Pandemic and Avian Influenza Vaccines:

Global Collaboration for Prevention, Mitigation, and Intervention,
A Strategic Initiative for Implementation via International Engagement

Critical Analysis—A Systematic Review and Summary with Recommendations
for Program Planning and Policy Development

by

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ABSTRACT

The objective of this paper is to examine the potential for international collaboration in order to maximize prevention and mitigation efforts with respect to pandemic influenza preparedness and response. It is imperative that international leaders and experts become exquisitely engaged in efforts to prepare for this potentially devastating event. Successful mitigation of a pandemic depends upon incorporating the use of vaccines in a preemptive fashion. International organizations, backed by the political and economic will of the U.S., must take a more active role via the establishment of an effective partnership along with a true commitment toward sustaining these efforts over the next decade.

If the generation of a novel virus strain occurs with the dramatic ability to efficiently infect the world population, sustained human-to-human transmissibility may progress to a worldwide pandemic, affecting populations on a truly global scale. The case-fatality rate for H5N1 in humans is still over 65% as of June 2007. The H5N1 virus strain has not only evolved, but has already spread to over nine countries in Southeast Asia and East Asia. The “Great Influenza” of 1918 was caused by the emergence of a pandemic strain of avian origin similar in process to the evolution of H5N1.

Most experts consider vaccines to be the primary means to both prevent and mitigate the health consequences of pandemic influenza. Medical interventions, including vaccination and antiviral treatment & prophylaxis, and non-pharmaceutical interventions may be utilized as mitigation strategies. Swift and targeted antiviral prophylaxis combined with prepandemic vaccination may achieve containment of a pandemic even if only moderate protection is provided by vaccination. An emergent strain may strike via multifocal outbreaks in various regions spread out over several countries, thus a global strategy is needed which incorporates prevention with vaccination as the cornerstone, to be utilized optimally both prior to and during pandemic onset. Vaccination represents the only medical intervention strategy which may be instituted proactively.

An ideal approach involves a sequential “two-step” strategy consisting of a “universal” or cross-protective vaccine as a primer for prevention, followed by a subsequent strain-specific vaccine for mitigation during a pandemic. Production capacity may be improved through “antigen-sparing” strategies
which utilize immunogenic adjuvants. Even moderate levels of protection may prevent or decrease transmissibility, severe disease, and death. The ultimate prepandemic priming vaccine may be a bivalent product which would provide cross-protection against more than one clade of H5N1.

‘Coping capacity’ for all nations would be bolstered by accelerated development of pandemic vaccines and expanded production capacity. Availability of a pandemic vaccine must become an absolute priority, resting squarely at the top of the international agenda. Nations need to have the opportunity to acquire sufficient pandemic vaccine supplies, and priorities must be established for global vaccine distribution. The Global Pandemic Vaccine Challenge is to define the most antigen-sparing formulation that guarantees the production of the largest number of doses of an economically viable pandemic vaccine. The most significant hurdles are organizational, logistical, and political. Vaccine efforts may be strengthened by a Multinational Pandemic Influenza Vaccine Master Program backed by U.S. leadership. A preferred policy initiative is one which supports a “two-step” process involving the best possible prepandemic vaccine as a primer, whether it be mismatched but cross-protective or a true “universal” vaccine, followed by only one dose of a “strain-specific” vaccine with a more manageable temporal window after pandemic onset.

The global population will need to find inspired leadership quickly in order to execute better pandemic influenza vaccine policy. Real leadership needs to be proactive, and mechanisms to achieve consensus among governments must be sought with the U.S. and other developed nations leading the way, in concert with international partners worldwide. “Influenza Vaccines for the World” must become a shared vision among political and public health leaders alike, along with pressure from the international community to address issues of equity and transparency of the overall process. International coordination and distribution of vaccine resources are crucial for the effective implementation of pandemic vaccine policy. The public health principle of “the greatest good for the greatest number” must always be kept in mind, as the utilization of a priming prepandemic vaccine as part of a comprehensive vaccine strategy can maximize the chances of successful prevention and mitigation of a pandemic through hopefully, a confluence of, as opposed to a conflict of, global interests.
Section I: Introduction

International collaboration ideally will take place on a truly global scale, involving stakeholders from nations throughout the world, including those both with and without access to extensive economic resources. Armed with the knowledge that infectious disease does not recognize international boundaries and tends to be relatively indiscriminant in its selection of available human hosts, it becomes imperative that international leaders and experts from diverse positions and professional backgrounds become exquisitely engaged in efforts to prepare for this potentially devastating event.

The essence of Public Health, and in this case, Global Health, is prevention. Although no single intervention strategy stands alone as a “magic bullet,” successful mitigation of the potential impact posed by an influenza pandemic depends upon approaching this problem in a preemptive fashion, incorporating the use of vaccines. The need for coverage of the global population must be recognized and acknowledged as a Public Health imperative. (Nabarro, 2007)

Although the challenges presented by the integral components of any vaccine program including: new vaccine research and development with subsequent availability, production capacity, and means of distribution along with fairness and equity are indeed extensive, vaccination still remains our number one weapon potentially available to prepare for the prospect of an influenza pandemic and to combat it successfully.

International organizations such as the World Health Organization, backed by the political and economic will of strong industrialized nations such as the United States, must take a more active role in pandemic influenza preparedness via the establishment of an effective partnership along with a true commitment toward sustaining these efforts over the next decade. Three major
criteria are deemed necessary in order for a global influenza pandemic to occur upon the emergence of an influenza strain: 1) The virus is genetically unique with almost universal susceptibility in the global population, which lacks preexisting immunity to this novel strain, 2) Usually, the strain has the capability of causing significant disease in humans and is therefore, highly pathogenic due to its increased virulence, as with H5N1, and 3) It is readily and efficiently transmitted from human to human (World Health Organization, 2006). Of these criteria, the first two have already been achieved by H5N1, while the last has not (Osterholm M. T., 2006).

Pandemic Influenza has served as an intermittent although potentially devastating infectious disease threat throughout history, with multiple pandemics having struck global populations during the 20th century. “The Great Influenza,” or so-called “Spanish Flu,” wreaked havoc in 1918 and stands as the worst pandemic to date (Barry, 2004). Mortality rates in the United States during the 1918 influenza pandemic reached over 2,000 per 100,000 persons for the infant and elderly age groups, and a total of over 50 million persons were killed nationwide by the virus (Taubenberger & Morens, 2006), more deaths in a single year than those caused by the bubonic plague (Osterholm M. T., 2006). Scientists feel that the next influenza pandemic is imminent which becomes all the more disturbing when this statement is examined in detail.

Each of the three 20th century pandemics were caused by the emergence of a novel viral strain. Both the 1918 pandemic and the present Avian Influenza epidemic in Asia have a common pure Avian influenza viral origin, H1N1 for the 1918 pandemic and H5N1 for the present scourge in Asia. In contrast, both the 1957 and 1968 pandemics were caused by viruses produced as a result of a mixture of avian and human influenza genes, resulting in H2N2 and H3N2 respectively (Monto A. S., 2005). While the present epidemic of “Bird Flu” is still
technically in the pre-pandemic stages and limited to primarily bird-to-human transmission, the case-fatality rates presently seen for H5N1 continue to hover in a range as high as 60-70% (World Health Organization, 2007).

Highly pathogenic avian H5N1 influenza viruses are endemic among bird and poultry populations in Asia. Sporadic cases as well as clusters of bird-to-human transmission have been present in Asia since 1996. The number one concern is that the H5N1 virus may eventually be capable of either adaptive mutation and/or genetic reassortment, and thus lead to the generation of a novel viral strain. Influenza viruses contain the ability to rapidly evolve in order to adapt to changing environmental conditions.

Antigenic drift usually consists of a relatively minor change within the influenza viral subtype due to point mutations, whereas antigenic shift comprises an exchange of gene segments that occurs specifically in influenza A viruses, resulting in a novel and distinct antigenic profile. Not only does the prospect of increased virulence and pathogenicity emerge, but an increase in host susceptibility to viral transmission tends to occur as novel antigens in a human infection resulting from a shift in viral strains are not readily recognized by the immune system. As a result, the unique and previously unknown antigenic makeup of the new virus may allow for a dramatic increase in its ability to efficiently infect the world population (The Chatham Institute, 2007). Antigenic shift, or genetic reassortment between viruses, is facilitated by the agricultural practices and close proximity of humans, birds, and mammals which is often found in Southeast Asia, where novel virus strains typically emerge. Thus, a major change involving an entirely new subtype may occur (See Appendix A). This event may then lead to increased potential for the emergence of pandemic influenza, and although this genetic reassortment mechanism tends to occur infrequently, the effects can be devastating from a global standpoint. If such a novel
strain evolves, sustained human-to-human transmission capability may arise with progression to a worldwide pandemic, which may then involve the ultimate crisis in Public Health, affecting populations on a truly global scale while sparing virtually no one. Furthermore, the apparent similarity between the genesis of the 1918 Spanish influenza and the emerging avian H5N1 strain should serve to heighten international concern (Russell & Webster, 2005). See Figure 1 below.

Figure 1

The Two Mechanisms whereby Pandemic Influenza Originates. In 1918, an H1N1 virus closely related to avian viruses adapted to replicate efficiently in humans. In 1957 and in 1968, reassortment events led to new viruses that resulted in pandemic influenza. The 1957 influenza virus (Asian influenza, an H2N2 virus) acquired three genetic segments from an avian species (a hemagglutinin, a neuraminidase, and a polymerase gene, PB1), and the 1968 influenza virus (Hong Kong influenza, an H3N2 virus) acquired two genetic segments from an avian species (hemagglutinin and PB1). Future pandemic strains could arise through either mechanism.
Since H5N1 was first isolated from a human patient in Hong Kong ten years ago, as of early 2007 a total of 273 confirmed human cases of H5N1 avian influenza have been reported to the World Health Organization, and 166 of these have resulted in death. The virus has also shown evidence of mutation over the last decade, becoming more persistent and virulent. According to the Institute of Medicine report on influenza in March of 2005, the “current ongoing epidemic of H5N1 avian influenza in Asia is unprecedented in its scale, in its spread, and in the economic losses it has caused (Garrett, The Next Pandemic?, 2005).”

Since the reemergence of H5N1 in humans occurred in China in 2003 after a period marked by a lack of further reported cases following the mass culling of poultry, the number of countries with human cases has risen from just two in 2003 (China and Vietnam) to ten in 2006. Indonesia stands as the most severely affected country, reporting 74 total cases with 54 deaths. Cases appeared in five new countries in 2006, including Egypt, Iraq, and Turkey. By 2007, human disease had spread to Laos and Nigeria, and increasing concern has been expressed with regard to the emerging avian influenza threat on the African continent, where complex issues, including those involving socio-economic vulnerability, pre-existing infectious diseases such as malaria, tuberculosis, and HIV/AIDS, and poor veterinary services capacity combine to increase the risk for the potential expansion of the virus across the continent. Appendix C details the geography of confirmed cases since January 2007 and Appendix D illustrates the confirmed cases of H5N1 since 2003. Close contact with infected poultry continues to be responsible for the vast majority of cases to date worldwide (World Bank, 2007).

No human or avian cases of H5N1 are currently known to exist in North America. Since late 2003, antigenically distinct and highly pathogenic H5N1 viruses caused both extensive and unprecedented multiple outbreaks among poultry throughout Asia. The Food and Agriculture
Organization (FAO) reports that over 220 million domestic birds have either died or been culled (slaughtered) in efforts to control and contain the worldwide outbreak in infected poultry. Most of these birds are owned by poor farmers in developing countries, and economic losses in the poultry industry have been estimated to be approximately $10 billion for Southeast Asia and $60 million for Africa. The World Bank continues to pledge funds in order to compensate poor farmers whose poultry have been culled due to exposure to H5N1 virus (World Bank, 2007).

The impact on the millions of poor households for whom the raising of poultry tends to be linked not only to their livelihoods, but also to their nutrition or even both, is certainly extensive. However, the well-being of lower socio-economic status households exposed to this highly pathogenic animal-derived virus is also at stake. Approximately 70% of new and/or emerging infectious diseases affecting humans are of animal origin (Nabarro, Enhancing commitment and action on influenza threats, 2006).

In addition to the emerging threat posed by domestic poultry, migration of infected wild birds adds to the mix. Outbreaks among migratory birds raise the concern that future wild bird migration could contribute further to the spread of avian influenza throughout Africa. Such events serve to further underscore the gravity and significance of continuing outbreaks of highly pathogenic avian influenza with respect to the evolving threat of spread of this disease across continents, along with the subsequent need for collaboration between nations (World Bank, 2007).

