pre-pandemic procurement of each of these technologies faces unique challenges but policy solutions can be used to bring about change and we have used our technologies unique characteristics to highlight this.

Upon the emergence of a pandemic virus, immediate demand surges can be expected. Anticipating shortages, governments have already begun to stockpile key technologies such as anitivirals and facemasks. However, even with adequate funds for purchasing supplies, market conditions will render some technologies unavailable without other government interventions. Government procurement can improve the supply of technologies needed for pandemic response. The ability of the government to procure pre-pandemic supplies of technologies, and the urgency for doing so, depends heavily on the market conditions for each technology.

It is worth repeating that the scope of this report is restricted to procurement of technologies limiting the effects of a human pandemic specifically. Therefore, our analysis of procurement is limited to the critical technologies targeted for humans.

Markets and the Technology Map

In looking holistically at the set of technologies discussed in our preceeding technologies section, we observed that technologies found on the left side of our technology map are less likely to be adequately supplied by the market. Government pre-pandemic preparations will be especially important for these technologies, targeting the containment, treatment, and/or prevention of pandemic influenza in humans. These technologies include vaccines, antiviral drugs, facemasks, and ventilators.

In contrast, we found that technologies on the right side of the map would generally be provided by the market in adequate supply. Procurement of these technologies is less relevant to pre-pandemic preparedness as they have only minimal roles in emergency response (Friscino, D, Interview with authors, Nov 2006). This distinction is illustrated in Figure 6.

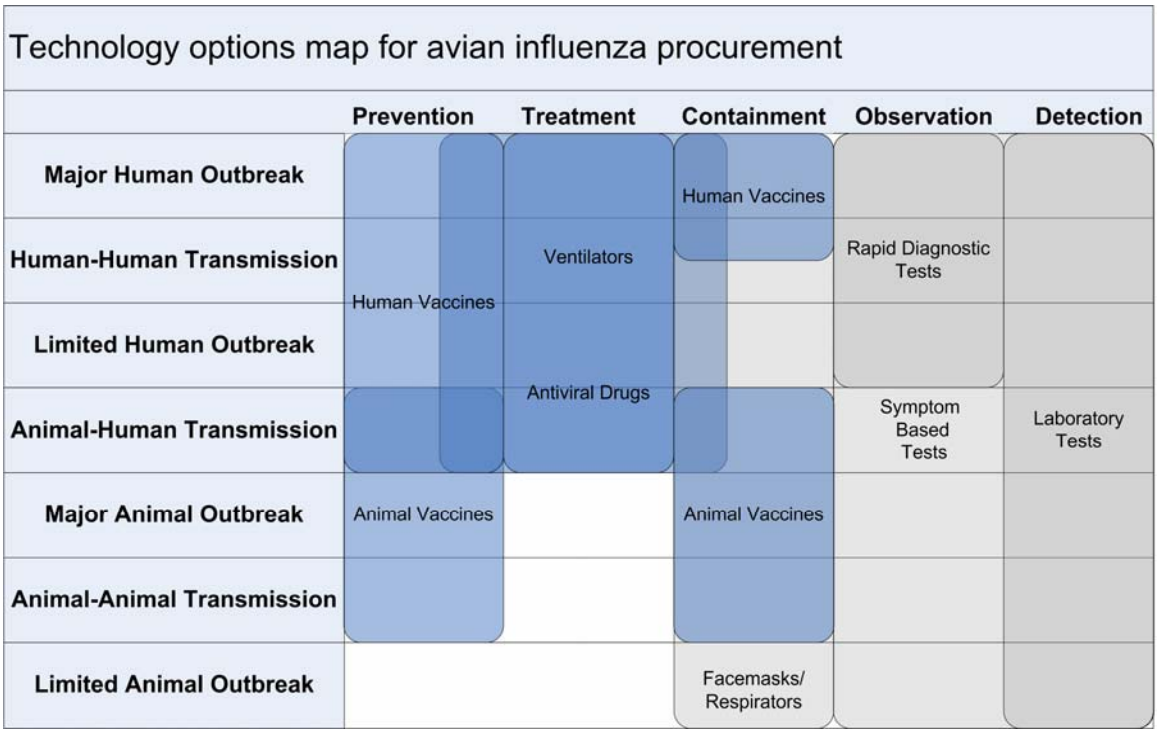


Figure 6: Technology Map with Market Distinctions

Technologies which are likely to be well provided by the market are denoted in grey boxes. While technologies which have barriers to pandemic readiness are marked in blue.

Pandemic readiness

Industries currently experiencing rapid demand growth are the most likely to be able to respond to the demand surges inherent to pandemic response. In general, these industries can be characterized by competitiveness, diversity of products, and expanding capacity. Of the technologies we analyzed, rapid diagnostic tests and ventilators both exhibit these characteristics. Pandemic readiness does not imply that supplies of these technologies are currently sufficient; rather, it implies an ability to increase output with minimal government intervention.

Competitiveness

A competitive market is a market with many producers that provides incentives for efficient production, innovation, and declining costs. Both the ventilator and rapid diagnostics markets exhibit these qualities.

