Pandemic Influenza: Using History to Look Into the Future

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Seasonal influenza kills mainly the elderly and the very young each year, and also sickens large numbers of otherwise healthy individuals. Type A and B influenza viruses are involved and both change antigenically from year to year. Rarely, there is a more complete change in type A viruses, often related to reassortment with avian viruses. Then, because there is little or no immunity in much of the population, a pandemic occurs. The virus spreads all over the world in a relatively short period of time.

Historically, pandemics have been identified going back millennia because of their characteristic features. These identifications are sometimes questionable. Modern epidemiologists are often uncomfortable with some of these historic attributions, given the sometimes fragmentary data on populations affected and global involvement. In any event, until the 20th century, there was no laboratory confirmation that these events were truly influenza and until 1889, no clear description of occurrence in various population groups.

History of influenza outbreaks

Perhaps for the first outbreak, thought by some to represent influenza, was the “plague of Athens”. As reported by Thucydides, the plague was one of the causes of Athens losing to Sparta, which changed the course of world history. Pandemics appear to have occurred in 1510, 1557 and 1580. This and other observations may have been the source of the statement, probably not true, that there are on average three pandemics per century. Pandemics were identified through following centuries up to the 1800’s. In most attack rates were high, but mortality was relatively low. However, in some there was appreciable mortality affecting day to day life.

The first pandemic that was almost certainly influenza, based on indirect laboratory evidence, started in 1889. It began in Russia and then continued to spread: Europe and North American ports were affected by the end of the year, and the Mediterranean and North Africa by January 1890. South America, Singapore, India and coastal China were affected by February; Australia and New Zealand by March, and sub-Saharan Africa by May 1890. Two further waves of infection occurred in 1891 and 1892 and were probably due to previous seeding. Population attack rates ranged between 25 and 50%, and the number of deaths worldwide was estimated at 300,000. The majority of deaths were in the elderly. Data are available from the state of Massachusetts in the US, confirming this pattern. However, there is also a report from the UK that previously healthy young adults, generally heavily infected in pandemics but not experiencing severe outcomes, did die during this outbreak at higher than expected numbers. This is the earliest pandemic for which there is serological evidence about the origin of the virus responsible. Studies on serum samples collected before 1957 from people who were alive in 1889 showed A/H2 antibodies, indicating exposure to an A/H2 virus before the 1957 A(H2N2) pandemic began. Some believe there was another
pandemic starting in 1898 and there is similar serologic evidence that A/H3 viruses were involved.

**Pandemics of the 20th century: 1918**

The most infamous influenza pandemic and the one still affecting policy began in its severe form in mid to late 1918. Some believe it began to spread in 1916, and there are competing theories about whether it came from France or North America. In any event, the “signature” of this pandemic was the fact that it caused deaths in healthy adults, those who generally sickened but did not die when infected. This signature has allowed tracking the emergence of severe disease across Europe, including Spain in the middle of 1918, from which the term “Spanish influenza” originated. The lethal autumn wave began in late August in the United States, introduced probably by ships into Boston, MA. The infection spread through the country in little more than 10 weeks, during a period when there was no travel by plane and little by car. Some communities tried to restrict trains from stopping in their localities. The impact of this outbreak in the US has been well documented, with approximately 600,000 deaths being attributed to influenza in all waves of the infection. The global mortality estimate used to be put at 20 million, but has now been raised to 50-60 million, because of the past undercounting of what are now termed the underdeveloped countries. Even contemporaneous reports put the number of deaths in India at 12.5 million, at a time when the population of the subcontinent was much lower than it is now.

For many years, it was thought, based on the serologic studies similar to those described above, that this pandemic was caused by an A(H1N1) swine-like virus. In the last decade, with new molecular techniques, it has been possible to confirm the H1N1 nature of the pandemic from pathologic specimens collected from US service men who died during 1918. This virus appears to have been of avian origin, but was related to viruses later isolated in swine. Also of note in the post-mortem cases is the cause of death, which in many cases was bacterial; debate has arisen on the proportion of the deaths that were purely viral. This might have implications on the role antibiotics would have on the course of a similar pandemic taking place today.