H5N1 infection has been detected in migratory wild birds and imported domestic poultry in Europe, (Greece, Romania, Croatia, Turkey, and the U. K.) other countries in Asia, (Russia, Japan, India, North Korea, Pakistan, Afghanistan, and Bangladesh) and Africa. (Nigeria and Egypt) Recently, in May 2007, the West African nation of Ghana was also found to have its first
outbreak of H5N1 in domestic poultry at a chicken farm near its capital. Outbreaks have also been noted in mammals, including cats, dogs, pigs, and other animals and multiple nations in Europe have recently (2006 & 2007) reported positive H5N1 infections in cats (Nature Reports, 2007).

With the spread of the avian influenza virus from Southeast Asia into Europe, the Middle East, and Africa, the question arises as to when and if the virus will reach the Western Hemisphere. Many experts have stated that it is inevitable that H5N1 infection in birds will be found in North and South America. Importation of live poultry, migration of wild birds via major flyways, or even through smuggling of infected birds and poultry, all serve as potential routes for H5N1 to reach the North and South American continents.

In addition, Brazil and the United States are the world’s largest poultry exporters. Although U.S. and Brazilian flocks are primarily concentrated in large commercial or industrial farms, unlike regions of Southeast Asia and Africa where poultry live outdoors and mingle freely with each other and with wild birds, there still remains the risk presented by live markets and backyard farms (Butler & Rutimann, 2006). Thus, complex and diverse mechanisms exist for avian influenza outbreaks in birds to originate in various regions of the world, with subsequent spread of infection leading first to human disease and eventually precipitating a worldwide pandemic if the virus acquires sustained human-to-human transmission capability through mutation or genetic reassortment.

Surveillance data for human cases as of May 2007 reveal a preponderance of cases occurring in Indonesia and Egypt. Thailand and Vietnam have shown dramatic decreases in cases for 2006 through 2007, and China has also demonstrated a decrease in cases so far in 2007. Culling of infected poultry in these countries has prevented not only these birds from continuing to serve as
hosts to a rapidly mutating virus, but has also removed the potential for birds which they would have subsequently infected from becoming hosts as well. The lack of occurrence of an H5N1 pandemic is most likely attributable to this intervention. Therefore, highly pathogenic avian influenza as manifest by H5N1 can appear in different parts of the world, but not necessarily persist (World Health Organization, 2007).

Decreases in the incidence of infection in poultry, wild birds, and humans in some countries in recent years lends credence to the control measures instituted via the culling of infected birds with subsequent reduction in the risk of transmission to other birds, animals, and humans. However, avian influenza may recur when high biosecurity conditions for the raising of poultry are relaxed in a given region, thus giving rise to fluctuating surveillance data involving human cases of H5N1 (World Health Organization, 2007).

While the total incidence of confirmed human cases of avian influenza showed a 20% increase from 2005 to 2006 worldwide, with a corresponding 90% increase in deaths, World Health Organization surveillance data for early 2007 does not show evidence thus far of new outbreaks of human cases, with the notable exception of Indonesia and Egypt as described. Therefore, while there was indeed greater concern for the potential onset of a pandemic in early 2006, the overall risk of such an event taking place is considered to be relatively stable at present. Even so, as long as the potential for adaptive mutation and/or reassortment remains, the emerging pandemic threat persists as well (World Health Organization, 2007).

The possible occurrence of human-to-human transmission of H5N1 is critical in determining the ultimate pandemic potential of avian influenza. The presence of family clusters has not yet been definitively established and is still inconclusive, although there has been some evidence of human cases suspicious for this event. In Thailand early in 2005, a mother without apparent risk
factors for bird-to-human transmission contracted illness caused by H5N1 while caring for her ill
cild stricken with the disease. A few other small family clusters have also been reported, and in
May of 2006, a large family cluster in Indonesia was detected involving seven cases of human-
to-human transmission, with one of the cases being consistent with possible second generation
transmission. As of January 2007, an official in Indonesia reported a total of 10 cumulative
clusters, all involving cases in blood relatives (Pierce, 2007).

Limited and unsustained transmission of H5N1 as suspected in these rare examples is
consistent with the current initial phase of pandemic alert as defined by the World Health
Organization. If there is significant evidence for human-to-human transmission as demonstrated
by a dramatic increase in the number of cases per cluster over an extended period of time, then
this progression to more advanced phases of pandemic alert could herald the onset of a true
pandemic as defined by the presence of efficient and sustained human-to-human transmission
(World Health Organization, 2007)

**Section II: Epidemiology**

A pandemic may be defined as a global infectious disease outbreak, which may result from
the emergence of a new influenza virus strain for which the human population lacks significant
immunity, and for which there is no specific vaccine readily available. By definition, the virus
causes disease which is transmitted easily from person-to-person, leads to serious illness, and has
the potential to spread across continents and eventually, around the globe in a relatively short
period of time.

Avian influenza is caused by Influenza A (refers to classification by its core protein) avian
viruses occurring naturally among birds, and these known viruses are divided into many different
subtypes, all of which may be found in the bird population. The H5N1 subtype is the current
strain causing the most concern due to its inherent pandemic potential, as defined earlier by its genetic uniqueness and high pathogenicity, although human disease as measured by global cases is currently rather limited without evidence for sustained human-to-human transmission. Less prevalent avian influenza A subtypes have also caused human infection, including: the H9N2 subtype identified in Hong Kong in 1999 and 2003, the H7N7 subtype occurring in the Netherlands, and the H7N3 subtype found in Canada, both of which were detected in 2003. Theoretically, these virus strains also possess the potential to give rise to the next pandemic (U.S. Food & Drug Administration, 2006). In contrast, H1 and H3 represent the current circulating seasonal (human) influenza subtypes.

All birds worldwide are theoretically susceptible to infection with avian influenza viruses, although many wild birds may serve as a reservoir for infection while remaining asymptomatic. Other bird species, primarily domestic poultry to date, may contract disease from viral infection as either a common but mild form, or a rare but highly lethal one. The mild form of the disease can cause outbreaks which may escape detection unless regular viral testing is in place. The highly pathogenic form in birds, which was actually first identified in 1878 in Italy, is usually characterized by severe disease of sudden onset, with rapid transmission leading to an overall mortality rate which may approach 100% within 48 hours (World Health Organization, 2006).

Influenza virus subtypes are categorized by the presence of 16 possible HA (Hemaglutinin) and nine possible NA (Neuraminidase) surface glycoprotein antigens, and all of these subtypes are known to infect wild birds or waterfowl, providing an extensive reservoir of influenza viruses that perpetually circulate in bird populations, with the vast majority of these viruses not causing disease. All outbreaks to date of the highly pathogenic form of avian influenza have been attributed to infection with the H5 and H7 subtypes, which possess a distinctive amino acid
profile in the cleavage site of the HA protein that is associated with high virulence while distinguishing these viruses from all other avian influenza strains (World Health Organization, 2006).

Although not all H5 and H7 virus strain subtypes are highly pathogenic, most are thought to have this potential. After circulating for short periods at times in poultry, H5 and H7 viruses of low pathogenicity may evolve into highly pathogenic strains via mutation. Transmission of highly pathogenic H5N1 from infected domestic poultry back to migratory birds in western China may also prove problematic. Although evidence has long suggested that wild birds may only introduce avian influenza viruses which are of low pathogenicity to poultry flocks, at least some migratory waterfowl species are now suspected of serving as reservoirs for the highly pathogenic form of the H5N1 virus, while spreading it to new geographical regions along their flight routes or “flyways” (World Health Organization, 2006).

The case-fatality rate for H5N1 in humans was almost 70% in 2006, and is still over 65% as of June of 2007. Indonesia, alone, accounts for almost half of all human cases worldwide for 2006, and the first five months of 2007, with a case-fatality rate over 80% (World Health Organization, 2007). See Tables 1 and 2 below, and Appendices B and C.
### Table 1

**Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO**

29 June 2007

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Total number of cases includes number of deaths. 
WHO reports only laboratory-confirmed cases. 
All dates refer to onset of illness.

**SOURCE:** (World Health Organization, 2007)
Table 2

Cumulate Human Cases of and Deaths from H5N1

[Graph showing cumulative cases and deaths from 2004 to 2007]

Source: (World Health Organization, 2006c)

“The incidence of human cases peaked, in each of the three years in which cases have occurred, during the period roughly corresponding to winter and spring in the northern hemisphere. If this pattern continues, an upsurge in cases could be anticipated starting in late 2006 or early 2007.”

Avian influenza--epidemiology of human H5N1 cases reported to WHO

(The regression curve for deaths is \( y = a + e^{kx} \), and is shown extended through the end of April, 2007)

Another striking feature of the current H5N1 avian influenza outbreaks is that cases occur predominantly in children and young adults. During the 2004-2005 outbreaks in Asia, the majority of human cases were less than 25 years of age, as reported in Vietnam and Thailand. A June 2006 World Health Organization report on 203 cumulative confirmed H5N1 influenza cases demonstrated that the median age of cases was 20 years, and that 90% of these infections occurred in those under 40 years of age (World Health Organization, 2006c).
A total of 229 confirmed H5N1 human cases reported to the World Health Organization from
ten countries in Asia, Africa, and Europe during the two and a half years leading up to July of
2006 revealed a skewed age distribution of these cases toward children and young adults, with
relatively few cases in older age groups. Although a range of behavioral, biological, and
demographic factors may theoretically account for this observed pattern of age bias, it is more
likely that this skewed age finding is consistent with a biological model of geographically
widespread immunity to H5N1 which may be present in those born more than 35 years prior to
the onset of the extensive outbreaks in domestic poultry in 2003-2004. This proposed
explanation would account for the similar rates of disease found across all younger age
categories, the sudden and pronounced decrease in cases in those >30-35 years of age, and an age
pattern that appears to transcend the sociocultural and demographic contexts of nations and
continents. Theoretically, an element of immunity to H5N1 may exist in older populations,
possibly associated with other geographically widespread influenza A events corresponding to
pandemics occurring prior to and during 1968 (Smallman-Raynor & Cliff, 2007).

Most recognized human cases of H5N1 have involved direct contact with poultry, with types
of exposure identified to date consisting of high-risk behaviors such as: 1) handling diseased
poultry, 2) consuming raw or undercooked poultry products, such as blood, and 3) touching
surfaces contaminated with poultry feces or secretions. Risk factor analyses in a case-control
study of all laboratory-confirmed human avian influenza cases in Vietnam in 2004 revealed
significant associations with preparation of ill or dead poultry for consumption, sick or dead
poultry in the household within the week prior to illness, and lack of indoor water sources (Dinh,
2006).
The evidence thus far suggests that avian influenza A (H5N1) infections in humans occur primarily via weak bird-to-human transmission, along with other mechanisms including possibly environment-to-human, and limited and non-sustained human-to-human transmission (World Health Organization, 2005). A prevalence rate of up to 10% for anti-H5 antibody has been observed in asymptomatic poultry workers in Hong Kong, as demonstrated in 1997-1998 (Bridges, et al., 2002) By 2003, circulating H5N1 viruses had undergone significant antigenic changes in hemagglutinin genes, with subsequent further increase in their virulence and pathogenicity. Mammal-to-mammal transmission has recently been observed in household cats, tigers, and ferrets (Ginsberg, 2006).

Limited human-to-human transmission has been suggested by family clusters, through the postulated mechanism of intimate physical contact without the use of precautions. There is no evidence to date of person-to-person transmission via the aerosolized route, as opposed to the known mode of transmission for human influenza viruses (World Health Organization, 2005). Serologic surveys have not been indicative of asymptomatic infections among contacts of active cases, nor has there been documentation of nosocomial transmission to health care workers (Hayden & Croisier, 2005).

The incubation period of H5N1 may perhaps be longer than what is known for other human influenza viruses. Most cases had occurred within two to four days after exposure, but more recent reports indicate ranges of up to eight days. Intervals in household clusters have generally been consistent with an incubation period of 2 to 5 days, although the finding of an upper limit of 8 to 17 days complicates the picture. This may stem from other unrecognized exposures to infected birds or animals or even environmental sources (World Health Organization, 2005). Overall, estimation is uncertain since in most cases exposure to poultry is ongoing. If and when
a pandemic arrives, it should be noted that human-to-human transmission can occur prior to the onset of symptoms.

The current case definition for Highly Pathogenic Avian Influenza (HPAI) may be met by the presence in hospitalized patients of:

1) Pneumonia confirmed by chest x-ray, acute respiratory distress syndrome, (ARDS) or other severe respiratory illness for which there is no established alternative diagnosis, and 2) Travel within 10 days of onset of symptoms to a country with documented H5N1 avian influenza in birds and/or humans.

In hospitalized or ambulatory patients, the case definition is met for patients with:

1) Documented fever >100.4 degrees F (38 degrees C) and
2) One or more of the following symptoms: cough, sore throat, shortness of breath, and
3) History of contact with poultry or a known or suspected human case of influenza A (H5N1) in an H5N1-affected country within 10 days of onset of symptoms.