First, the market for ventilators remains highly competitive, with innovation and growth increasing primarily as a result of the increasingly wealthy and aging population's trend toward home health care (Frost & Sullivan, 2005). While the market for ventilators has traditionally been driven by replacement of existing equipment, recent growth has been fueled by increased demand for portable and home use ventilators. Ventworld, an internet

marketplace for mechanical ventilation products, lists more than 100 manufacturers of mechanical ventilators. [11]

Second, the production of rapid diagnostic tests lies within the rapidly expanding and highly competitive biotechnology sector. The competitive nature of the market has been an asset for the development of rapid diagnostic tests for avian flu. In fact, biotechnology companies have already developed several profitable technologies that are aiding the development of rapid diagnostic tests.

The WHO's recommendations of July 2005 on the use of rapid testing for influenza list 19 commercially available diagnostic tests (WHO, 2005). This indicates that conditions for competitive production and development of diagnostic tests are in place (Berndt E, Interview with authors, Nov 2006). In addition, several new tests are in varying stages of the FDA approval processes (Park, 2006). FDA approval of multiple tests would increase competition in the market for avian flu detection, leading to improvements in test sensitivity, specificity, and lower costs.

Diversified markets

Rapid demand growth and competition commonly result in product diversity, a second important market characteristic for pandemic preparedness. The presence of diverse products within a single technology market implies numerous sources of supply as well as flexibility in product choice.

A primary reason for the diversified markets we observed was the presence of existing and varied demand for products in the absence of avian flu. For example, rapid diagnostic technologies have many applications in medicine beyond AI.

The following advances cited by Park (2006) exemplify the level and variety of innovation that is occurring within the industry. For example, CombiMatrix, a company in Washington state, launched a DNA microarray that can detect and identify a number of different flu strains, including H5N1. Tm Bioscience, a Toronto-based company, has developed a test that can detect all major human respiratory viruses, including H5N1, and is currently working with FDA on gaining expedited review. Genaco Biomedical Products, based in Alabama, already has a commercially based test that can detect all known avian influenza strains, as well as 20 other respiratory ailments, and identify the virus within 4 hours using polymerase chain reaction techniques. (Seigenthaler Public Relations, 2005). As the virus evolves diagnostic tests will have to be updated in order to be able to identify the latest H5N1 subtype.

The ventilator market is also characterized by significant product diversity. Beyond the $30,000 hospital ventilators, governments have the possibility of procuring portable ventilators for less than half of that cost, or smaller ventilators such as those used in homes for a few hundred dollars (McNeil, 2006). While features vary among these products, the possibility of procuring different models provides important options to policymakers facing preparedness decisions with limited time and resources.

[11] See www.ventworld.com

Manufacturing capacity

The availability of excess capacity is essential to a technology being able to deal with a pandemic. This characteristic is generally most common in industries experiencing rapid growth. In addition, it is important to consider the ease with which industries can expand capacity given a rapid demand surge.

The ventilator industry currently has excess capacity. A representative for Drager Medical, a German company that leads the world in ventilator production, noted that given sufficient demand, the company could double manufacturing capacity over the course of a week, providing an additional 10,000 ventilators in a year (McNeil, 2006). Given this fact and the large number of manufacturers on the market, it appears feasible that the US could significantly increase the quantity of available ventilators over the next several years in the absence of a pandemic. Of course, this expansion would not happen without large purchases for stockpiles.

In addition, with rapid growth in the diagnostics market, evidence suggests that most companies specializing in diagnostics are planning increases in manufacturing capacity. While we were unable to locate estimates of projected and planned capacity increases, a recent survey of biomedical companies in California found that more than 70% of companies expected to expand their manufacturing capacity within the US in the next two years (California Health Care Institute, 2006). While this data represents only California companies, it suggests a trend that bodes well for the ability of the US to manufacture diagnostic tests in the event of a pandemic.

Barriers to pandemic readiness

With the exception of vaccines, all the technologies on the left side of our map (those shown in blue in Figure 6) exist in the market but are unable to meet the high demand associated with a pandemic. Vaccines also suffer from a lack of manufacturing capacity, but significant other factors compound the problem. These include poor historical government interventions, as well as the fact that vaccines cannot be produced until the pandemic strain has emerged. Box 1 details the decline of US vaccine manufacturing capability.

Demand uncertainty

Demand uncertainty reduces the incentives of individual companies to invest in research and development. This is an acute problem in the case of pandemic influenza vaccine development.

In addition, demand uncertainty limits the incentives companies have to invest capital towards new manufacturing facilities that may not ultimately be needed. In the case of vaccines, new manufacturing plants can require four years of lead time and hundreds of millions of dollars of capital investment (Daems, Del Guidice, Rappouli, 2005). Such an investment can only be justified by forecasted long-term demand. Similar circumstances have negatively influenced the development and availability of new antivirals.

Cost of entry

Developing and manufacturing some technologies, such as vaccines and antivirals, requires huge capital investments, with an uncertain payoff that at best will occur many years in the future. For example, in the vaccine market, companies must finish building the full manufacturing facility for a vaccine before the FDA approves phase III clinical trials—a process that typically costs $30 million (Grabowski & Vernon, 1997; IOM, 2003). Even a foreign pharmaceutical company with an approved, proven drug sold outside the US must perform full FDA clinical trials before it can sell that drug in the US (IOM, 2003). The high cost of entry may stifle innovation in these industries, as it prevents risk-taking by the big firms and prevents startups from entering the market. Government intervention to increase research and development in these industries is often beneficial, especially when public goods are involved.