**Pandemics of the 20th century: 1957, 1968 and other events**

Two pandemics followed during the 20th century, which returned to the familiar pattern of severe disease and death limited to the old, the very young and possibly those with underlying medical conditions. The Asian flu pandemic was a global outbreak of avian influenza A(H2N2) that started in Yunnan Province, China in February 1957. The spring and autumn waves of the outbreak were well documented in Japan, which was invaded by the virus directly from China. Timing of these two waves were similar to the experience in North America during the recent A(H1N1) pandemic. In the US and Europe the infection was seeded during the spring with only sporadic outbreaks. Major spread started in August/September when the autumn school term started. In the US there was another wave of spread in mid-winter.

The clinical presentation of A(H2N2) in humans was more typical of pandemics before 1918 although high mortality was noted in pregnant women and there was a preponderance of secondary bacterial pneumonia due to Staphylococcus aureus. The majority of deaths were in the very young or old. The case fatality rate was less than 0.5% overall and over one million people died. Although significant, such a level of mortality is several magnitudes lower than is thought to have been the case in 1918.

The 1968 influenza pandemic also started in China through a process of antigenic reassortment where avian and human viruses combined producing the A(H3N2) viurs. The
outbreak spread to Hong Kong in July 1968 causing 500,000 cases in just two weeks (therefore the original name ‘Hong Kong flu’), from where it rapidly spread to the whole world. The pandemic virus reached the US in September 1968. By December 1957 the illness was widespread across the US and morbidity and mortality were nearly as high as in the 1957-58 pandemic. In Europe the disease was diagnosed from September 1968 onwards; symptoms were mild, excess deaths negligible and demands on medical services were not excessive. However, the number of fatalities due to influenza sharply increased in Europe one year later, during the 1969-70 winter season, and in the UK the epidemic peaked in December 1969. The virus eventually reached South America and South Africa in mid-1969, much later than expected. Therefore, in North America, the majority of deaths during this pandemic occurred during the first pandemic wave, while in Europe and Asia the pattern was reversed and the majority of deaths occurred in the second wave. The virus was rapidly identified as influenza A(H3N2) and vaccine manufacture began within two months of the virus being isolated. However, only 20 million doses were ready by the time the epidemic peaked in the US and, because of late deployment, this did not prove a useful control measure.

Since the documented interval between the 1957 and 1968 pandemics was only 11 years, there was concern about when the next pandemic would occur. Also, based on the seroepidemiology described above, a theory developed that the influenza virus A subtypes recycled. Therefore, it was thought that the next pandemic virus might be A(H1N1) and that it might be of swine origin. Thus, when swine-origin H1N1 virus occurred in military recruits in Ft Dix, NJ in 1976, there was a pandemic alert and vaccine was even developed and used in the US. No pandemic followed. However, the next year, the A(H1N1) virus did return to the world, in a form similar to that seen in 1950. The virus caused a global “pseudopandemic”, with infections restricted to the young and with little mortality. The virus continued to remain prevalent in the world since, until replaced recently by the 2009 H1N1 virus.

**Into the 21st century**

During the latter part of the 20th century, as time from the previous pandemic got longer, serous planning for the next pandemic began. This accelerated in 1997, when it was realized, in Hong Kong, that a highly pathogenic avian A(H5N1) virus could spread to humans directly from birds. Of the 18 documented human cases, 6 died. Concern died down, but was revived when two events took place in 2003 which captured the world’s attention. The first was the rapid spread globally of the coronavirus causing SARS. Case fatality was often high and the economic and societal impact was major. SARS left behind a sensitization to the health impact of an emerging infection and the value of measures to control transmission. The SARS outbreaks were followed by the return in 2003 of the highly pathogenic avian A (H5N1) in humans, initially in South East Asia. The case fatality, sometimes as high as 80%, jolted the biomedical world. Since all influenza pandemics of the 20th century were of avian origin, the possibility that this virus could mutate or reassort with other influenza viruses and become easily transmissible among humans raised the specter of an influenza pandemic even more serious than 1918. These events, created a supposition that the next pandemic would be of avian origin and would be severe. What occurred instead was the swine-origin H1N1 pandemic of 2009.

Details of this pandemic will be described in the document related to Panel 4. It is of interest that waves of this pandemic continued through the last northern hemisphere winter, and that vaccine again became available too late to affect the early course of the pandemic, a period when only antivirals were available. Going forward, we still have to be concerned about the fact that A(H5N1) influenza is regularly occurring in wild and domestic birds occasional spread to humans in countries such as Indonesia and Egypt. Other pandemic
candidate viruses also exist. However, if we are to have sufficient vaccine to take care of a pandemic in the world, we must use vaccine to control seasonal infection. It is impractical to expect manufacturers to produce vaccine which can only be used three times a century.