Laboratory testing for the first group of patients is indicated, and testing should also be considered on a case-by-case basis for the second group of patients in consultation with health agencies. (23) Laboratory confirmation of human cases is performed by viral isolation, detection of H5-specific RNA by RT-PCR assay, or both (World Health Organization, 2005).

By 2003, the H5N1 virus strain had evolved further, leading to the generation of the so-called “Z strain,” which had already spread to over nine countries in Southeast Asia and East Asia. This strain is pathogenic in a greater number of animal species than are affected by other strains, can infect an expanded host range in avian species, and has increased environmental stability. Analysis of the genome of this “Z strain” from bird and human isolates indicates that this genotype has become dominant, and also reveals its evolution into two distinct “clades,” each
with its own geographic and temporal distribution. A clade refers to the presence of traits, i.e. genetic sequences, which form a distinct group on analysis of the evolutionary connections between such traits (Reid, Taubenberger, & Fanning, 2004). Clade 1 encompasses isolates from Southeast Asian countries, including Thailand and Vietnam, and originated in southern China in 2003. Clade 2 is distributed primarily in Indonesia and China, and is the most recent to emerge. This second clade has since been further subdivided into three “subclades,” corresponding to new geographic areas as H5N1 has continued its emergence and spread since 2004-2005:

- Subclade 1 (western China to Indonesia)
- Subclade 2 (western China to Russia, Turkey, and Egypt)
- Subclade 3 (eastern China to Southeast Asia—thus, “overlapping” with the prior emergence and spread of Clade 1 as demonstrated in Figure 2 below.)

(Webster & Govorkova, World Health Organization Global Influenza Program Surveillance Network, 2006)
The shaded area across southern China is the hypothetical epicenter for the emergence of H5N1 clades and subclades. The H5N1 viruses are being perpetuated in the domestic birds of the region, despite the use of universal vaccination of all domestic poultry. The red dot in the time line denotes the occurrence of the first human case, followed by the number of confirmed human cases in that country. The green and blue solid bars represent documented H5N1 infection in domestic poultry and wild birds, and dashed bars indicate that H5N1 in the avian
population is suspected. These limited surveillance data are adapted from the World Health Organization and the U.N. Food and Agriculture Organization (www.fao.org). HA denotes hemagglutinin (Webster & Govorkova, 2006).

The host immune response to H5N1 may also have ramifications for the pathogenesis and expression of clinical disease and its severity. H5N1 may cause the induction of excessive host inflammatory responses which then exacerbate lung injury, leading to more severe clinical infection and disease. This paradoxical “cytokine storm” response from uncontrolled exuberant immune system modulators would be expected to be stronger and thus more lethal in otherwise healthy children and young adults (Osterholm M. T., 2006), perhaps explaining both the observed age distribution of H5N1 infections as well as deaths from H5N1 disease, which have also occurred primarily in children and young adults. The presence of high case-fatality rates is also consistent with deaths occurring predominantly in this age range. Studies of H5N1 cases in Southeast Asia in 2003-2004 suggest that “cytokine storm” phenomena does indeed occur in these patients, leading to ARDS in severe cases. In addition, studies performed in mice utilizing genetically engineered influenza strains which have a genome similar to that of the 1918 H1N1 pandemic strain, have also identified the “cytokine storm” mechanism as a factor in the pathogenesis of pandemic influenza (World Health Organization, 2005).

In contrast to seasonal influenza, where the highest morbidity and mortality tends to occur in infants, toddlers, and the elderly, the present H5N1 avian influenza strain strikes primarily in older children and young adults. This was especially pronounced during the 1918 pandemic, with nearly half of influenza-related deaths occurring in those aged 20 to 40 (Ginsberg, 2006). This “Great Influenza” of 1918 was caused by the emergence of a pandemic influenza strain of avian origin, (H1N1) similar in process to the emergence and evolution of present-day H5N1 (Belshe, 2005).
The ability of the H5N1 virus strain to recognize specific human receptors in the upper respiratory tract affects the efficiency of transmission of avian influenza viruses. Bird-to-human transmission is still relatively inefficient, most likely due to the lack of appropriate avian virus cell receptors in the human respiratory tract. If the H5N1 virus were able to adapt through a mutation which allowed it to easily recognize human cell receptors and thus attach itself to host cells in the respiratory tract, a subsequent cascade of infection leading to clinical disease would then be initiated in the human host (Yamada, et al., 2006). The potential increase in viral replication in the human respiratory tract could then result in an increase in transmissibility, enhancing the likelihood of ongoing human-to-human transmission. If the virus adapts and reaches this threshold, then it will have become a true human pathogen (Shinya, 2006).

Differences in host susceptibility may also play a role in the limited human-to-human transmission seen thus far in familial clusters. If a certain human subpopulation were to have a higher proportion of avian influenza virus-like receptors in their upper respiratory tracts, human hosts in this subpopulation would then be expected to have greater host susceptibility to H5N1, based upon the receptor recognition mechanism described above. Thus, a genetic predisposition for these avian virus receptors could be seen among family members, allowing a person to be infected more easily (more “efficiently”) while causing this person to be more infectious to other family members with similar host susceptibility. The epidemiologic findings pertaining to familial clusters, including those found in Indonesia, are supportive. Almost all clusters of limited human-to-human transmission have occurred solely among blood relatives. Interestingly, spouses have rarely been infected, and when instances of infection are found in spouses they tend to be less ill (Pierce, 2007).
No specific occupational high-risk group has been identified to date, making it difficult to target any such group for protective measures. Clinical cases have not been detected in health care workers, even with a history of episodes of close unprotected contact with severely ill patients. The most vulnerable or high-risk population, consistent with sociocultural, behavioral, and environmental factors, is the subpopulation of rural subsistence farmers along with family members, who occasionally become infected as part of a familial cluster as described (World Health Organization Global Influenza Programme, 2005).

The threat posed by avian influenza for this subpopulation may be compounded by the tendency for human cases to occur in the absence of readily apparent or reported new outbreaks in poultry. With the virus now firmly established in the poultry populations throughout many countries, including much of Asia along with more recent areas of spread to Africa and Eastern Europe, there may be less opportunities to detect warning signals from visibly ill or dead poultry in rural areas of the Asian continent. Either way, education of rural populations is vital in regard to the need to take special precautions when handling, slaughtering, and preparing poultry for consumption, especially since those in large rural areas depend on poultry for their livelihood and food (World Health Organization Global Influenza Programme, 2005).

Children play a unique role in the transmission of infectious disease, with seasonal human Influenza A as an example. A vicious cycle of heightened transmissibility may be created as children may serve as the link between childhood illness and adult illness. Infection may be spread from day care, preschool, and school-aged children to other children, family members, and other close contacts. A transmission cycle may then ensue involving greater dissemination of infection to the community-at-large, including high-risk populations. Although models exploring this phenomenon were based primarily upon seasonal ("interpandemic") influenza,
their application to pandemic influenza is certainly relevant, and could prove to be of even
greater significance if and/or when a pandemic arrives (Edwards, 2007).

The public health dilemma presented by the prioritization of preparedness for an inevitably
recurring emerging infectious disease event such as pandemic influenza creates a complex and
challenging situation. Globally, the presence of many other immediate and urgent public health
threats, from infectious diseases or other sources, compete for precious economic resources,
especially in more poorly developed countries where the potential for the onset of a pandemic is
greatest (World Health Organization Global Influenza Programme, 2005). This problem is
compounded by the prospect of preparedness for an event of unpredictable timing which tends to
be viewed by many present-day governments and their leaders in the context of a low-
probability, high-risk occurrence, albeit one with potentially devastating and catastrophic
consequences in terms of the ultimate outcome which may affect the entire global population.

Pandemic influenza tends to strike as a series of successive outbreaks, occurring in waves.
Each wave may last for 2-3 months then subside, with recurrence several months later (Ginsberg,
2006). In 1918, the pandemic was characterized by three waves within approximately one year,
and the second wave produced the most morbidity and mortality (Barry, 2004). Appendix D
illustrates the worldwide spread waves of the 1957 Asian Flu pandemic.

Section III: Surveillance

The overall objective during the early phase of the pandemic alert period, the present situation
as defined by the six phases outlined by the World Health Organization in their Global Influenza
Preparedness Plan (World Health Organization, 2007), should be to ensure rapid characterization
of the new virus subtype by genotype, and to aim for early detection, notification, and response
to additional cases (World Health Organization Global Influenza Programme, 2005).
The determination of whether a pandemic influenza virus can successfully emerge by different evolutionary mechanisms will affect the overall scope and focus of surveillance efforts and subsequent preventive measures. Improved sampling and surveillance of wild animal populations in order to detect additional reservoirs of influenza could be a wise approach given the possible consequences of missing an emergent pandemic strain, especially one as virulent as the 1918 pandemic influenza virus (Reid, Taubenberger, & Fanning, 2004).

Early detection and rapid containment are strictly time-dependent for the successful containment of an emerging pandemic virus strain. Several assumptions are limiting steps upon which the feasibility of this approach depends: 1) Emerging virus causes moderate-to-severe acute respiratory disease, allowing the event to be visible and thus increasing the likelihood of detection, 2) If case clusters are identified, they should serve as an immediate trigger for appropriate clinical, epidemiologic, and laboratory investigations, and 3) Rapid notification and assessment of the event occur, moving from local, state, and national levels to the international and global domain. The World Health Organization must be informed immediately in order for the international community to be alerted and for additional support mechanisms to be put into action, 4) External assistance for the purposes of investigation and response is requested in a timely fashion. Epidemiologic signals are likely to serve as the most reliable indicators of viral transition to efficient and sustained human-to-human transmission, with the most important signal expected to be the detection of case clusters which are closely related with respect to temporal window and geographic region (World Health Organization, 2006c).

Case cluster detection serves as an epidemiologic signal within the context of its expression as an increase in unexplained respiratory illness in a population in a defined area over a relatively short time period. The pattern of such illness should also differ qualitatively from the
background or baseline usually observed. It is frequently difficult, however, to determine during cluster investigation whether those infected acquired the virus from each other, from some shared exposure involving animals or the environment, or perhaps from some combination of both (World Health Organization, 2006c).

In addition, human cases of H5N1 infection have been shown to be rare events based upon the experience to date (although a bias could exist in that mildly symptomatic patients may not be ascertained). In regions where viral infection is widespread in poultry which are maintained in close contact with households, this still holds true, most likely due to poor or inefficient bird-to-human transmission of H5N1. The epidemiology of H5N1 disease at present, including the rare occurrence of human infection, should increase the likelihood that if the evolution towards enhanced transmissibility via the continued emergence of better adapted novel strains does occur, this would then result in a sufficiently unusual outbreak of human cases (World Health Organization, 2006c) which would correspond to progressive phases of pandemic alert. (Phases 4 & 5, as outlined in Appendix E). (World Health Organization Global Influenza Programme, 2005). Cases of human infection would then hopefully be detected more quickly and easily by clinicians.

Comparative studies of viral isolates can also be helpful as an indicator of enhanced transmission, signaling a substantial increase in the risk of pandemic onset. At present, routine investigation of H5N1 outbreaks conducted via the WHO network of H5 reference laboratories, includes such studies of H5N1 strains isolated from birds, mammals, and humans. Virologic changes considered significant, triggering a rapid global response, would be expected to fall into one of two categories: 1) detection of a virus with novel genes and antigens which have evolved via reassortment, containing both avian and human genes, or 2) isolation of an avian virus from a
human case with evidence for multiple point mutations not seen in prior avian isolates (World Health Organization, 2006c).

Presently, the WHO Global Influenza Surveillance Network serves as the global alert mechanism for the emergence of influenza viruses with pandemic potential, and includes the National Influenza Centres which sample patients with influenza-like illness and then submit representative isolates to the WHO Collaborating Centres for antigenic and genetic analyses. National Influenza Centers recognized by WHO include 118 institutions from 89 countries, including the CDC in the U.S. There are four centralized WHO Collaborating Centers that participate in the Network, located in Australia, Japan, the United Kingdom, and the U.S. (World Health Organization, 2007c) Approximately 80 individual WHO Collaborating Laboratories, as well as 50 National Respiratory (and Enteric Virus) Surveillance System labs, are distributed throughout the U.S. Most of the U. S. WHO collaborating labs report the viral subtype isolated, (H5N1, H7, H9, or others) along with demographic information including ages of human cases from whom isolates were sampled. Some of these influenza viruses are then sent to CDC for further testing (Centers for Disease Control & Prevention, 2006).

The Global Outbreak Alert & Response Network consists of a technical collaboration of existing scientific institutions and networks which pool human and technical resources for rapid identification, confirmation, and outbreak response to agents of international significance, including potential pandemic influenza virus strains (World Health Organization, 2007c).