Lack of manufacturing capacity

As mentioned previously, the availability of excess capacity is essential to a technology being available in the event of a pandemic. Unfortunately, key technologies such as vaccines, antivirals, and facemasks have insufficient capacity and little or no surge capacity. Moreover, domestic manufacturing capacity will be critical in the event of large scale international supply chain disruptions.

Even if vaccine production plants operate 24 hours a day at full capacity, the supply of vaccines would still fall far short of the potential need, as shown in Table 3. Somewhat optimistically, the WHO estimates that by 2009, pandemic vaccine production could expand to only 2.3 billion doses for a world population of nearly 7 billion. Furthermore, it is possible that pandemic flu and seasonal flu vaccine production will compete for capacity simultaneously, reducing available capacity. (WHO, Sep 2006)

Estimate of production capacity for current influenza vaccine:	350 million doses (inactivated trivalent vaccine containing 15 ug of HA per dose).
Estimate of production capacity for potential influenza vaccine, if manufacturers optimize current output (e.g. by working 3 shifts/24 hours):	500 million doses (inactivated trivalent vaccine containing 15 ug of HA per dose).
Planned expansion for extra vaccine production-capacity in the next 2-3 years (280 million):	780 million doses (inactivated trivalent vaccine containing 15 ug of HA per dose).
Estimate if production should switch to monovalent pandemic influenza vaccine, assuming only 15ug per does (2009 projection):	2340 million doses of pandemic vaccine (inactivated monovalent vaccine containing 15 ug of HA per dose).

Table 3: Short-term potential availabilty of influenza vaccine per year (WHO, Sep 2006)

While the respirator market has some ability to respond successfully to demand surges, fear of pandemic flu has led governments, hospitals, and businesses to attempt to stockpile disposable respirators, causing production bottlenecks. For example, 3M plants are currently running at maximum capacity but the company has responded with increased investment in manufacturing capacity (DePass, 2006).

While the US has three major producers of N95 respirators, additional competition exists from foreign companies, particularly in China. Chinese respirators became particularly important during the SARS outbreak in Canada, as businesses had difficulty acquiring facemasks produced by American companies. (Saunders, 2005). It is also important to consider that many US companies produce facemasks overseas. Osterholm (2005) notes that many mask components produced by US companies also come from overseas. He argues that in the event of a global pandemic that involves border closings, it may be impossible for US firms to produce facemasks. While there has been little focus on overseas inputs to critical technologies, supply chain disruptions will also likely have implications for other technologies (Osterholm M, Interview with authors, Nov 2006).

Lack of diversity

Product diversity helps to ensure availability and multiple technology options. Among the technologies the committee studied, the lack of diversity in the antivirals market is particularly worrisome. While Tamiflu capacity has expanded significantly, the possibility of antiviral resistance implies a need for greater product diversity in the antiviral market. Cases of antiviral resistance have been documented in Vietnam (Roos, 2005). However, Peramivir is the only new antiviral drug for avian influenza in clinical trials. The need for additional antiviral drugs suggests a role for government promotion of such development.

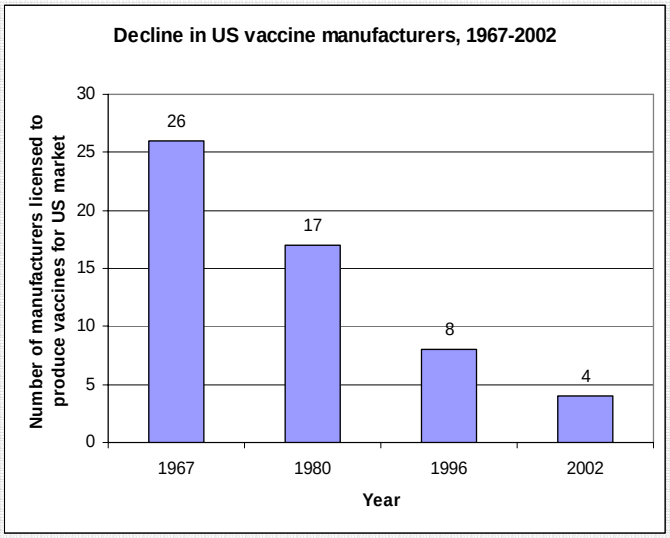
Box 1: The decline of US vaccine manufacturing

Vaccine development is impeded by a number of factors. First, the costs of complying with FDA approval processes are high. Vaccines must meet stringent safety and efficacy standards before approval, and they are subject to review and licensing procedures that extend beyond those required for most pharmaceuticals. Each individual vaccine batch must be approved and licensed, and costs associated with each step of the regulatory process are high. For example, FDA requires that vaccines used in Phase III clinical trials be manufactured in a facility that will actually be used for production of the vaccine if it is improved. This implies that a company might spend on the order of $30 million on preparation of a production facility before a vaccine is granted approval (Grabowski and Vernon, 1997; IOM, 2003).

