

The epidemiology and clinical impact of pandemic influenza

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Abstract

It is impossible to predict when the next pandemic of influenza will occur; however, it is almost 35 years since the last pandemic, and the longest inter-pandemic interval recorded with certainty is 39 years. The next pandemic virus is likely to emerge in southeast Asia, as have two of the last three pandemic viruses. Complete global spread is likely to occur in 6 months or less, due to increased travel and urbanisation. It is likely that the usual inter-pandemic pattern of age-specific mortality will deviate temporarily towards higher mortality in younger adults. The extent to which this will happen is unclear, as the shift was extreme in 1918–1919 but less so in subsequent pandemics. Nevertheless, this may have important implications for the protection of essential workers such as health care, emergency service and military personnel. The extent to which elderly persons will be affected will depend upon previous exposure to similar influenza viruses. It is impossible to predict the likely increase in excess mortality that will occur when a new pandemic virus emerges. However, whilst mortality on the scale experienced in 1918–1919 is probably unlikely, there was a high level of mortality among those infected with the A/H5N1 virus in 1997, so it cannot be assumed that a future pandemic will be as mild as those in 1957–1958 or 1968–1969. There is likely to be more than one wave of infection and health services in most countries will be hard pressed to provide vaccines or to manage populations with clinical attack rates of ≈ 25 –30% and concomitant increases in demand for both primary and secondary health care services.

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Key messages

- **It has been 35 years since the last influenza pandemic, and the longest interval between pandemics recorded with certainty is 39 years.**
- **In the 21st century, the global spread of pandemic influenza is likely to be very rapid.**
- **In a pandemic, most health services in all countries are likely to come under severe pressure for several months.**
- **Morbidity and mortality may be extremely severe, and young adults and children may be affected in large numbers.**

1. Introduction

The occurrence of influenza in human populations has been documented in considerable detail for at least the past 3 centuries, but actual accounts of influenza in humans probably date back further than this, to the 12th century [1]. Pos-

sible pandemics are documented as far back as 1510, but the first one to be clearly recognised was in 1580 [2,3]. Even so, reliable epidemiological data are sparse until the pandemic of 1889–1892. Most lessons about the epidemiology of pandemic influenza have, therefore, been learned from the three well-documented pandemics of the 20th century, which occurred in 1918–1919, 1957–1958 and 1968–1969.

It should be noted that the influenza virus was first isolated in 1933 [4]. However, through retrospective analysis of sera collected from individuals born as early as 1857, there is evidence that influenza A/H2N2 virus circulated from ≈ 1889 until 1901 and may have been responsible for the 1889–1892 pandemic. Influenza A/H3N8 virus circulated from ≈ 1900 to 1918 and may have caused a mild pandemic in 1900; influenza A/H1N1 virus circulated from ≈ 1908 onwards [5–10]. The pandemics of the 20th century are now known to have been due to an A/H1N1 virus related to swine influenza in 1918–1919 [11,12], an A/H2N2 virus in 1957–1958 [13] and an A/H3N2 virus in 1968–1969 [14]. Thus, there is evidence that at least two of the pandemics of the 20th century were associated with the re-emergence of viruses similar to those which circulated in previous eras, a process referred to as *antigenic recycling*.

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2. Virological mechanisms for pandemic influenza

Influenza pandemics occur when a novel influenza virus emerges against which the vast majority of the world's population has no immunity. This has been observed only with influenza A viruses, which exist in nature as a number of antigenically distinct subtypes, and is due to the emergence of a novel haemagglutinin on the surface of the virus, with or without a concomitant change in neuraminidase, the other major surface antigen. This process is referred to as *antigenic shift*. Fifteen haemagglutinin and nine neuraminidase antigens are known to exist in viruses that infect animals (wild aquatic birds, domestic poultry, pigs, seals and other mammals), providing substantial opportunities for the emergence of new pandemic viruses [15–18]. However, to date, only three haemagglutinins (H1, H2 and H3) and two neuraminidases (N1 and N2) have been firmly implicated in pandemic influenza.

In addition to the occurrence of an antigenic shift, a virus which causes a pandemic must also be associated with little or no pre-existing immunity in the world's population, have the potential to infect humans causing clinically apparent illness, and transmit readily from person to person. These features result in global outbreaks of disease that affect a high percentage of individuals and cause increased mortality.

3. Pandemic threats and alerts

In addition to the antigenic shifts known to have been responsible for the three pandemics of the 20th century, a true antigenic shift also occurred in 1977 when influenza A/H1N1 virus was re-introduced into circulation after an absence of 20 years [19]. However, infections occurred mainly in younger persons and were not sufficiently widespread to produce a pandemic [20]. Furthermore, this re-emergent virus began to co-circulate alongside influenza A/H3N2 virus without displacing it or establishing dominance [21,22]. This was not the case in 1957 when A/H2N2 replaced A/H1N1, and in 1968 when A/H3N2 replaced A/H2N2.

One year earlier, in 1976, there had been a pandemic alert when a novel A/H1N1 swine-like virus caused an outbreak of virulent influenza among military personnel at Fort Dix, NJ, USA [23,24]. A pandemic similar to the one in 1918–1919 was widely anticipated. Although a programme for mass vaccination was undertaken in the USA, the virus failed to transmit successfully outside the confines of the military barracks in which the outbreak occurred [25–28]. The occurrence of a number of cases of influenza in Hong Kong in 1997, involving a highly virulent A/H5N1 virus novel to humans, provided another pandemic alert [29–33]. However, despite the fact that large proportions of the local population were probably exposed through contact with infected poultry, clinically apparent illness was rare, albeit severe (6 of the 18 hospitalised cases died), and significant person-to-person

transmission did not occur [34,35]. In 1999, also in Hong Kong, two children suffered mild influenza-like illnesses associated with influenza A/H9N2 virus [36]. This virus was later characterised as being of avian origin and genetically similar to the A/H5N1 virus identified in 1997 [37]. These incidents in 1976 and 1997 illustrate the constant threat of pandemic influenza viruses emerging from animal reservoirs. The pandemics of the 20th century occurred at intervals ranging from 11 to 39 years. It is now 34 years since the occurrence of the last pandemic in 1968.