Scientists have stated that they would welcome an international proposal for state-of-the-art labs to monitor emerging diseases in developing nations, since they feel that the present worldwide avian influenza crisis has exposed glaring deficiencies in global veterinary and human disease surveillance systems. In Indonesia, number one in H5N1 incident human cases in 2007,
there is felt to be a total lack of any systematic surveillance program. Scientists from the US Department of Defense Global Emerging Infections Surveillance and Response System in Maryland have proposed a global network of laboratories modeled on existing US military facilities in order to help avert an influenza pandemic. This network of facilities would improve surveillance of and preparedness for avian influenza and other emerging infections in poor regions, including sub-Saharan Africa, rural regions in Asia, and parts of South America. Creation of such a network may also be strengthened by cooperation between China and the U.S. in regard to global surveillance, as has been proposed (Chretien, Gaydos, Malone, & Blazes, 2006).

Section IV(a): Overview of Strategies for Prevention and Mitigation

The need for a consistent prevention strategy for H5N1 avian influenza, while highlighting the growing complacency among poultry farmers and government authorities worldwide, is further demonstrated by the recent occurrence of the first human case-fatality in Vietnam since October of 2005. No new outbreaks in poultry had been reported for about one year in Vietnam, a country which had once been the number one nation affected by avian influenza when it endured three waves of H5N1 poultry and human cases in 2004 and 2005. New infections toward the end of 2006 led to intensified efforts to cull poultry, and only sporadic outbreaks had been reported in early 2007, until a recent spike in four human cases was seen in May. Nationwide poultry vaccination programs in Vietnam, once serving as a model for other nations, have become less consistent in their implementation as the urgency once felt by those most at risk seems to have dissipated over time. In June 2007 alone, Indonesia reported another death, bringing its
cumulative toll to 80, while five people in Malaysia were quarantined due to suspicion of H5N1 infection (Zeller, 2007).

The control of avian influenza caused by H5N1, which today is still the strain with the most pandemic potential, may be approached by eradicating the virus at the source in domestic poultry via the quarantine and culling of infected birds. These measures have been further reinforced by improvement in biosecurity at poultry facilities when feasible, most notably in more developed Asian nations such as Japan and South Korea. Unfortunately, this overall strategy may turn out to provide only a temporary respite from H5N1 outbreaks; the occurrence of new cases in humans may herald the resurgence of the virus strain in the poultry population, as was the case in Thailand in 2006 (Webster & Govorkova, 2006).

Vaccination of poultry also has limitations due to the poor overall quality of these vaccines, which have been noted to promote antigenic drift or mutation as an adaptive mechanism, allowing subsequent emergent strains to evolve as defined by new clades and subclades. Vaccination of uninfected birds in conjunction with quarantine and culling, a strategy employed in China, Vietnam, and Indonesia, has not been shown to be successful. Control of H5N1 outbreaks in poultry has been achieved through vaccination, however, in Hong Kong since 2004.

More recently in Vietnam, the adoption of a strategy involving the vaccination of all poultry with an inactivated, “oil-emulsion” H5N1 vaccine has been associated with both a dramatic reduction of infections in poultry and in human cases. The reemergence of H5N1 in waterfowl in Vietnam in the fall of 2006 is consistent with the hypothesis that any vaccination strategy is likely to be limited by a lack of vaccine efficacy in waterfowl, which may serve as an asymptomatic reservoir for the ongoing propagation of infection with highly pathogenic avian influenza virus, or HPAI, in Asia (Webster & Govorkova, 2006). See Appendix F.
Any and all measures which may theoretically serve to prevent a pandemic, or at least mitigate its impact, should ideally be in place prior to its onset. The chaos which would undoubtedly ensue during WHO Phase 6, (defined by the efficient and sustained human-to-human transmission achieved by an influenza virus strain as the cause of a pandemic) would make ongoing mitigation measures exceedingly difficult if prior pandemic preparedness strategies had not been undertaken on a global level (World Health Organization Global Influenza Programme, 2005).

Most experts would consider vaccines to be the primary means to both prevent pandemic influenza in the present pandemic alert period and mitigate its health consequences during the onset of a pandemic. Pandemic preparedness plans, such as those outlined in a recent review of over 25 European nations, reveal somewhat vague approaches in addition to deficiencies in certain areas, including the stockpiling of antiviral drugs (Shortridge, 2006). Treatment with these agents is further complicated by the growing high-level resistance to the current preferred agent, Oseltamivir, (Tamiflu) a neuraminidase inhibitor which is most effective when rapid laboratory confirmation of the diagnosis is made and treatment is started early without delays. Increasingly resistant strains isolated since 2004 have been shown to require higher antiviral doses and more prolonged administration in order to achieve similar drug effects and survival (World Health Organization, 2005).

Antiviral resistance acquired through mutation by the ever-evolving H5N1 virus strain is especially seen in Southeast Asia, the region serving as the source for most outbreaks, as well as the area which already has and will most likely continue to have the greatest need for intervention if a pandemic arises. In addition to the logistical challenges posed by the need for rapid treatment, the less developed nations comprising much of Southeast Asia also face limited
availability of antiviral medications. Cases involving three clusters of patients in Indonesia in 2006 were treated with antiviral medication as late as five to seven days after initial infection, primarily due to delay in diagnosis, which is another issue (Webster & Govorkova, 2006).

An even greater quantity of drugs would be required for post-exposure prophylaxis, making the treatment of ill cases the main priority (Inglesby, Nuzzo, O'Toole, & Henderson, 2006). Thus, control strategies which involve antiviral agents as their primary intervention mechanism may fail to take into account ongoing transmission. This may be further complicated by the relatively high rate of antiviral resistance already seen in children with seasonal human influenza, as a similar pattern would be expected for H5N1 cases (World Health Organization, 2005), and children are known to have enhanced transmissibility. This may serve as an additional complicating factor if antiviral prophylaxis is not or cannot be instituted on a grand scale. One advantage of antiviral therapy and prophylaxis over vaccination is that an immunosuppressed subpopulation may fail to mount a sufficient and prolonged immune response to a vaccine provided during either the interpandemic or pandemic period. Regardless, these individuals would be expected to receive maximum intervention or interventions in a priority fashion.

Non-pharmaceutical interventions, (NPI) such as voluntary home quarantine, that are aimed at the control and mitigation of the spread of disease have been proposed as an effective and more practical response mechanism in the event of a pandemic. The potential implementation of any such intervention, however, must be evaluated in the context of feasibility. Thus, logistical assessment would need to include the resources available, the process involved in the assurance of voluntary, or even mandatory, compliance on the part of the public, and finally, the duration of time during which measures would need to be maintained. It is estimated that such measures
would need to be maintained for the duration of the epidemic at the community level, comprising a presumed period of at least eight weeks, and possibly as long as eight months or more nationwide (Inglesby, Nuzzo, O'Toole, & Henderson, 2006).

The 2003 SARS outbreaks in Toronto serve as an illustration as to the difficulty involved in attempting to utilize voluntary home quarantine as an intervention to mitigate transmission of a highly infectious disease, albeit one which is considered be even less transmissible than potential pandemic influenza virus strains. Public health resources needed to provide education and information as to the rationale behind this intervention. Additionally, the practical considerations involved in compliance were further taxed by the need to arrange for basic support services. The efficacy and feasibility of large-scale, home quarantine policies may be questioned further, especially if World Health Organization officials were to attempt to implement these measures worldwide during the onset of a pandemic (Inglesby, Nuzzo, O'Toole, & Henderson, 2006).

Although the necessity for global vaccination remains paramount to preventing a pandemic, probably the most important intervention which could be taken to decrease transmission of disease and curtail its spread within communities during a pandemic involves the isolation of symptomatic influenza patients, either at home or in the hospital. Patients with severe clinical symptoms, and therefore, presumed to be highly infectious, will most likely be hospitalized in medical and critical care units, resulting in sustained huge demands on surge capacity. Hospitals may also serve to amplify the spread of infectious disease due to close proximity of highly infectious patients to healthcare workers as well as to other ill patients, including those who are more vulnerable to infection. Ideally, these patients should wear surgical masks in order to control transmission (Inglesby, Nuzzo, O'Toole, & Henderson, 2006).
Current CDC guidelines for the control of influenza transmission during a pandemic distinguish between long-range and short-range aerosol transmission, corresponding to airborne and droplet precautions, respectively (Inglesby, Nuzzo, O'Toole, & Henderson, 2006). While the institution of droplet precautions involves the use of surgical masks to protect healthcare workers, the recommendation for airborne precautions in health care settings states that “it would be prudent” for N95 respirator masks, which are already in short supply, to be utilized during the routine care of suspect or confirmed pandemic influenza patients (Pandemic Flu, 2006). The latter recommendation underscores the uncertainties of the transmission potential of a given virus strain during the onset of a pandemic (Inglesby, Nuzzo, O'Toole, & Henderson, 2006).

Other non-pharmaceutical measures which have been proposed may be described as “social distancing,” more specifically, the prohibition of large-scale social gatherings and public events along with the closing of schools and other points of assembly. Problems arising from widespread implementation of these measures, especially if sustained throughout a pandemic, may produce diminishing returns over time while having adverse social and economic effects. These general measures also have dubious efficacy and may prove more beneficial if used only in specific situations and communities, and for a specified amount of time at the beginning of a pandemic. In addition, travel restrictions are felt to be impractical and without apparent benefit (Inglesby, Nuzzo, O'Toole, & Henderson, 2006). Recent U.S. guidelines have been developed for community mitigation strategies focusing upon early, targeted, and layered use of non-pharmaceutical interventions. Such efforts would most likely result in delay and decompression of the initial peak in projected cases occurring in the absence of intervention, but non-pharmaceutical interventions may just prolong the first wave of transmission in the epidemic curve by more than 2-3 months (Pandemic Flu, 2007). See Figure 3 below.
An overriding principle is that communities tend to respond best and with the least amount of anxiety when the normal social functioning of a given community is least disrupted (Inglesby, Nuzzo, O'Toole, & Henderson, 2006). Leaders in government and public health worldwide need to weigh the likely benefits of these non-pharmaceutical interventions against the potential consequences, including the possibility of subsequent loss of essential services and loss of confidence in the ability of governments to manage an uncertain and rapidly evolving crisis event effectively on an ongoing basis (Shortridge, 2006).
Epidemic modeling has been utilized over the past couple of years in order to estimate the global consequences of a potential influenza pandemic. Baseline transmission dynamics have been studied via computer models, and specific interventions have been examined in the context of epidemic curves outlining the wave (or waves) of transmission. The objective of these modeling tools concerns the evaluation of outcomes arising from policies designed to contain or mitigate the spread of a potential pandemic influenza virus strain, such as H5N1. Likely patterns of spread may be ascertained, and the potential benefits of varied control measures, either alone or in concert, may theoretically be assessed (Ferguson, 2007).

In order for pandemic spread to be contained effectively as measured by quantitative parameters for transmissibility and attack rates, certain criteria need to be met in order to meet the desired objectives:

- Containment of the initial outbreak (“at the source”)
- Slowing of international spread
- Local Mitigation

According to one of the preeminent investigators in the epidemic modeling arena, the cornerstone of containment of a pandemic rests upon the implementation of mitigation measures at the local level, raising the key question: Is local control possible? The proportion of transmission occurring in each particular setting represented by households, schools, workplaces, hospitals, and the local community is inherently variable and uncertain among communities within a given nation as well as internationally (Ferguson, 2006). This may serve as a reminder that a unique set of assumptions in regard to transmissibility must be factored in to any computer model which attempts to estimate and predict global transmission as it plays out over time, place, and populations during an influenza pandemic.
Uncertainties about the biological and epidemiological properties of the next pandemic virus limit the ability of any model to predict precisely the speed of spread and the overall impact on population health, especially worldwide. The relative effectiveness of different mitigation options may also differ from one country to the next, making universal and global recommendations for disease mitigation problematic (Ferguson, 2006). Analysis of historical data for influenza transmission may theoretically help to refine estimates of the effectiveness of control measures, but validation of pandemic influenza containment models is hindered by the last pandemic having occurred 40 years ago, and historically, the pandemic influenza virus which H5N1 most resembles on a antigenic basis emerged way back in 1918. Thus, it becomes more difficult to match the rate of spread and proportion of the population infected from past pandemics in order to extrapolate this information to present-day models, although past data has suggested a relatively high rate of transmission for pandemic influenza (Ferguson & Cummings, 2006).

