



appendix B: pandemic influenza background

Pandemics of influenza are extreme infectious disease outbreaks. Although many infectious disease outbreaks (e.g. Severe Acute Respiratory Syndrome [SARS], Ebola, HIV, or West Nile Virus) can cause devastation, these infections are typically limited in their spread to either localized areas or regions, or to at-risk populations. Pandemic influenza, by contrast, is an explosive global event in which most, if not all, populations 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 today given modern travel patterns.

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 one of the most feared emerging infectious disease threats.

A. Influenza viruses

The agent of pandemic influenza is the influenza virus, which is also responsible for causing seasonal influenza, known by most persons as the flu. Seasonal influenza, a common disease characterized by symptoms such as fever, fatigue, body pain, headache, dry cough, and sore throat, affects large numbers of people each year. Although most people infected with flu recover, it is still responsible for approximately 36,000 deaths and 226,000 hospitalizations each year in the U.S.

Influenza viruses are negative-stranded RNA viruses that have been classified taxonomically as orthomyxoviruses; they are divided into two types: "A" and "B" viruses. Influenza type C is not known to cause disease in humans and so is not applicable to this discussion. 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 in humans: H3N2 and H1N1. The emergence of both of these subtypes in the 20th 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. **Influenza pandemics are believed to have occurred for at least 300 years at unpredictable intervals.**

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B. Why influenza pandemics occur

1. Drift and shift

An important feature of 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.

a) 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 continuous ongoing 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 are already 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.

b) 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.

C. Animal reservoirs

Novel influenza viruses occasionally emerge among humans as part of the natural ecology and biology of influenza viruses. Wild birds are considered the 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 cross this 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.

D. 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 20th 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. In contrast, seasonal influenza virus strain variants are modified versions of influenza A viruses that are already in widespread circulation. Therefore, there is usually some level of pre-existing immunity to strain variants. Because of the frequent appearance of new variants, virus strains contained in seasonal interpandemic trivalent influenza vaccines must be updated annually.



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E. Impact of influenza and influenza pandemics

An annual influenza season in the U.S., on average, results in approximately 36,000 deaths, 226,000 hospitalizations, and between \$1 billion and \$3 billion in direct costs for medical care. 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, it is sobering to understand that 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.

It is clear that pandemic influenza has the potential to pose disease control challenges unmatched by any other natural or intentional infectious disease event. Pandemic influenza viruses have demonstrated their ability to spread worldwide within months, or weeks, and to cause infections in all age groups. While the ultimate number of infections, illnesses, and deaths is unpredictable, and could vary tremendously depending on multiple factors, it is nonetheless certain that without adequate planning and preparations, an influenza pandemic in the 21st 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 20th century.

Certain modern trends could increase the potential for pandemics to cause more illnesses and deaths than occurred in earlier pandemics:

- 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.

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 are not adequately prepared.

The 1957 pandemic, during an era with much less globalization, spread to the U.S. within 4–5 months of its detection in China, and the 1968 pandemic spread to the U.S. from Hong Kong within 2–3 months. As was amply demonstrated by the 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, isolation, and other control measures. Fortunately, no widespread community transmission took place. By contrast, because influenza spreads more rapidly between

Table B-1: Effects of Past Pandemics on the U.S.

Pandemic	Estimated U.S. Deaths	Influenza A Strain	Populations at greatest risk
1918-1919	500,000	H1N1	Young, healthy adults
1957-1958	70,000	H2N2	Infants, elderly
1968-1969	34,000	H3N2	Infants, elderly

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, whether natural or engineered, poses the same current threat for causing increases in infections, illnesses, and deaths so quickly in the U.S. and worldwide.

F. H5N1 avian influenza

Although it is unpredictable when the next pandemic will occur and what strain may cause it, the continued and expanded spread of a highly pathogenic—and now endemic—avian H5N1 virus across much of eastern Asia, Russia, and eastern Europe represents a significant pandemic threat. Human avian H5N1 influenza infection was first recognized in 1997 when it infected 18 people in Hong Kong, causing 6 deaths. Concern has increased in recent years as avian H5N1 infections have killed poultry flocks in countries throughout Asia and in parts of Europe. Since 2003, over 100 human H5N1 cases have been diagnosed in Thailand, Vietnam, Cambodia, and Indonesia. The H5N1 virus circulating in Asia has raised concerns about the potential for a pandemic because:

- The avian H5N1 virus is widespread and endemic in much of Asia with spread to Russia and Europe.
- The avian H5N1 virus is becoming more deadly in a growing number of bird species and mammals.
- Wild birds and domestic ducks may be infected asymptotically, providing a reservoir for infection of other domestic poultry species.
- The virus is able to transmit directly from birds to some mammals and in some circumstances to people.
- There is sporadic spread directly from animals to humans with suspected human-to-human transmission in rare instances.
- Genetic studies confirm that H5N1, like other influenza viruses, is continuing to change and evolve.

While H5N1 is the greatest current pandemic threat, other avian influenza subtypes have also infected people in recent years. In 1999, H9N2 infections were identified in Hong Kong; in 2003, H7N7 infections occurred in the Netherlands; and in 2004, H7N3 infections occurred in Canada. Such outbreaks have the potential to give rise to the next pandemic, reinforcing the need for continued surveillance and ongoing vaccine development efforts against these strains.