Second, liability risks to vaccine companies are great. This is partially because vaccines are administered to healthy individuals, making any side-effects easily attributable. In addition, vaccines pose inherent risks even when properly manufactured. With any vaccine there is a small possibility of severe reaction or death (Riddiough and Williams, 1980). IOM (2003) notes that liability insurance costs were a primary reason for the mass exit of firms from the vaccine industry during the 1980s. While policy attempted to address these costs through creation of the National Vaccine Injury Compensation Program in 1988, the program covers specific side effects from a limited number of vaccines, and therefore does not include a new pandemic vaccine without an amendment to the original act.

Third, government purchase programs, by placing downward pressure on vaccine prices, may have created disincentives for firms that supply vaccines. Government has historically been a major purchaser of vaccines, particularly for childhood vaccination programs. This has frequently been accomplished through low-bid contracts, limiting the price that manufacturers receive (IOM, 2003).

Due to the reasons described above, the number of vaccine producers has fallen from 26 to 4 during the period 1967-2002. (Graph derived from IOM, 2003)



Policy solutions and challenges

A variety of policy solutions exist that reduce the barriers to pandemic preparedness. This section outlines a variety of policy solutions and some of the challenges to their implementation. Most of these policies are important to adopt in advance of the emergence of a pandemic.

With the notable exception of vaccines, direct stockpiling of most technologies will facilitate the immediate response to an emerging pandemic. Direct procurement can be coupled with other policy mechanisms that promote private sector investment in technology development and ultimately, supply, by mitigating risk associated with product development or provision. These include the following: financial awards, advance purchase agreements, the subsidization of research and development, the extension of liability protections to some industries, and changes to regulatory approval process changes.

It is important to note that the impacts of some of these policies may overlap with more direct procurement policies, and that redundancies and subsequent inefficiencies may occur when numerous policy tools are being used to the same end. For example, guaranteeing market demand through procurement could make R&D subsidies redundant. Research by Acemoglu and Linn (2004) suggests that increasing drug market size is associated with a significant increase in drug development efforts.

The most appropriate policy selections depend on the specific characteristics of each technology. For example, when procurement is intended to create a new market for a non-existent product, the government might provide a financial award for successful product development. Similarly, in procuring a technology that provides a public good but for which private demand is highly uncertain, government might guarantee procurement of a certain quantity (Rolfstam, 2005).

Stockpiling

Direct stockpiling of technologies is most effective for technologies that can already be manufactured in large quantities and can be stored inexpensively for a significant amount of time. With respect to avian influenza preparedness antivirals, facemasks, and ventilators appear to be good candidates for stockpiling. However, the cost of purchasing ventilators may prohibit widespread stockpiling.

Shortages of antivirals are expected to persist despite planned increases in production capacity. Manufacturing of antiviral drugs requires significant lead times, and it therefore cannot be completed on-demand in response to a pandemic.[12] The United States is currently creating a stockpile of 81 million doses of Tamiflu while the WHO is creating stockpiles of at least 5 million courses of Tamiflu treatment for rapid delivery to the location of an emergent virus (Democratis et al, 2006).

[12] According to Roche pharmaceuticals, average lead time for the Production of Tamiflu is on the order of 12 months. See http://www.roche.com/med-cor-2005-08-24.

Stockpiling can also provide powerful motivation for manufacturers to increase capacity. Since 2004, Roche, the producer of Tamiflu, has increased its production capacity dramatically as a result of increased demand from government stockpiling policies. Roche has granted licenses to a number of manufacturers for generic production in order to achieve this growth. Roche's domestic capacity in the United States has increased to 80 million doses annually (Nutley, 2006).

Stockpiling of disposable facemasks is also important. IOM (2006) noted that in the event of a pandemic, there will be inevitable shortages of disposable masks. Therefore, a large stockpile of disposable masks may be the only solution to providing healthcare workers and other at risk employees during a pandemic. The US has procured 150 million N95 respirators for the Strategic National Stockpile. (HSC, 2005)

The major constraint to ventilator availability appears to result from challenges on the demand side. The estimated demand for ventilators in the event of a pandemic vastly exceeds current supply. As such, pre-pandemic stockpiling may be necessary. In March 2006, there were 105,000 ventilators in the country (McNeil, 2006), and HHS estimates a need for 742,500 in a severe AI pandemic (See Figure 2 on pg 12). Standard hospital ventilators cost approximately $30,000 each. At that price, hospitals cannot afford to stockpile units that may ultimately never be used. Hospitals keep little if any reserve ventilator capacity on-site. Currently, 100,000 ventilators are used during regular flu seasons. During peak flu season, many hospitals rent additional units in order to meet short-term spikes in demand. While portable ventilators can be purchased for about $6,000 each, Rubinson, Nazzo, Talmer, O'Toole and Kramer (2005) estimate that few hospitals can afford to double their capacity. As a result, it appears that the primary role of stockpiling hospital-quality ventilators will fall on the government. The Strategic National Stockpile currently holds 4,000 to 5,000 portable ventilators (McNeil, 2006). The US government plans to purchase an additional 6,000 ventilators over the course of 2006 (Russell, 2006). Some hospitals have begun to stockpile disposable ventilators that can run on a hospital's oxygen supply and can be purchased for $50 to $100 (McNeil, 2006).