Conclusions drawn from recent modeling studies ("large-scale epidemic simulation" for the U.K. and U.S.) focus upon the likely effectiveness of the two major mitigation strategy categories: 1) Medical interventions, such as antiviral treatment/prophylaxis and vaccination, and 2) Non-medical or non-pharmaceutical interventions, with respect to school closures, household quarantine, and isolation of cases as examples of “social distancing” measures (Ferguson & Cummings, 2006). Treatment with antiviral medications needs to be started within the first 12-24 hours of symptom onset in order to be effective, reducing transmissibility. If this can be achieved, attack rates during a pandemic may be cut by one eighth. Prophylaxis of household contacts can reduce illness by one third, assuming stockpile capacity for antiviral medications is 50% or greater. School closures were found by the model to be associated with a
decrease of 40% in the peak height of the epidemic curve, (as described above) but the total number of infected cases is essentially unchanged due to prolonged duration of the transmission wave (Ferguson, 2006).

Vaccination as a mitigation strategy, especially if targeted at children who may function as “superspreaders,” should lead to a reduction in overall illness by one third. This is supported by the model even for a scenario with only 20% stockpile availability of a vaccine which has only 30% efficacy (Ferguson, 2006). This scenario attempts to take into account the difficulties involved in trying to stockpile and select sufficient quantities of vaccine in advance, while achieving an accurate match of the selected vaccine strain to the pandemic strain (Ferguson & Cummings, 2006).

Without the availability of vaccine, “Targeted Layered Containment,” or “TLC,” may combine medical and non-medical interventions by the implementation of antiviral treatment and prophylaxis, home isolation of all outpatient cases, household quarantine, school closure, and “social distancing” measures in the workplace and community. Without all of the above non-pharmaceutical interventions (NPI), this mitigation policy will not likely be successful in containing transmission, as antiviral stockpiles and public health resources would prove insufficient to cope with attack rates as high as 10-20% or higher (Ferguson, 2006).

TLC can theoretically cause a dramatic reduction in overall attack rates, assuming:

1) It is triggered early enough—before the local attack rate in each community reaches 1%
2) School closure has a significant effect in line with modeling predictions
3) Home isolation of childhood cases for the duration of the pandemic is possible with >50% compliance in households
4) “Social Distancing” measures are capable of achieving a substantial decrease in contact rates in both the workplace and community (Ferguson, 2006).

This overall strategy is quite ambitious, and its requirements for success hinge upon a combination of measures which may or may not be feasible. The economic viability and logistics involved in the support of such an all-encompassing strategy would pose a daunting challenge for most governments, especially for those of less developed nations. Modeling reveals that a more realistic mitigation strategy would combine pharmaceuticals/biologics or medical interventions with non-medical social distancing, relying primarily on antiviral treatment & prophylaxis along with stockpiling of H5N1 vaccine. NPI measures would be limited mostly to home isolation of cases and school closure. If supported by a Tamiflu stockpile well in excess of 25% capacity, and a “large” H5N1 vaccine stockpile, modeling scenarios show an approximately 67% to >90% fall in attack rates. Factors which could potentially have a negative impact upon containment using this scenario include: vaccine strain mismatching, antiviral drug resistance, and drug delivery (Ferguson, 2006).

Utilizing a similar computer model to simulate an avian influenza outbreak among a rural population of 500,000 people in Southeast Asia, another scientific team concluded that by combining the use of swift and targeted antiviral prophylaxis at the earliest stages of a potential pandemic with vaccination prior to pandemic onset, containment of an outbreak with successful mitigation of a pandemic is achievable for a highly transmissible strain such as H5N1, even if only moderate protection is provided by the vaccine. Adding voluntary home quarantine to the mix would provide equivalent results for a pandemic strain of even higher transmissibility (Longini, Nizam, Ungchusak, Hanshaoworakul, Cummings, & Halloran, 2005). A subsequent model based upon the U. S. population suggests that rapid production and distribution of
vaccines, even if poorly matched to circulating pandemic influenza strains, could significantly slow spread of highly transmissible disease while containing cases to <10% of the population, especially with targeted vaccination of children (Germann, Kadau, Longini Jr, & Macken, 2006).

According to the World Health Organization, the success of any combination of interventions via the use of stockpiles in risk-prone countries depends on effective disease surveillance and early reporting, both of which must be strengthened in order to be able to take advantage of the brief temporal window for action as outlined in modeling studies. Unlike the SARS outbreak in 2003, which originated in China with a subsequent large outbreak in Toronto, an emergent pandemic influenza strain may strike simultaneously as multifocal outbreaks in various regions spread out over several countries, which may also tend to be vast, relatively isolated, and poorly developed.

During a pandemic, for any model to move from the realm of theory to that of reality, it would need to be applied within a few days to weeks to be effective in mitigation. Intervention will involve “...an enormous undertaking that will require cooperation among governments on a large scale” (Ferguson, 2005). Prevention and mitigation are certainly key, but containment of an emerging influenza pandemic strain of avian origin is by itself far from ideal as a solitary approach. In order for a global strategy to be successful, one must not only consider the benefits of prevention, but an ideal strategy should also highlight vaccination as its cornerstone, to be utilized optimally both prior to and during the onset of a pandemic.

**Section IV(b): Pandemic Vaccine and Current Strategies for Implementation**

Scientists have concluded that there is indeed, no “magic bullet” to completely control and contain an influenza pandemic in the human population worldwide, but that a combination of
measures could perhaps diminish the total number of cases. Computer modeling has suggested that the greatest impact could be achieved by stockpiling of prepandemic vaccine, early immunization of school-aged children, and antiviral prophylaxis of households. Vaccine impact is predicated upon its need to be available within the first two months of a pandemic, thus emphasizing the need for prepandemic vaccine (Ferguson & Cummings, 2006).

An eventual vaccine matched to the emerging pandemic strain could theoretically take four to six months to be made available for distribution, far too late for mitigation of the initial huge wave of infections (Ferguson & Cummings, 2006), a scenario which could actually become a self-fulfilling prophecy if preventive vaccine is not properly utilized in the prepandemic or “interpandemic” period. Subsequent multiple waves of transmission, which could theoretically occur with or without prepandemic and/or early intrapandemic vaccine intervention, would still have the dubious advantage of providing “catch-up” time during the pandemic for the availability and implementation of a strain-specific vaccine.

The use of antiviral medications as a pandemic influenza control strategy is limited by its role which involves exclusively mitigation and containment of an emerging pandemic strain. The need for prophylaxis of household contacts, in addition to treatment of human cases, may also require nations to stockpile enough drugs to cover 50% or more of their population, while many countries are planning on a stockpile sufficient for treatment of only about 25% (Ferguson & Cummings, 2006). Vaccination represents the only medical intervention strategy which may be instituted proactively as a preventive measure.

While vaccination may offer the best opportunity for the prevention of disease and death caused by a pandemic influenza virus strain, limitations on the implementation of a vaccine strategy center upon the issues of timeliness, availability, and cost. Accurate identification of a
pandemic strain could be followed by a six month or even greater period before the successful production of a matched vaccine occurs. In spite of an increase in global influenza vaccine production capacity over the past decade, current capacity for manufacturing a monovalent pandemic influenza strain vaccine formulated with sufficient levels of a targeted hemagglutinin antigen would still not be sufficient to meet global needs (Schwartz & Gellin, 2005).

This issue is further complicated by the possibility that a “two-dose schedule” would be required to achieve immunogenicity to a novel avian influenza virus strain, and that close to 100% of the world’s population would be susceptible hosts. As an example, U.S.-based production over a one-year period would only result in full vaccination of about 50% of the U.S. population. Therefore, there is an urgent need for both expansion of manufacturing capacity worldwide and for determination of the optimal amount of vaccine antigen to be produced (Schwartz & Gellin, 2005).

Stockpiling of a prepandemic vaccine in anticipation of its use prior to pandemic onset can allow countries to be preemptive in their plans, as opposed to responding in a reactive manner after the pandemic threat has already materialized. Instead of just “chasing” the transmission wave of infection and disease as described by modeling experts, a plan which includes vaccination both during the pandemic alert and pandemic periods, as outlined by the World Health Organization’s six phases, would be optimal.

It has been suggested by the WHO Global Influenza Preparedness Plan that “Phase 6,” essentially the pandemic period, could be further subdivided according to the burden of human disease caused by pandemic influenza in a given country. Related issues would involve the degree of trade or travel links a particular nation may have with another, and whether or not its transmission wave has subsided as opposed to its being in the midst of a subsequent wave.
(World Health Organization Global Influenza Programme, 2005). Such considerations only serve to highlight the importance of prepandemic planning involving vaccination as the prime strategy for medical intervention, especially given that the World Health Organization has put the worldwide population on notice since early 2004 that we continue to be in Phase 3 of the Pandemic Alert period, *(beyond the Interpandemic period)* in reference to the family clusters with suspected limited human-to-human transmission which continue to be identified in Southeast Asia.

Regardless of the means of intervention either at the onset of a pandemic or during the ongoing pandemic itself, assuming the choice of vaccination in combination with other measures as described, a sequential strategy or “two-step” process would still serve as an ideal proactive and preemptive approach to the emerging pandemic threat posed by the avian influenza virus and its evolving strains, clades, and subclades:

1) “Universal” vaccine as a *primer* for prevention of pandemic influenza

2) Strain-specific vaccine for mitigation of pandemic influenza

Major barriers to this strategy do exist, including: uncertainty over the timing of pandemic onset, accurate prediction of the pandemic influenza strain subtype, and matching of the stockpiled vaccine to the actual pandemic strain. Prepandemic vaccine would need to be effective in priming all recipients in the population worldwide, thus allowing a subsequent strain-specific vaccine to be protective when administered early on in the pandemic (Schwartz & Gellin, 2005). The additional dose of vaccine to be given as part of a “two-dose schedule” during the ongoing pandemic would also probably not be needed, increasing the likelihood that sufficient quantities of vaccine would be available.
Influenza strains tend to undergo antigenic drift, complicating the choice of hemagglutinin antigen used in any prepandemic vaccine which is to be stockpiled as the antigen would most likely differ from that of the actual pandemic virus strain. High rates of protection have been shown in mice and seroconversion has been achieved in humans, however, when candidate H5 vaccines containing differing strains are utilized (Schwartz & Gellin, 2005). These studies are somewhat limited by the inconsistent and insufficient degree of immunogenity shown, but they do provide a framework for further development and testing of pandemic vaccine candidates, and for ongoing assessment of the overall effectiveness of pandemic vaccination strategies, including novel priming strategies for prevention (World Health Organization Global Influenza Programme, 2004).

Vaccine availability during a pandemic may be enhanced by the development of vaccine reference strains tied to novel influenza viruses which could eventually be implicated as the cause of pandemic influenza. This proactive measure could shorten the actual time required to produce the first doses of a strain-specific vaccine when a pandemic finally strikes. Production capacity may essentially be improved and expedited through “antigen-sparing” strategies which effectively result in greater quantities of vaccine being available due to the use of immunogenic adjuvants. These adjuvants enable a smaller amount of antigen to be needed for each dose of vaccine (Schwartz & Gellin, 2005).

The ultimate goal lies in the development of an optimal pandemic vaccine which is capable of producing both a broad-spectrum and long-lasting immune response to a relatively stable antigen that is present in all influenza subtypes. As formidable a challenge as this may represent, available strategies to enhance immune response and the global importance attached to the implementation of prepandemic influenza vaccine, argue for an aggressive approach to funding
and research efforts in order to make this outcome a reality (Schwartz & Gellin, 2005). Vaccine strategies are influenced and complicated by the need to establish an appropriate target antigen or antigens. Through the process of “reverse genetics,” rapid generation of nonvirulent vaccine viruses from recent avian influenza (H5) virus isolates allows for the study of candidate vaccines (World Health Organization, 2005). On the basis of geographical spread, epidemiology, and the antigenic and genetic characteristics of H5N1 viruses isolated from human cases during 2006-2007, the World Health Organization has recommended eight emergent H5N1 strains as potential candidate vaccine reference viruses for the development of a vaccine which would target the evolving hemagglutinin (H5) antigen (World Health Organization Global Influenza Programme, 2007). See Table 3 below.

Table 3

<table>
<thead>
<tr>
<th>Clade 1</th>
<th>Hong Kong 2003</th>
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<tr>
<td></td>
<td>Vietnam 2004 (“1194”)</td>
</tr>
<tr>
<td></td>
<td>Vietnam 2004 (“1203”)</td>
</tr>
<tr>
<td>Clade 2/Subclade 1</td>
<td>Indonesia 2005</td>
</tr>
<tr>
<td>Clade 2/Subclade 2</td>
<td>Qinghai/western China 2005</td>
</tr>
<tr>
<td></td>
<td>Mongolia 2005</td>
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<tr>
<td></td>
<td>Turkey 2005</td>
</tr>
<tr>
<td>Clade 2/Subclade 3</td>
<td>Anhui/eastern China 2005</td>
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Between August 2006 and March 2007, the majority of HA sequences of H5N1 viruses which have continued to circulate or have re-emerged in avian species and which have been associated with sporadic human infections in Africa, Asia and Europe fall into the previously designated phylogenetic clades and subclades. Clade 1 viruses were responsible for outbreaks in birds in Vietnam and Thailand and human infections in Thailand. Clade 2.1 viruses have continued to circulate in poultry and cause human infections in Indonesia. Clade 2.2 viruses have caused outbreaks in birds in some countries in Africa, Asia and Europe and have been associated with human infections in Egypt, Iraq and Nigeria. Clade 2.3 viruses have been isolated sporadically in Asia and have been responsible for human infections in China and Laos.

