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DRAFT

### **I. Introduction**

Pandemic influenza can be considered the most extreme example of an acute infectious disease outbreak. Many infectious disease outbreaks – including ones such as Severe Acute Respiratory Syndrome (SARS), Ebola, HIV, anthrax, or West Nile Virus – can have devastating effects. However, these disease outbreaks typically are limited in their spread to either localized areas or regions, or to certain at risk populations because of demographic, climactic, behavioral or other factors. Influenza pandemics, by contrast, are explosive global events in which most, if not all, persons worldwide are at risk for infection and illness. In past pandemics, influenza viruses have spread worldwide within months and are expected to spread even more quickly given modern travel patterns. Pandemic viruses also have the ability to infect, within a year, one third or more of large populations and lead to tens of millions deaths.

It is the sheer scope of influenza pandemics, with their potential to rapidly spread and overwhelm societies and cause illnesses and deaths among all age groups, which distinguishes pandemic influenza from other emerging infectious disease threats and makes pandemic influenza the most feared emerging infectious disease threat of all.

### **II. Influenza Viruses**

The agent of pandemic influenza is the influenza virus, which also is responsible for causing seasonal influenza, known by most persons as the flu. Influenza is a common but frequently serious disease characterized by signs and symptoms such as fever, fatigue, body pain, headache, dry cough and sore throat that affects large numbers of people each year. Although most people infected with influenza recover, it is still responsible for approximately 36,000 deaths and 114,000 hospitalizations each year. The familiarity of seasonal influenza epidemics in the U.S. has led to a great under-appreciation of their true health impact.

Influenza viruses are negative-stranded RNA viruses that have been classified taxonomically as orthomyxoviruses; they are primarily divided into two types: “A” and “B” viruses. The remarkable variation of influenza strains – particularly type A – and their ability to cause annual epidemics of respiratory illness of varying intensity and severity, continue to be the focus of intense investigation.

Only type A viruses are known to cause pandemics. Type A viruses are further divided into subtypes based on the specific hemagglutinin (H) and neuraminidase (N) proteins on the virus surface. Currently, two subtypes of A viruses are in worldwide circulation: H3N2 and H1N1. The emergence of both of these subtypes in the 20<sup>th</sup> century led to separate pandemics. For example, the 1918 pandemic resulted from the emergence and spread of the H1N1 virus while the 1968 pandemic was associated with the H3N2 virus. The 1957 pandemic was associated with the emergence and spread of the H2N2 virus, however, this virus subtype stopped circulating in 1968. Pandemics are believed to have occurred for at least 300 years at unpredictable intervals.

### **III. Why Influenza Pandemics Occur**

#### **A. Shift and Drift**

An important feature about influenza viruses that helps to explain much of their epidemiological patterns is the ability and propensity of these viruses to modify (drift) or replace (shift) two key viral proteins,

hemagglutinin and neuraminidase, on the viral surface. Because these proteins are the main targets for the immune system, changes in these proteins can have minor to profound effects on the antigenicity of influenza viruses.

#### *Drift*

Influenza viruses can change through antigenic drift, which is a process in which mutations to the virus genome produce changes in the viral H or N. Drift is a continuously evolving process that results in the emergence of new strain variants. The amount of change can be subtle or dramatic, but eventually one of the new variant strains becomes dominant, usually for a few years, until a new variant emerges and replaces it. In essence, drift affects the influenza viruses that already are in worldwide circulation. This process allows influenza viruses to change and re-infect people repeatedly through their lifetime and is the reason the influenza virus strains in vaccine must be updated each year.

#### *Shift*

In contrast to drift, pandemic viruses arise through a process known as antigenic shift. In this process, the surface existing viral H and N proteins are not modified, but are replaced by significantly different H and Ns. Since influenza A viruses that bear new (or “novel”) H or H/N combinations are perceived by immune systems as new, most people do not have pre-existing antibody protection to these novel viruses. This is one of the reasons that pandemic viruses can have such severe impact on the health of populations.

### **B. Animal Reservoirs**

Novel influenza viruses occasionally emerge among humans as part of the natural ecology and biology of influenza viruses. Large reservoirs of influenza viruses that naturally infect circulate among other animal species, notably wild birds. Wild birds are considered the ultimate reservoir for influenza viruses because more influenza A subtypes (15) circulate among wild birds than humans or other animal species. Normally, animal influenza viruses do not infect humans. However, avian influenza viruses can sometimes “jump” the species barrier and directly infect humans. This was demonstrated in 1997, when an outbreak of avian influenza A (H5N1) viruses infected both domestic poultry and humans in Hong Kong, leading to 18 hospitalizations and 6 deaths. Since then, other outbreaks of avian viruses (such as H9N2 in 1999, H7N2 in 2002, H7N7 in 2003, and H5N1 again in 2004) have occurred and been found to directly infect people. Fortunately, these avian viruses lacked the ability to spread easily from person-to-person and therefore did not precipitate larger outbreaks or a pandemic.