Financial awards

Supply can also be increased through the provision of financial awards. For example, the creation of award systems for prototype vaccine development has been proposed as a means of increasing manufacturing capacity (Booy, Brown, Grohmann & MacIntyre, 2006). Under award systems, vaccine manufacturers would be encouraged to develop prototype vaccines based on strains similar to the one likely to cause a pandemic. The manufacturers would carry out clinical trials on these vaccines and receive regulatory approval. Then once a pandemic emerged the companies could submit applications to regulatory agencies considering the new vaccines simply 'variants' or their previous products rather than entirely new vaccines (requiring the same rigorous clinical studies and approval processes).

In April of 2005, the government awarded a $97 million contract to Sanofi Pasteur for the development of a cell-based vaccine from current virus strains. More recently, in May of 2006, the government announced the provision of $1 billion in contracts split among five vaccine manufacturers to develop cell-based manufacturing capacity within the US (HHS,

2006). These types of awards may be critical to efforts to increase US domestic influenza vaccine capacity. These types of policies may also be applicable to the development of new antiviral drugs.

Advanced purchase agreements

Advance purchase agreements are another mechanism to give companies incentives to produce quantities of products the market would not induce them to produce. Advance purchase agreements are most appropriately applied to technologies that cannot be purchased currently since they have yet to be developed or commercialized. In these initiatives, governments agree to purchase a specified number of doses of a vaccine once it is developed. A secure market and specified price give companies the confidence to invest in what would otherwise be a risky investment. Similarly, stimulating the development of new antiviral drugs through advanced purchase agreements would provide incentive for new drug development while also enhancing the size of the US stockpile (Daems et al, 2005).

While advance purchase contracts would provide incentives for companies they could also waste government resources as governments would be locked into purchases regardless of whether the technologies turn out to actually be needed. Setting specific timeframes for the development of vaccines is critical in making these agreements work. However, setting rigid timelines may also reduce manufacturers' willingness to commit to production if the governments could back-out of the contracts if development took longer than expected.

The WHO (Sep 2006) proposes expanding current seasonal flu vaccine as a variant of advance purchase agreements. The expansion of seasonal flu vaccine programs would provide a guaranteed market for manufacturers for seasonal vaccines. In contrast to the case of pandemics, governments would actually be able to use most of the vaccine doses purchased each year. In addition, expanding seasonal flu vaccine demand would provide incentives for manufacturers to invest in new manufacturing capacity. This additional capacity could then be used to produce greater quantities of pandemic vaccines if a pandemic emerges. Expansion of seasonal vaccine programs could take the form of increased uptake of influenza vaccine in countries with existing seasonal vaccine programs or the creation of new seasonal vaccine programs in countries where no such programs currently exist.

Subsidize research & development

The subsidization of research efforts can also increase pandemic preparedness. Government subsidization of technology develop is most appropriate when R&D levels are insufficiently high due to either limited capital or due to the public good aspects of products.

The subsidization of research efforts could promote timely vaccine development. In anticipation of scarce supplies, the WHO has called for the support of research efforts into the design of more potent vaccines requiring fewer, smaller individual doses of antigens. Initial results in this area have been mixed, but research into more potent vaccines is ongoing. In addition, further research is needed into increasing the manufacturing yield of avian influenza vaccines. These efforts could significantly increase the global capacity for producing pandemic influenza vaccines.

Further research and development is also important in the area of facemasks. While the development of reusable facemasks may not be feasible in a short time frame, IOM (2006) noted that the government could fund research aimed at the development of decontamination techniques for use with disposable facemasks[13]. Facemask suppliers are already at capacity and are unlikely to be able to support these research efforts on their own.

Liability protection

Offering liability protection to manufacturers is appropriate when the government is attempting to procure a potentially harmful product that requires product development and manufacturing over a shorter than average time frame. Liability protection is not needed to ensure availability of existing, more mature technologies such as facemasks and ventilators.

The National Vaccine Injury Compensation Program was implemented in 1988 to provide liability protection for vaccine manufacturers. However it only covers specific side effects from a limited number of vaccines and would not cover a new pandemic vaccine without an amendment to the original act. The Biodefense and Pandemic Vaccine Drug and Development Act of 2006, now in committee, contains provisions that would remove barriers to rapid drug development and reduce manufacturers' liability in the event of a pandemic. Liability protections for vaccine manufacturers engaged in pandemic flu development would reduce the costs of manufacturing pandemic influenza vaccines. This would encourage additional manufacturers to invest in efforts to develop new vaccines.

Regulatory changes

The government can play an important role in expediting the approval and licensing of new drugs that could be effective against AI. Fast-track regulatory mechanisms would be critical for influenza vaccines and could be also is effective with regard to antiviral drugs (Daems et al, 2005; Gronvall & Borio, 2006). The FDA has promised to fast-track approval of Peramivir, an antiviral that thus far has been shown effective against AI (Roos, 2006). Fast-track approval processes would also reduce the costs associated with developing new drugs. These reduced costs would allow additional firms to enter the market in vaccines or antivirals.