Pre-pandemic vaccines are being developed by manufacturers using clade 1 and clade 2 viruses. Clinical trials have been conducted or are under way in several countries and stockpiling of clade 1 vaccines has begun in some countries. Because it is not known if the next influenza pandemic will be caused by H5N1 viruses or which of the clades or subclades of H5N1 would be responsible, should one occur, clinical trials using both clade 1 and clade 2 viruses should continue as an essential element in pandemic preparedness, to maximize data available on priming, cross-reactivity and cross-protection by vaccine viruses from different clades and subclades (World Health Organization Global Influenza Programme, 2007). See Figures 4 and 5 below.
Evolution of the H5N1 Haemagglutinin Gene

Candidate vaccine viruses

Clade 2.3

Clade 2.2

Clade 2.1

Clade 1

Scale
5 nucleotides

(World Health Organization Global Influenza Programme, 2007)
Although studies in ferrets have suggested that vaccine developed against one clade will not necessarily be protective for another clade, the same H5N1 vaccine has been shown to prevent death from avian influenza. This would support stockpiling of a pre-pandemic H5N1 vaccine as beneficial, especially since the overwhelming majority of the global population is immunologically naive in regard to prior exposure to H5 antigens. Therefore, the use of a pre-pandemic vaccine against a particular clade may still be effective as a primer (Webster & Govorkova, 2006).
Safe and effective vaccines can be looked upon as the single most important public health tool not only for prevention and mitigation of morbidity secondary to human-to-human transmission during an influenza pandemic, but also as a measure for decreasing the associated mortality and economic disruption that would most likely occur with a virulent strain capable of inflicting chaos on global societies and causing high case-fatality rates. This argument is made even more credible by the reported resistance of H5N1 to antiviral agents (Poland, 2006).

Even moderate levels of seroprotection, which may or may not be associated with protection from infection, may prevent or decrease transmissibility, severe disease and its complications, and death. A current vaccine candidate being stockpiled, developed against the Vietnam 2004 Clade 1 strain, may confer cross-protection against other clades. Ideally, more than one H5N1 (or perhaps even a different avian influenza subtype, such as H7 or H9) pandemic vaccine will be necessary, and candidates for vaccines against Clade 2 and its subclades will still need to be developed by the World Health Organization and its Global Influenza Programme network (Poland, 2006).

Vaccine effectiveness, especially for prepandemic vaccine, may be predicated on the ability of a given vaccine to achieve cross-protection or “cross-reactivity” against heterologous influenza strains (Poland, 2006). “Antigen-sparing” vaccines with adjuvants given with high doses of hemagglutinin antigen or adjuvant may further broaden immune responses, and live attenuated vaccine (LAIV) which requires only a single dose for immunogenicity, is also capable of inducing broad immune responses. These approaches may hold promise as important prepandemic vaccine options due to their potential ability to mimic priming by natural infection. Live attenuated vaccine has also been shown to be as, and perhaps, even more immunogenic in combating seasonal influenza epidemics than conventional vaccine (Weber, 2006).
LAIv can also be safely administered to immunocompetent individuals, including those most at risk who tend to generate strong immune responses leading to the pathogenic “cytokine storm” mechanism postulated as being responsible for the severe morbidity seen in this population after infection with pandemic influenza strains. This approach may also be advantageous logistically in developing countries, especially those in Southeast Asia where a pandemic would likely originate, since it may be administered intranasally, although cost issues may arise. U.S. companies involved in the development of therapeutic biologics may eventually be able to apply this “cold-adapted” live attenuated vaccine technology to the production of prepandemic and pandemic vaccine, which can then be safely administered to most healthy adults and children.

The use of a live attenuated vaccine is limited in that it cannot be administered to subpopulations that include infants and toddlers, the elderly and debilitated, and those with chronic medical conditions, especially those who are immunosuppressed secondary to either chronic disease or chronic immunosuppressive therapy. Immunocompromised individuals, including newborn infants and the elderly, would also likely require adjunct approaches (such as: passive immunization via administration of neutralizing antibody to H5N1, clades 1 & 2) to vaccination due to their predictably poor immune responses to any prepandemic or pandemic vaccine (Sambhara & Poland, 2006). See Figure 6 below.
Vaccine Strategies for Pandemic Influenza

(Sambhara & Poland, 2006)
This subpopulation would most likely need to rely primarily on early intervention with antiviral medications instituted at pandemic onset, both for treatment and prophylaxis. There remains a possibility that both prepandemic and pandemic vaccines in general could induce an active immune response to some degree in these individuals, with the expectation that any amount of protection conferred by the vaccine would more than likely wane over the course of the pandemic. Prepandemic doses, if repeated after a certain time interval, may still be efficacious, and pandemic vaccine may still be valuable during the all-important initial wave, hopefully helping to mitigate ongoing transmission as well as decreasing disease severity.

Global vaccine production capacity and rapidity of vaccine development serve as true rate-limiting factors which influence the implementation of any vaccine strategy, along with the all-encompassing consideration of economics and cost-effectiveness. Cell culture-based antigen production, viral-vector delivery systems, and new adjuvants and formulations including optimal prime-boost mechanisms which have shown potential in either animal models, humans, or both—these overall state-of-the-art strategies must be further investigated on an ongoing basis. A specific consideration for pandemic vaccine development involves the ability or inability of a vaccine to achieve cross-protection against strain variants by the induction of cross-reactive antibodies and/or cell-mediated immunity (Sambhara & Poland, 2006). Although this is still a concern, (as briefly described in reference to prior studies) the concept of a “universal” vaccine may serve as the ultimate initial step for a comprehensive pandemic influenza vaccine strategy.

Systematic investigation of diverse vaccine issues needs to be performed in an international and global context, and several high-priority vaccines should be evaluated at various dose levels and frequencies, with and without adjuvants (Monto A., 2006). The process of “reverse genetics,” a method by which influenza viruses can be generated entirely from segments of DNA
with the resultant creation of engineered viruses which are modified to be less virulent (Webby, et al.), allows the production of a candidate reference virus to occur in a relatively short time period, and has been utilized to enhance the rapid development of H5N1 vaccines (Luke & Subbarao, 2006). Recent H5N1 vaccine randomized controlled trials are shown below (Pierce, 2007), and more than 40 clinical trials involving prototype vaccines have been completed or are ongoing worldwide. The first H5N1 vaccine to gain FDA approval in the U. S. was found to be poorly immunogenic, but this vaccine could still theoretically help to reduce disease severity, pandemic influenza-related hospitalizations, and deaths (Center for Infectious Disease Research & Policy, 2007).

Table 3

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<thead>
<tr>
<th>H5N1 Vaccine---RANDOMIZED CONTROLLED TRIALS</th>
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<tr>
<td><strong>CLINICAL TRIAL</strong></td>
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<tr>
<td>---------------------</td>
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<tr>
<td>1 Treanor--March 2006/US</td>
</tr>
<tr>
<td>Sanofi-Pasteur*</td>
</tr>
<tr>
<td>2 Bresson--May 2006/France</td>
</tr>
<tr>
<td>Sanofi-Pasteur</td>
</tr>
<tr>
<td>3 G.S.K.--April 2007/Europe</td>
</tr>
<tr>
<td>* &quot;pre-pandemic&quot;</td>
</tr>
<tr>
<td>4 G.S.K.--July 2006/Europe</td>
</tr>
<tr>
<td>&quot;novel proprietary&quot;</td>
</tr>
<tr>
<td>5 Lin--Sept 2006/China</td>
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Immunologic priming with H5N1 vaccine during the pre-pandemic period is vital as a preventive strategy. The question arises, however, in regard to which vaccine methodology would be the most effective. A universal vaccine may be a promising approach: it induces a specific immune response to relatively conserved or stable influenza virus antigens, the matrix protein 2 or M2. Theoretically, a universal vaccine could provide protection against all types of influenza, eliminating the need to develop individual vaccines to specific viral subtypes, as defined by the H and N antigens. Unfortunately, none of the universal vaccines studied to date in animal models have achieved the level of protection provided by current vaccines, although there is evidence that an optimized universal vaccine may still prevent clinical disease in spite of its inability to protect against infection. Thus, the ideal role of universal influenza virus vaccine may be to serve as an adjunct to current vaccines while providing extra insurance against emerging influenza virus strains which continue to evolve, including new subtypes (Gerhard, Mozdzanowska, & Zharikova, 2006).

The ideal pre-pandemic vaccine candidate to be utilized to prime the global population during the present pandemic alert period, as defined by the World Health Organization, may be an antigen-sparing vaccine which confers cross-protection or cross-reactive immunity (Infectious Diseases in Children, 2007). Such a vaccine can serve as an integral component of a proactive pre-pandemic vaccination strategy, and recent clinical trials indicate that the GlaxoSmithKline candidate pre-pandemic split antigen H5N1 vaccine provides a substantial level of cross-immunity against diverse H5N1 strains (Center for Infectious Disease Research & Policy, 2007).

The subsequent immune response obtainable with this vaccine may be successful as a priming strategy, enabling humans to rapidly respond to H5N1 strain variants and therefore protect populations worldwide in the event of a pandemic. At the onset of a pandemic, the goal of
strain-specific vaccine would then be vigorously pursued in order to mitigate the spread of infection and disease. Researchers at the National Institutes of Health hope to eventually investigate the possibility of using a Clade 1 vaccine as a primer, to be followed by a subsequent Clade 2 vaccine as a booster. The urgency of such a plan may be heightened due to the cumulative increase in human cases and deaths in Indonesia to date. The ultimate prepandemic priming vaccine could turn out to be a bivalent product which would provide cross-protection against both clades (Pandemic Influenza: The State of the Science, 2006).

Section V: International Engagement and Global Intervention Strategies for Pandemic Influenza Vaccine

At the November 2005 meeting in Geneva, Switzerland, the World Health Organization identified five priority actions for the international community:

- Reduce human exposure to the H5N1 virus
- Strengthen the early warning system
- Intensify rapid containment operations
- Build coping capacity
- Coordinate global research, including accelerated development of pandemic vaccines and expanded production capacity

The last suggested priority action may be the most significant one. Epidemiology and surveillance, rapid containment of transmission, (mostly via reliance on the WHO antiviral drug stockpile) and preparedness plans for all countries with additional resources for implementation are all important areas of focus for the global community. Of these five areas, pandemic vaccine development and expansion of production capacity comprise priority actions with the greatest likelihood of success from both a prevention and mitigation standpoint (World Health
Organization, 2005). Given that WHO has officially warned governments worldwide that global risk characterization has progressed from the interpandemic period to the current pandemic alert period, (“Phase 3”) pre-pandemic vaccination coupled with vaccination at the onset of a pandemic represents a global intervention strategy with the greatest likelihood of success. Control and mitigation measures involving antiviral drug treatment and prophylaxis, along with NPI such as home isolation of cases and school closure, could also be implemented in order to complement vaccination efforts (Ferguson, 2006).

WHO states in their 2005 Summary Report that “…The characteristics of a pandemic, and the best control measures for responding to it, could not be known until after the new virus emerges. WHO as it monitored, in real time, the evolution of the pandemic and translated that emerging knowledge into pragmatic advice on control” (World Health Organization, 2005). Response and containment are vital components to global intervention, and do depend upon rapid and accurate characterization of the emergent pandemic influenza virus strain, but ‘coping capacity’ for all nations may be built best by investing precious resources in a proactive “two-step” vaccination strategy. Priming of the global population with prepandemic vaccine would be followed by the development and distribution of “strain-specific” vaccine.

The speed of vaccine development by novel scientific methods, the industrial capacity to produce vaccine, and the ability to make vaccines available and accessible to the global population in a fair, equitable, and timely manner both prior to and early on during a pandemic are the challenges facing the international community. Most of all, a sense of urgency must prevail among all nations which need to share responsibility for pandemic influenza planning. The challenge facing all nations may be best described as the need to achieve “solidarity before a shared - and complex - threat” (World Health Organization, 2005). The international and
collaborative implementation of vaccination measures should provide substantial benefits to global health by its emphasis on prevention of infection and the control of transmission, morbidity, and mortality.