Pandemic viruses can also arise when some of the genes from animal influenza viruses mix or reassort with some of the genes from human influenza viruses to create a new hybrid influenza virus. This can occur when a single animal (for example, a pig or, possibly, a person) is simultaneously co-infected by both a human influenza virus and an avian influenza virus. In this situation, genes from the human and avian viruses can reassort and create a virus with the surface proteins derived from the avian virus (hence, creating a new subtype) and the internal proteins derived from the human virus, enhancing the transmissibility of the hybrid virus. The process of reassortment is not theoretical. Reassorted viruses have been frequently identified and are thought to have been responsible for the 1957 and 1968 pandemic viruses. In contrast to these naturally occurring reassortment, the development of molecular techniques makes it possible to create such reassorted viruses in the laboratory.

#### **IV. Distinguishing Pandemic from Seasonal Influenza**

Several epidemiological features distinguish pandemic influenza from seasonal influenza. Pandemics of influenza are unusual events and their timing cannot be predicted. For example, only three pandemics occurred in the 20<sup>th</sup> Century (1918, 1957, and 1968). The infrequency and unpredictable timing of these events is explained by the fact that influenza pandemics occur only when a new (or novel) influenza A virus emerges and spreads globally. By definition, most people have never been exposed to these viruses and therefore are susceptible to infection by them. By contrast, seasonal influenza virus strain variants are modified versions of influenza A viruses that already are in widespread circulation. Therefore, there usually is some level pre-existing immunity to strain variants. Because of the frequent appearance of new variants, virus stains contained in influenza vaccines must be updated annually.

#### **V. Impact of Influenza and Influenza Pandemics**

An annual influenza season in the U.S., on average, results in approximately 36,000 deaths, 114,000 hospitalizations, and between \$1 billion and \$3 billion in direct costs for medical care in the United States. This impact occurs because influenza infections result in secondary complications such as pneumonia, dehydration, and worsening of chronic lung and heart problems. Despite the severity of influenza epidemics, the effects of seasonal influenza are moderated because most individuals have some underlying degree of immunity to recently circulating influenza viruses either from previous infections or from vaccination.

By contrast, pandemic influenza has the potential to pose disease control challenges unmatched by any other natural or intentional infectious disease event. Pandemic influenza viruses can spread world-wide within months, or weeks, and are capable of causing infection in all age groups. Although the ultimate number of infections, illnesses and deaths is unpredictable an influenza pandemic in the 21<sup>st</sup> century has the potential to cause enough illnesses to overwhelm current public health and medical care capacities at all levels, despite the vast improvements made in medical technology during the 20<sup>th</sup> century.

While the medical care system is very different today than it was at the time of the 1918 influenza pandemic, certain modern trends might be increasing the potential for pandemics to cause more illnesses and deaths than occurred in earlier pandemics. There are several reasons for this assessment.

- First, the global population is larger and increasingly urbanized, allowing viruses to be transmitted within populations more easily.
- Second, levels of international travel are much greater than in the past, allowing viruses to spread globally more quickly than in the past.
- Third, populations in many countries consist of increasing numbers of elderly persons and those with chronic medical conditions, thus increasing the potential for more complicated illnesses and deaths to occur.

Taken together, this combination of factors suggests that the next pandemic may lead to more illnesses occurring more quickly than in the past, overwhelming countries and health systems that have not made adequate preparation.

The 1957 pandemic, during an era with much less globalization, spread to the U.S. within four to five months of when it was first detected in China and the 1968 pandemic spread to the U.S. from Hong Kong within two to three months. As was amply demonstrated by the recent SARS outbreak, modern travel patterns may significantly reduce the time needed for pandemic influenza viruses to spread

globally to a few months or even weeks. The major implication of such rapid spread of an infectious disease is that many, if not most, countries will have minimal time to implement preparations and responses once pandemic viruses have begun to spread. While SARS infections spread quickly to multiple countries, the epidemiology and transmission modes of the SARS virus greatly helped to contain the spread of this infection in 2003, along with quarantine and isolation and other control measures. Fortunately, no widespread community transmission took place. By contrast, because influenza spreads more rapidly between people and can be transmitted by those who are infected but do not yet have symptoms, the spread of pandemic influenza to multiple countries is expected to lead to the near simultaneous occurrence of multiple community outbreaks in an escalating fashion. No other infectious disease threat poses the same threat for causing increases in infections, illnesses and deaths so quickly in the U.S. and worldwide.

## **VI. Global Influenza Pandemic Planning**

The World Health Organization (WHO) has developed guidelines for national or regional planning to assist medical and public health leaders to better respond to future threats of pandemic influenza. The six pandemic phases, as defined by WHO, under which preparation and response can be organized are discussed in the core plan and further details can be found on the WHO website listed in Websites and References.

In addition to the pandemic phases, the WHO guidelines note that contingency plans should deal with various attack rates: a 10 percent would be stressful for the community while a 25-35 percent attack rate would severely disrupt community services and stress hospital and medical care facilities. Therefore, given the wide range of possibilities, pandemic planning must emphasize rapid initial assessment of disease impact, and assure capability for flexible response to differing levels of disease, such as varying recommendations for (1) priority groups for vaccination and receipt of antiviral drugs, (2) possible school closings and limits on public gatherings, and (3) possible international travel alerts.

In addition to addressing national needs for preparedness and response, pandemic planning in the United States should reflect the worldwide impact of pandemic influenza. WHO notes that many countries lack sufficient resources to prepare appropriately for a pandemic, and expects that important issues will emerge that will require continued international consultation to resolve.