Uncoordinated regulatory approval processes in differing countries also serve as a barrier to greater pandemic vaccine production. Clinical trials must often be duplicated in many countries in order to receive approval for new vaccines. Gronvall and Borio (2006) propose regulatory harmonization across different countries and regions as a method for easing the introduction of new vaccines. Under these proposals each country would still need to approve new vaccines and other medicinal products but the countries could use the same clinical trial data. It is envisioned that vaccine manufacturers would submit a common application for approval from each of the different regulatory agencies. Certainty that a vaccine could be sold in international markets without additional regulatory costs would reduce the risk of investing in vaccine development.

[13] Ideally these techniques would allow disposable masks to be decontaminated in a fashion that would not cause harm to users of the mask and would retain the mask's integrity and performance.

Recommendations & Conclusion

In this report, we surveyed the technologies available for detection, observation, containment, treatment, and prevention of an AI pandemic. We focused our analysis on those technologies that the US government may need to procure prior to or during a human pandemic. Despite the much-publicized federal emphasis on stockpiling of antiviral drugs and H5N1 vaccines, there are other technologies that should be considered as well. Laboratory tests are needed to track genetic changes in AI and to determine which flu cases are due specifically to the H5N1 strain. Laboratory tests also provide critical information needed for the production of effective antiviral drugs and vaccines. Rapid diagnostic tests can be used to determine appropriate treatment. Facemasks and respirators are inexpensive technologies that may be effective at slowing the spread of influenza.

Recommendations

After analyzing the landscape of technologies available, and based on the policy findings discussed in the previous section, we have reached five recommendations.

> **Recommendation 1:** Government should limit research and development support for technologies that are adequately provisioned through market forces.

We recommend that the government focus research and development funding to those technologies that are not supported fully by the market. Research and development funding is most critical when conditions do not exist for the competitive production and development of technologies in the market. There are many demands on the funding that has been made available for pandemic influenza. For technologies such as vaccines and antivirals, there is a clear need for government support of R&D efforts.

Conditions for competitive production and development of diagnostic tests are in place (Berndt E, Interview with authors, Nov 2006) as indicated by the wide commercial availability of products (WHO, 2005). There appears to be no shortage in the supply of these tests and production could be significantly increased if demand were to increase. For this reason, the industry appears to be well positioned to face a pandemic surge in demand. Also, in latter stages of a major pandemic, many healthcare providers would likely immediately give patients antivirals or other medications instead of using rapid diagnostic tests.

The potential role of facemasks in reducing the extent of an influenza pandemic is unclear. Funds should be allocated to allow researchers to establish clear guidelines concerning the use of facemasks during a pandemic. If research shows that facemasks could be effective, additional research into the design of inexpensive, reusable facemasks will also be needed.

The primary challenge in implementing this recommendation involves how the government sets its research priorities. Funding decisions are currently decentralized among a range of different organizations including the National Institutes of Health, the National Science Foundation, and the Department of Health and Human Services. Many of these organizations have a long history of self-regulating the allocation of resources, giving priority to those technologies which are farthest from commercialization. The variety of sources available for funds ensures that no single paradigm or set of metrics are used to determine how funds should be committed. This distributed approach to the allocation of funds should not be eliminated.

However, a formal mechanism could be designed that allows scientists, economists, public health officials, and health care providers to work together to establish research priorities with respect to influenza preparedness. Researchers and other recipients of funds should be encouraged to contribute to the debate on specific research directions. In order to gain the support of researchers, it must be made clear that this recommendation does not result in a cut in funding but rather a reallocation. The methodology and specific analysis tools used in establishing these guidelines should be made available to the public. This will allow both the scientific community and private industry to engage with the process, inform the research, and understand the current direction of funding. The research priorities established by this mechanism should be endorsed at the highest levels of government and be used to guide agencies in allocating their funds.

The government has a great deal of influence in determining the direction of research efforts as the primary source of funding in many fields. Other organizations, such as private trusts, may intervene either by lobbying or by funding additional research if they feel that the government's funding priorities are unwise. These independent efforts should be encouraged as they will likely strengthen public discussions of what technologies are most critical to fund. The response of private funding agencies should be monitored and the government should adjust its own funding priorities in order to ensure that government funds are being directed where they are needed most.

Recommendation 2: Government must stockpile critical technologies that are available.

The timeframe governing the emergence of a pandemic is highly uncertain. Markets do not work efficiently when there is uncertainty in demand. Since emergence of a pandemic virus is uncertain, private companies have little incentive to significantly increase production prior to the emergence of a pandemic. Even in those industries that have significant production capabilities, such as facemasks and ventilators, there will be a delay between the pandemic emerging and significant increases in production. Therefore, it is critical that the government stockpile the supplies that are likely to be needed immediately upon the outbreak of a pandemic. The government is on the right track with its goal of stockpiling 81 million doses of antivirals by 2008. However, stockpiling targets for other technologies such as ventilators should be reexamined in light of our analysis.

Recommendation 3: The US government should actively provide markets for critical technologies where a market does not currently exist.