International engagement in order to begin to properly prepare for the onset of a pandemic must occur through the earnest and proactive involvement of many nations and organizations, beginning with the United States and its Global Health agencies, the United Nations and World Bank, and the World Health Organization. In February of 2007, WHO experts reported encouraging progress on advances in pandemic influenza vaccine development (World Health Organization, 2007d). Sixteen vaccine manufacturers from ten countries are in the process of developing prototype vaccines against the H5N1 avian influenza virus, and vaccines designed to be effective against other avian influenza viruses (H9N2, H5N2, and H5N3) are also being developed. Currently, influenza vaccine production is limited to the following countries (Infectious Diseases in Children, 2007):

- Australia
- Canada
- France
- Germany
- Italy
- Japan
- The Netherlands
- Switzerland
- The United Kingdom
- The United States
Most of the completed or ongoing clinical trials (more than 40) have studied vaccine efficacy, coverage, and safety in healthy adults, with initiation of trials in the elderly and in children. To date, all vaccines tested have been shown to be safe and well tolerated in all age groups. Results have demonstrated convincingly that newly developed vaccines can induce a potentially protective immune response against H5N1 virus strains found in various geographical locations. Effective vaccines utilizing relatively low antigen doses allow for significantly more vaccine doses to be made available in the event of a pandemic (World Health Organization, 2007d).

Reference vaccine strains corresponding to H5N1 viruses provided from the WHO Collaborating Centers are being used by most manufacturers, and several new recombinant H5N1 prototype vaccine strains representative of various genetic virus subtypes have been developed by WHO, including a vaccine strain developed from the emergent 2005 Indonesia strain. (Clade 2, Subclade 1) The WHO Global Influenza Programme has continued to rely on close collaboration with affected countries for timely sharing of H5N1 virus strains, both from humans and animals (World Health Organization, 2006).

WHO continues to emphasize, however, that worldwide manufacturing capacity still does not meet the potential demand for global pandemic influenza vaccine. In order to respond to this problem, the Global pandemic influenza action plan (GAP) was created by WHO in 2006 to increase vaccine supply, an effort involving a ten billion dollar expenditure over ten years. As an integral component of this plan, WHO is currently collaborating with several vaccine manufacturers, primarily in developing nations most affected by highly pathogenic avian influenza (H5N1) as a cause of severe disease in humans. The objective is to provide these less industrialized countries with the most sustainable and reliable response to the looming pandemic
threat through the transfer of technology in order to facilitate the establishment of their own influenza vaccine production facilities (World Health Organization, 2007d).

In April and May of 2007, WHO awarded grants to six developing nations to produce influenza vaccines, and a plan was approved to stockpile H5N1 vaccines, establishing guidelines for fair and equitable distribution while taking into account economic considerations. Even more recently, WHO updated their International Health Regulations, stating that “WHO member nations are legally obliged to respond and provide technical assistance for the containing, at source, any health threat of international concern,” including novel flu strains such as H5N1. One of the top priorities covered by these regulations relates to the assessment and notification of ‘public health events’ as part of the collaborative process between WHO and member countries; to “ensure adherence to reporting requirements and verification of public health events” (Avian Flu Timelines: Policy and Politics, 2007).

Dr. Michael T. Osterholm, Director of the Center for Infectious Disease Research and Policy at the University of Minnesota, describes vaccination as “...the only meaningful weapon to combat the next pandemic.” He goes on to discuss the “20-year struggle by public health officials in industrialized nations to increase private sector vaccine production for seasonal flu epidemics...” He argues that poor infrastructure for the manufacturing of vaccine, combined with national and international failures to lobby for the need for universal vaccination, has resulted in vulnerability of the global population not only to annual seasonal influenza outbreaks, but also to the next pandemic. If a vaccine against a pandemic strain was to be manufactured using the current egg-based technology, production would likely be too slow to cope with pandemic influenza, and would not be available for at least six months. Vaccine supply would also only
serve 14% of the global population if efforts are not made to expand and expedite current global production capacity (Osterholm M. , 2005).

Osterholm describes the need for a ‘wake-up call’ to the international community, demanding “nothing less than an international effort to develop a new type of influenza vaccine that can be manufactured on a much shorter timescale.” Implementation of a global intervention strategy with vaccination as its cornerstone will require new production methods, surge capacity for crisis response, and a definitive and collaborative distribution plan. A purely “national” approach would be short-sighted and overly simplistic, failing to capture the essence of modern global society. Availability of a pandemic vaccine must become an absolute priority, put squarely at the top of the international agenda (Osterholm M. , 2005). In 2005, The World Health Organization made the statement:

“Never before had a pandemic been preceded by a warning signal, such as that sounded by the H5N1 avian influenza outbreaks in Asia; never before had industry, regulatory agencies, and governments had an opportunity to find joint solutions on the possible brink of a pandemic.” (Gronvall & Borio, 2006)

Global production capacity can be further expanded if governments ‘harmonize’ their regulatory policies. The U.S., the European Union, and Japan represent three regions which produce the majority of the world’s seasonal influenza vaccine. It has been suggested that these nations rapidly converge on regulatory requirements, intellectual property considerations such as the proprietary technique of reverse genetics, the use of recombinant DNA techniques for vaccine production, and technical issues affecting the composition of a pandemic vaccine (Gronvall & Borio, 2006).
A “mock-up” pandemic vaccine, or “pandemic-like” vaccine, may also allow vaccine-producing countries to accelerate the overall process. A “mock-up” vaccine contains an influenza virus from a subtype, such as H5, known to have pandemic potential (World Health Organization Global Influenza Programme, 2005). It anticipates and mimics the characteristics of a pandemic virus and is designed to confer protection against it (World Health Organization Global Influenza Programme, 2004). The European Union recently approved a vaccine manufactured by the Swiss pharmaceutical company Novartis which was originally submitted as a “mock-up” vaccine, containing a proprietary immune-boosting adjuvant (World Health Organization, 2007d). Based on past pandemics, more severe disease tends to arrive with the second wave of transmission, thus re-emphasizing the importance of vaccine availability as the additional time would be invaluable for vaccine supply (World Health Organization Global Influenza Programme, 2005).

The United States International Engagement on Avian and Pandemic Influenza is a U.S. Department of State program, and is part of an International Partnership announced at the General Assembly of the United Nations in September of 2005 with the following goals:

- Elevate the avian influenza issue on national agendas
- Coordinate efforts among donor and affected nations
- Mobilize and leverage resources
- Increase transparency in disease reporting and improve surveillance
- Build local capacity to identify, contain, and respond to an influenza pandemic

The first goal may be the most significant as it may be difficult to embrace the overall program without proper priority given to the issue on worldwide national agendas. It should be noted that pandemic vaccine as a global intervention strategy is conspicuous by its absence from
the overall program description, both in terms of the implementation of prepandemic and pandemic vaccine as prevention and containment measures, respectively. In January 2006 in Beijing, the global community pledged $1.9 billion to combat avian influenza worldwide, the U.S. leading the way with a $334 million contribution. Of the $392 million pledged by the U.S. as of September 2006, $56 million in funds is for the development of stockpiles, (primarily antiviral drugs) $36 million is to support pandemic influenza-related activities of the WHO and other international agencies, and an additional $41 million is pledged for international research (The U.S. Department of State, 2006).

The National Strategy for Pandemic Influenza: Implementation Plan was released by the U.S. Homeland Security Council in May of 2006 with the intention of advancing the national pandemic planning effort. Experts voiced concerns that the plan should be more ambitious in pursuing vaccine for a pandemic influenza strain for all Americans. It was noted that if just one action could be taken, it would be that the “...government put its weight more fully behind rapid vaccine development, manufacturing, and distribution. Not only would this be the single most important development in preparing the nation for a pandemic, but a sufficiently ambitious program could radically change what the U.S. would be able to offer the rest of the world” (Center for Biosecurity of UPMC, 2006).

The international component of the plan appears to fall short in terms of providing assistance for vaccine and antiviral acquisition for poorly developed countries. An operational plan, backed by the U.S. and other countries demonstrating the willingness to lead on this issue, is necessary for the substantial augmentation of global influenza vaccine development and production capacity in order for worldwide nations to have realistic opportunities to acquire proper and sufficient supplies of pandemic vaccine. This intervention effort should serve as the
“centerpiece” of the plan’s international component. Priorities for both vaccination and antiviral drug distribution would also need to be established in the U.S., with the purchase of all pandemic vaccine by the Federal government for the purpose of distribution through systems established by state, local, and Federal agencies in advance of a pandemic. This issue would be amplified in the context of the international arena, with difficult decisions needed to be made in the establishment of priorities for global distribution of pandemic vaccine, especially after the onset of a pandemic during which global cooperation and crisis leadership will be essential (Center for Biosecurity of UPMC, 2006).

The CDC’s Advisory Committee on Immunization Practices has recommended the “tiered use” of strain-specific pandemic influenza vaccine in the event of a lack of adequate vaccine supply during a pandemic, a discrepancy which may be inevitable both nationally and globally, especially at pandemic onset. Tiered vaccine priority groups are based on:

- High risk for serious complications or death from pandemic influenza infection
- High risk for acquiring infection and spreading it to others
- Critical role in pandemic response, provision of medical care to the ill, manufacturing of influenza vaccine, or maintenance of critical societal infrastructure.

Health-care workers, children and elderly persons, (specifically, those with chronic medical conditions) pregnant women, and household contacts of severely immunocompromised persons and young infants comprise the upper tier priority groups, which can be re-evaluated during a pandemic. Re-evaluation of tiered vaccine priority groups, specifically for those groups in lower tiers, would likely be necessary for emerging avian strains such as H5N1 due to their increased virulence demonstrated in healthy young adults, indicative of an age distribution of severe cases.
and deaths similar to that of the 1918 pandemic (Centers for Disease Control & Prevention, 2005). Table 5 illustrates the current recommendations for the upper tier.

Table 4

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<tr>
<th>Tier</th>
<th>Group description</th>
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<tr>
<td>Tier 1A</td>
<td>Health care workers</td>
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<tr>
<td>Tier 1B</td>
<td>Highest-risk groups</td>
</tr>
<tr>
<td>Tier 1C</td>
<td>Household contacts and pregnancy</td>
</tr>
<tr>
<td>Tier 1D</td>
<td>Pandemic responders</td>
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A computer model developed to help communities in the U. S. prepare for the mass dispensing of vaccines in the event of a public health emergency such as pandemic influenza may have practical applications for urban and rural communities in other countries, as well (Agency for Healthcare Quality and Research, 2004). This issue illustrates the added significance of a program employing a two-step approach. Prepandemic vaccine would most likely be distributed under more controlled circumstances without the same time constraints as that which would be expected to occur during a pandemic.

In July of 2006, an international group of experts convened in Italy to discuss how social justice considerations could be incorporated into pandemic response and planning.
acknowledging the reality that “socially and economically disadvantaged groups are almost always the worst affected by epidemics.” This subpopulation also includes many of those in southeast Asia where human cases are already on the rise. International efforts need to be focused on the promotion of equitable access to prepandemic and pandemic vaccine, both between and within nations (Berman Institute on Bioethics, 2006).

At the Sixtieth World Health Assembly in May of 2007, the agenda included the issue of the sharing of influenza viruses and access to vaccines, reaffirming the obligations of nations under the International Health Regulations. Request was made to establish an international stockpile of vaccines for influenza viruses with pandemic potential, to be utilized by those in need, especially in developing countries, in a timely manner. The development of mechanisms and guidelines aimed at the assurance of fair and equitable distribution of pandemic vaccines was also requested at the Assembly (Sixtieth World Health Assembly, 2007). The pharmaceutical company GlaxoSmithKline recently announced plans to donate 50 million doses of its prepandemic H5N1 vaccine to a global stockpile designed specifically for poorly developed nations, and the vaccine manufacturer Sanofi-Pasteur stated that it is ready to supply a ‘significant’ number of vaccine doses to the World Health Organization (Deitch, 2007). A global initiative for the sharing of avian influenza data has been proposed to expand and complement existing efforts through the creation of a global consortium to foster international sharing of avian influenza isolates for the purpose of vaccine production, requesting the support of the international scientific community (Bogner, Capua, Lipman, Cox, & others, 2006). Indonesia, the country with the highest number of human cases and deaths at present, had presented a resolution at the recent World Health Assembly providing for equitable access to pandemic vaccines produced from the viral samples submitted by Indonesia and other developing countries (Chamberlain, 2007). Indonesia resumed
the sharing of H5N1 virus strain samples in March 2007 after a previous five-month period of withholding candidate strains from the WHO Collaborating Centres, which had posed a threat to “global public health security” (World Health Organization, 2007e).