For pandemic vaccines as well as new antivirals government should actively participate in the creation of markets for critical technologies both by supporting their production and through demand stimulation. Potential policies include advance purchase agreements and the creation of award systems for prototype vaccine development. These policies could give companies the confidence to invest in what would otherwise be a risky investment. In addition, expanding current seasonal flu vaccine programs could provide immediate demand incentives to expand capacity or improve manufacturing efficiency.

For advance purchases and award systems, the primary stakeholders are government and the pharmaceutical companies. With advance purchase, government faces a risk that the technologies being procured may ultimately not be needed or effective. Setting an appropriate timeline that ensures the government receives products while they could still be of use is essential. However, a timeline that is too rigid could reduce willingness on behalf of pharmaceutical companies to commit to development. Pharmaceutical companies face a risk that the government could back out from the agreement should delays arise. In order to achieve their desired end, these agreements must adequately balance the need for rapid production with reasonable consideration of possible delays.

Where advance purchase agreements are being considered for manufacturers in the US, individual states become important stakeholders as they will compete for the economic activity that a new manufacturing plant would provide. Competition for these economic assets raises numerous equity concerns that the government must consider.

In the case of awards for vaccine development, vaccine manufacturers would be encouraged to develop prototype vaccines based on strains similar to the one likely to cause a pandemic. The manufacturers would carry out clinical trials on these vaccines and receive regulatory approval. Then once a pandemic emerged the companies could submit applications to regulatory agencies considering the new vaccines simply 'variants' of their previous products rather than entirely new vaccines (requiring the same rigorous clinical studies and approval processes). For these awards to be effective, the government must set clear and specific expectations for the end products. These statements must be balanced to ensure useful products are developed while companies are not discouraged by overly burdensome requirements.

Finally, it may be possible to increase pandemic vaccine supply indirectly by expanding current seasonal flu vaccine programs. The expansion of seasonal flu vaccine programs would provide a guaranteed market for manufacturers for seasonal vaccines, and encourage near term capacity expansion or improved yields within existing plants. Additional capacity created through this process could then be used to produce greater quantities of pandemic vaccines if a pandemic emerges. A primary challenge to this approach is that it would require increased buy-in from citizens in order to be successful. If the government is not able to successfully encourage demand increases for seasonal influenza vaccines, it will have wasted valuable resources. In addition, it will be difficult for the government to predict in advance the

potential capacity expansion that might result from increasing the demand for influenza vaccines, so it is likely that this policy is best used as a complement to other policies for increasing demand.

> **Recommendation 4:** The US government should institute emergency fast track approval and liability protection for vaccine and antiviral manufacturers.

Development of a vaccine targeted at pandemic AI cannot commence until the pandemic virus strain has been isolated, and development alone is likely to take on the order of six months. Thus, it will be necessary to use fast-track approval for a new vaccine in order to provide for production and distribution that is as rapid as possible after the onset of the pandemic. In addition, the importance of vaccines in limiting the loss of lives during a pandemic warrants liability protection for manufacturers. Similar treatment is also necessary for new antiviral drugs. Current reliance on one antiviral drug leaves antiviral resistance as a large vulnerability. Alternative antiviral drugs should be considered for fast track approval by the FDA.

The pharmaceutical industry has grown tremendously since 1976 refining both drug development and manufacturing processes. This makes it less like that newly developed drugs would have harmful side effects similar to the vaccine developed during the "Swine Flu" scare. Adverse impacts are more apparent with large scale drug or vaccine use. The government should create a compensation fund and procedural mechanisms for compensating individuals in the event that new drugs have side effects.

The public's safety should be the dominant consideration in the implementation of this recommendation. Fast track approval and liability protection both provide shortcuts for drug manufacturers and potentially expose the public to greater risk. Implementation would also directly involve pharmaceutical companies, who, even with liability protection would be exposing themselves to risk by expediting development and production of new drugs in the event of a pandemic. In order to work most effectively, pharmaceutical companies will have to believe that the liability protection and fast track approval offered by the government will significantly reduce their costs and allow them to bring new products to market before the pandemic has ended. Given the government's reliance on pharmaceutical production for addressing AI, it is conceivable that pharmaceutical companies will have a significant amount of input into how the liability protection and compensation mechanisms work. Prior to the emergence of a pandemic the government should engage pharmaceutical companies and other stakeholders in studies of what types of liability protection are most appropriate. Health care providers, who face liability risk from the provision of the pharmaceuticals, should also be considered.

A balance must be struck between protecting pharmaceutical companies from unforeseeable problems with new drugs and encouraging strict adherence to quality manufacturing practices. Liability protection should not exempt companies from damages due to reckless development strategies or unsafe manufacturing environments. Further, in order to limit costs associated with vaccine or drug administration, it may make sense for the government to include health care providers in liability protection associated with these drugs. To maintain the trust of the public and health care providers, the combination fast-tracking and liability protection should

be limited to crisis-response. One possible mechanism for this would be an expansion of the National Vaccine Injury Compensation Program for use in emergencies with a sunset clause.