This not only highlights the critical need for collaboration between governments and the international public health community, but also calls attention to realistic concerns on the part of many developing nations that pandemic vaccine may not be affordable and available. As a further illustration of this dilemma, it was reported that Indonesia had requested enough vaccine to cover approximately 10% of its population, which was calculated to be equivalent to one-third or one-half of the proposed WHO stockpile (Chamberlain, 2007).

David Nabarro has proposed the building of a platform for global collaboration in regard to pandemic influenza vaccines. He describes a ‘Public Health Imperative’ with the need for global coverage which may depend upon adequate economic incentives for manufacturers and researchers to respond. This platform would form the basis for an initiative for action on the part of worldwide stakeholders, including global governments and international organizations such as the World Health Organization, the United Nations, and the World Bank (Nabarro, 2007).

Global intervention strategy for pandemic (and prepandemic) influenza vaccine would compose a new initiative, based upon the WHO Global Action Plan to increase vaccine access and supply (World Health Organization, 2006). Components include: the increased use of seasonal influenza vaccine, increased production capacity for pandemic vaccines, independent of seasonal vaccine use, and research and development of new technologies and novel vaccines. Challenges to be addressed in this initiative for global vaccine implementation are many:

- *Ensuring there is worldwide political support for international attention to pandemic vaccines, as funding “follows a political wind”*
• **Selection of technology:** Speed and cost of production, streamlined regulatory review, safety and intellectual property issues, administration route

• **Establishing the demand:** Need for developing as well as developed countries to agree on potential demand in a context of uncertainty: willingness to stockpile, *to vaccinate before a pandemic*, to “guarantee” supply to poor countries

• **Clarifying the supply potential** – specifically the potential for steady-state manufacture and for surge capacity in the event of a pandemic: determining the risks that industry will face

• **Preparing an initiative:** Options for different partners to work together on:
  a) demand analysis, b) Research & Development, c) intellectual property protection, d) production, e) regulation and post-marketing surveillance,
  f) distribution issues, and g) advance purchase

• **Structure and program for the Initiative** (Nabarro, 2007)

  In his Keynote Address at the Vienna Senior Officials’ Meeting on Avian and Pandemic Influenza in June of 2006, Nabarro highlighted the areas of international support and scientific initiatives, among others, as issues in need of attention from the international community. Meeting participants asked for ever increasing back-up of countries and regional entities by bilateral aid organizations, specialized UN agencies, the World Organization for Animal Health, the World Bank, major volunteer organizations, and the private sector. More synergy and continued action was requested in order to improve networking, coordination, and accountability within the international system, and the need was expressed for increased cooperation between governments and non-governmental organizations at both the national and international levels. Scientific progress in the understanding of the H5N1 avian influenza virus is strongly dependent
on openness and cooperation, and researcher-manufacturer-government interaction was described as crucial for improving the utility and availability of vaccines (Nabarro, Vienna Senior Officials' Meeting: Keynote Address-Issues to Tackle, 2006).

The *Global Pandemic Influenza Action Plan to Increase Vaccine Supply* was issued by WHO in October of 2006, responding to a prior World Health Assembly resolution calling for WHO to “seek solutions with international and national partners, including the private sector, to reduce the present global shortage of influenza vaccines by looking at strategies for economizing on the use of antigen and transferring production technologies from industrialized to developing countries.” In the event of a pandemic, an anticipated gap of vaccine doses in the ‘billions’ is presently forecast. To address this gap, 120 influenza vaccine stakeholders met at WHO in Geneva in May 2006 to outline the above action plan, at which time three fundamental areas of focus were identified:

- Increased use of seasonal influenza vaccine—to help nations prepare to respond to a future pandemic, to give the vaccine industry a better forecast for vaccine demand, and to stimulate increased production capacity
- Increased global influenza vaccine production capacity via improvement of yields and immunogenicity of vaccines, and utilization of vaccine formulations which may require lesser quantities of agent to confer protection
- Increased research into the development of novel influenza vaccines, including broad-spectrum vaccines, and improvement in vaccine efficacy evaluation methods

It is estimated by WHO that the implementation of this action plan will not only require a $3-10 billion investment from the international community, but will also necessitate a 5-10 year global commitment to sustaining the effort. Since the target population for vaccination could
potentially be the entire globe, or over six billion people, comprehensive resources would be required to support operational and logistic demands in many countries (Nuzzo & Chamberlain, 2006).

The Global Pandemic Vaccine Challenge is to define the most antigen-sparing formulation which guarantees that the largest number of doses of an economically viable pandemic vaccine can be produced on a worldwide basis by all companies. Publicly funded, international collaborative trials should be conducted which include candidate prepanademic vaccines. The most significant challenges for pandemic vaccination as a global prevention and intervention strategy may be categorized as organizational, logistical, and political. WHO must somehow take a leadership role in organizing and managing the development, production, and distribution of pandemic vaccines. The process created to ensure that the goal of vaccination of the global population is achieved must be backed by international political legitimacy, managerial authority, and financial accountability in order for it to be successful (World Health Organization, 2006).

Section VI: Recommendations for Change--Program Planning & Policy Development

In its Pandemic and Seasonal Influenza Principles for U.S. Action, the Infectious Diseases Society of America recommends the strengthening of pandemic vaccine efforts by the establishment of a Multinational Pandemic Influenza Vaccine Master Program, backed by the principle that “The widespread use of a pandemic vaccine should be the central strategy for protection of human health during a pandemic event.” It is also suggested that the U.S. government lead this effort by working with public and private partners while engaging the international community, and that the U. S. should make an investment of $3 billion or more
over the next four years to both initiate the Master Program as well as serve as a catalyst for additional international financial support. The Department of Health & Human Services has invested more than $1 billion and $132 million in the advanced development of cell-based vaccine technologies and antigen-sparing vaccines, respectively (Infectious Diseases Society of America, 2007).

In an analysis of the economic impact of vaccine-based interventions during a pandemic, it was estimated based on models and the use of a societal perspective that vaccination of 60% of the U.S. population would generate the greatest economic returns, but that this may not be logistically feasible within the short time frame dictated by the onset of a pandemic, especially with a two-dose requirement (Martin, Cox, & Fukuda, 2007).

Global vaccination programs must be supported by policies which promote strategic initiatives for international engagement via incremental and achievable interventions, focusing upon new vaccines and their implementation. There are vast economic and geopolitical implications for the adoption of policy recommendations which strive to achieve the admirable objective of prevention of pandemic-mediated disease and death, and containment of the frequency of these outcomes if prevention efforts turn out to be only partially successful.

The stakes, however, are too great for the potential occurrence of a high-risk crisis-generating event such as an influenza pandemic—it may be fairly easy for some to characterize this risk as “low-probability” while dismissing the need for urgent action, but the alternative to aggressive policymaking is either to do nothing, or to wait until the crisis finally does arrive. The latter could involve “chasing” the wave of transmission around the world while attempting to rapidly operate amidst global chaos and panic with public health weaponry limited to: antiviral drugs,
isolation and quarantine, various “social distancing” measures, and yes, even pandemic vaccine which may or may not match the emergent pandemic influenza virus strain.

A preferred policy alternative is one which supports a “two-step” process involving:

1) **Prepandemic vaccine**--the best possible “universal” vaccine as a primer for the prevention of a pandemic, whether it be an antigen-sparing vaccine which is cross-protective, conferring cross-reactive immunity to both Clades 1 and 2, (and Clade 2 *subclades*) or a true universal vaccine containing other antigens that is found to be effective in the prevention of pandemic influenza infection and disease (prepandemic strain could be incorporated into the annual seasonal influenza vaccination).

2) **Pandemic vaccine**--“strain-specific” vaccine for mitigation of a pandemic, with the requirement of only one dose, and hopefully, with a more manageable temporal window.

The acquisition of the economic and political will required to institute and implement proactive pandemic influenza vaccine policy continues to elude leaders of governments and international bodies. If an effort “on the scale of the Apollo space project” is truly required to “systematize and coordinate the development of a vaccine” (Infectious Diseases Society of America, 2007), then the global population will need to find inspired leadership quickly. Unfortunately, competing priorities of worldwide governments, economic realities and disparities, and liability issues make this policy even more problematic. Only through the leadership of the United States and other developed nations, in addition to international partners such as the United Nations, the World Bank, and the World Health Organization, can mechanisms to achieve consensus among governments and nations be successful.

A series of intergovernmental meetings in 2005 and 2006 have provided an important framework for the purpose of sustaining high-level political commitment and fostering
partnerships between nations. Successful implementation of any measure within a given country as a response to the threat of pandemic influenza depends upon certain determinants of success common to all nations. These were outlined as follows by David Nabarro, Senior UN System Coordinator for Avian and Human Influenza:

- **Political leadership**
- Effective alliances between stakeholders
- Resources and capacity to scale up implementation
- Effective management systems
- Social mobilization for sustained adoption of new practices
- Incentives and compensation

Nabarro describes successful political leadership as “consistent, high-level political commitment to implementing the strategy and ensuring that results are achieved” (Nabarro, Enhancing commitment and action on influenza threats, 2006).

Centralization and consolidation of vaccine policy implementation is probably needed at some level in order to provide efficiency and maximum benefit to the global population, but “top-down” leadership may fail to include the needs of rural populations in poorly developed nations, in addition to being prone to the competing self-interests of the respective stakeholders, especially during a crisis event such as an influenza pandemic. Health advocates worldwide are asking critical, long-ignored questions, including: Who should lead the fight against disease? Who should pay for it? What are the best strategies to adopt (Garrett, 2007)? Real leadership means being proactive. As tough as decision-making and prioritization may appear to be now, this perceived difficulty pales in comparison to the dilemmas which will likely face assorted players such as the U. S., the G8 and European Union, and international organizations such as
the UN and WHO *after* the onset of a pandemic, during which time “reactive leadership” can be expected to take center stage (Osterholm M., 2005).

A potentially shaky international coalition spanning health departments worldwide all the way up to and including World Health Organization could also undermine Global Health response to the emerging pandemic threat. If efforts continue to be underfunded and undermined by conflicts between global public health, sovereignty of member states, and the high stakes of trade and economics (On a wing and a prayer, 2005), then the decisiveness and purpose needed to create a pandemic vaccine which has a chance of making a difference on a global level will be lacking, possibly with dire consequences (Osterholm M., 2005).

Former political leaders with a conscience, and with a recent history of “doing the right thing,” may help to pave the way for U.S., WHO, and United Nations leadership. Former U.S. Presidents Bill Clinton and Jimmy Carter are prime examples of talented leaders (no longer preoccupied with running for political office) who may now be exercising their best judgment and good will, along with a keen eye toward global population concerns. Interestingly enough, the recent election of a South Korean to the post of Secretary-General of the UN may help to maintain the focus of the international community on the H5N1 avian influenza outbreaks causing avian and human disease throughout Southeast Asia and China.

The Multinational Pandemic Influenza Vaccine Master Program, proposed and supported by the Infectious Disease Society of America (IDSA) and the Trust for America’s Health, is a major step in the right direction. The program plan requires tremendous financial support from the U.S., with the backing of the President and Congress; needs to be implemented over a several year period, and involves working in concert with the World Health Organization, vaccine manufacturers, and other public and private international partners. In order to accomplish
“Influenza vaccines for the world in the face of an emerging pandemic threat,” a shared vision among political and public health leaders alike, along with pressure from the international community addressing equity and openness, must be present in order to give “teeth” to recommendations made by an international governing body without true political authority such as the World Health Organization.

Ultimately, international coordination and distribution of vaccine resources, with transparency of the overall process, are instrumental in the implementation of effective pandemic influenza vaccine policy. The public health principle of “the greatest good for the greatest number” must be adhered to, investigating “ways in which the least amount of virus can immunize the largest number of people.” Utilization of a priming prepandemic H5N1 vaccine, even if possibly unmatched, should definitely be considered as a proactive first step toward pandemic prevention, especially in Southeast Asia (Monto A., 2006).
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Appendix A
Appendix B

Influenza A Virus

Hemagglutinin (H) - 16 subtypes (attachment, penetration)
Neuraminidase (N) - 9 subtypes (release)
8 viral genes (assembly, replication, etc.)
M2 Protein (penetration)

Courtesy of Anthony S. Fauci, MD, Director, National Institute of Allergy and Infectious Diseases
Appendix D
Worldwide Spread in 6 Months
Spread of H2N2 Influenza in 1957 “Asian Flu”

* Feb-Mar 1957
  “Orange” Apr-May 1957
  “Brown” June-August 1957

68,000 Deaths, U.S.

(Weber, 2006)
The World Health Organization proposes that syndromic surveillance of detected clusters which meet specific criteria be followed by urgent cluster investigation for evidence of infection caused by a novel influenza A virus strain, enabling rapid response to and early containment of the outbreak if a novel strain and common risk factor for exposure are indeed found.
Appendix F
Works Cited