A second challenge likely to arise in the implementation of this recommendation is managing the public's confidence in the safety of drugs; individuals must be willing to receive the new drugs. The public will likely want guarantees that manufacturing and safety standards are being met in pharmaceutical manufacturing plants. Compensation provided by the government to victims would have to be of a sufficient size, transparency, and speed to discourage individuals from seeking damages in the courts.

> **Recommendation 5:** The government should provide incentives for manufacturers to increase domestic manufacturing capacity of critical technologies.

If pandemic influenza reaches the US, it will probably already have affected other parts of the world. Pandemic emergencies abroad will likely lead to international supply chain disruptions. Foreign manufacturing facilities may not fulfill contracts if the country in which they are based experiences a pandemic crisis. Without domestic manufacturing capacity, the US cannot ensure adequate supplies of vaccines, antiviral drugs, and other crucial AI technologies.

Increasing domestic manufacturing capacity requires that the government provide economic incentives to manufacturers of critical technologies. These incentives should encourage both domestic and foreign manufacturers to expand or build plants in the US. Incentives should also address production time. For example, advance purchase agreements might take into account manufacturing time by having the government pay more to vaccine companies if they produce vaccines faster. However, the emphasis on time must be balanced concerns for the public safety. Alternatively, the government could directly subsidize manufacturing expansion, or provide tax incentives to entice foreign firms to build plants in the US.

Another advantage of domestic manufacturing capacity is increased government scrutiny and response. For example, British vaccine manufacturer Chiron discovered contamination in several influenza vaccine batches in 2004. The US government stopped importation of Chiron's vaccines, leaving the US with only half its expected supply (Pearson, 2004). Had this problem occurred in a US facility, the FDA may have been able to respond quickly and work with the manufacturer to resolve the problem, thereby preventing the supply disruption.

Government policy already addresses this recommendation to some degree. The government recently gave $1 billion to five vaccine manufacturers to install domestic vaccine plants that use new, efficient cell-based production methods. Additionally, the government has negotiated with Roche to increase its antiviral production capacity on US soil over the next several years.

Conclusion

Ten years after the first case of H5N1 in humans was documented in Hong Kong, most nations remain woefully unprepared for a pandemic. The amount of legislation and funding focused on preparing for a pandemic has increased dramatically in the past two years. To date, however, few studies have compared the various technologies that could be procured to limit the potential impact of a major human pandemic in the US. This study aims to help fill the gap by studying the importance of various AI technologies and their likely availability if a pandemic were to emerge. In the course of the study, we developed a technology map framework to help guide our analysis. In addition, we completed a comparative market analysis and matched technologies with policy options that could help to ensure their availability.

Some mature technologies - including laboratory tests, rapid diagnostic tests, and facemasks - have pre-existing markets and some degree of scaleable manufacturing capacities. Government procurement of these technologies appears not to be necessary. Other technologies including existing antiviral drugs and ventilators would likely not scale well facing a surge in demand. Stockpiling of these technologies by government and private organizations is important to ensure that adequate supplies are available at the onset of a pandemic. Stockpiling may also stimulate the construction of new manufacturing capacity.

Finally, the unique nature of vaccines and antivirals represent special cases where extraordinary measures such as extending liability protections and guaranteeing fast-track approval may be necessary to stimulate production to adequate levels. For these technologies the government may also need to utilize advanced purchase agreements or financial awards to ensure that adequate quantities of the products will be made available once a pandemic emerges.

The evolution of viruses is a highly unpredictable process. No one can predict whether an H5N1 avian influenza pandemic will emerge on the timeframe of weeks, months or years. The pandemic may never arise at all. However, the widespread disruption on unprecedented scales that such a pandemic could cause warrants careful, urgent pre-pandemic planning with an emphasis on ensuring the availability of the technologies that will be most effective in limiting negative impacts.

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involved in making sure enough vaccines are made. It also discusses possible reasons for why the number of US vaccine manufacturers has declined during the past few decades

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This newspaper article is about the increase facemask demand and resulting shortages that occurred during SARS.

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This press release that details the performance of the Genaco rapid diagnostic test.

Silverstein A. 1981. Pure Politics and Impure Science: The Swine Flu Affair. The John Hopkins University Press. 1981
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This brief online article focuses on problems with rapid tests, particularly their false negative results. It concludes that rapid tests are not good tools for surveillance

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Detailed USDA budget request. Was used to extrapolate how much money USDA was receiving from the $7.1 billion emergency fund.

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WHO. 2006 (September) *Global pandemic influenza action plan to increase vaccine supply*. Department of Immunization, Vaccines and Biologicals and the Department of Epidemic and Pandemic Alert and Response, World Health Organization

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WHO provides regular updates on the progression of the disease around the world. This was the most recent and used in our presentation and report.

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This journal article compares the Directigen and Binax NOW rapid diagnostic tests, and shows how they vary widely in accuracy and results based on what types of people samples are taken from

Woodward TE. 1994. *The Armed Forces Epidemiological Board : History of the Commissions*. Washington: Office of the Surgeon General. Pp. 142-20

This book details the history of various aspects of the military. Chapter 2 was used to understand the role of the military in the development of influenza vaccines. It also showed different early policies to the US government in particular in 1956 and 1967.