4. The epidemiology of pandemic influenza

The epidemiological impact of pandemic influenza is best appreciated when compared with the more familiar patterns associated with inter-pandemic disease. In inter-pandemic periods, in northern and southern temperate regions, the epidemiology of influenza is characterised by extremely low-level transmission of influenza viruses in the summer months [38–44], followed by an annual upsurge in winter seasonal activity [45–50]. The upsurge in winter activity is variable in intensity and duration, but usually produces clinically recognisable disease in the population for 8–12 weeks and, on occasions, epidemics lasting 4–6 weeks that impact on both primary and secondary care [46,51–53]. In tropical and sub-tropical regions, the disease usually occurs year-round, although seasonal peaks of increased activity may be observed [54–57].

5. Phasing and the geographical spread of pandemics

The phasing and geographical spread of influenza pandemics both have important implications for future planning; Potter has reviewed these features in detail [58]. Pandemic influenza is less constrained by season and in each of the three pandemics of the 20th century there were multiple waves of infection following the emergence of the virus. The evidence for this phenomenon is most clear in relation to the 1918–1919 pandemic. The first wave occurred in spring 1918 in the USA and among elements of the American Expeditionary Force disembarking in northern France. By June 1918, India, China, New Zealand and the South Pacific had also been affected. The second wave began in August 1918 and was far more devastating in terms of mortality. It appeared simultaneously in Africa and Europe but was slightly delayed until September–October 1918 in the USA. The third wave appeared in spring 1919 [58]. Only Australia managed to delay the introduction of the pandemic until January 1919, largely through a series of quarantine measures [59]. It appears that all major populations of the world were affected within 10 months, although data on the impact of the pandemic in South America are absent.

There is good evidence that the 1957–1958 pandemic originated in Yunan Province, China in February 1957

[2,13]. It spread throughout southeast Asia within 3 months and by mid-1957 infection was established on all major continents [60]. Similarly, the 1968–1969 pandemic began in China in July 1968 [14], spreading rapidly to the remainder of southeast Asia and Australia and then to the USA in September, via military personnel returning from Vietnam [61,62]. Although the virus was first isolated in Europe in September 1968, significant disease associated with the new virus was not apparent until the winter season of 1969–1970 [62–64]. The reason for this delay has not been established. Nevertheless, the virus had effectively spread globally within 6 months.

The reasons for the presence of several waves of infection are unclear, but may be linked to the process by which a novel influenza virus adapts to its human host and becomes more virulent [65] or to the influence of season [58], or both. There is genetic evidence that new subtypes may take a few years to adapt to the human host prior to emerging as pandemic influenza [66]. This may help explain the outbreak of influenza A/H5N1 in Hong Kong in 1997: it was due to a highly virulent virus but one that had not adapted to transmit from person to person [34,35].

6. Excess mortality in pandemics

A large number of studies have established that, during inter-pandemic periods, influenza-related complications and deaths are more likely to occur in persons suffering with underlying chronic illnesses who are principally but not exclusively elderly [67]. Childhood morbidity and mortality related to influenza are concentrated in those <3 years of age [68–73], and infants <1 year appear to be hospitalised at rates similar to those of high-risk adults [74]. The complications of influenza include severe conditions such as pneumonia, myocarditis, and pericarditis. In addition, influenza can destabilise pre-existing conditions such as diabetes, cardiac failure and chronic obstructive pulmonary disease and lead to the untimely deaths of many patients [75]. Thus, winter epidemics are frequently associated with excess mortality. For example, in England and Wales in 1989–1990, 26,000 excess deaths occurred in 56 days during a severe A/H3N2 epidemic [76]. In addition, as demonstrated by the recent severe outbreak in Madagascar, malnutrition and other factors may contribute significantly towards increasing mortality [77].

Compared with inter-pandemic periods, there is evidence that levels of mortality in pandemics can be considerably higher. In the 1918–1919 pandemic, 198,000 excess deaths occurred in the civilian population of England [78]. In the USA, 500,000 excess deaths have been attributed to the pandemic [79]. In San Francisco and New York City, deaths rates for pneumonia in autumn 1918 peaked eight-fold higher compared with those during the seven previous winters [80]. There were an estimated 1.5–2 million deaths in Africa [81] and 7 million in India [3]. It is conservatively estimated that

over 20 million persons died world-wide [82]. However, taking into account the fact that adequate mortality records did not exist in many countries in 1918–1919, the true figure is almost certain to lie in the range of 40–50 million [58].

The mortality experienced in 1918–1919 was without precedent, especially when compared with subsequent pandemics. In the 1957–1958 pandemic, the estimated number of deaths due to influenza in the USA was estimated to be 80,000 [83]. World-wide, the death toll was probably around 1 million persons [58]. The 1968–1969 pandemic was no worse than 1957–1958 in terms of excess mortality. In England and Wales, the 1969–1970 winter season was the first in which widespread influenza activity was attributable to the A/H3N2 pandemic virus [62,63,84], and almost 30,000 excess deaths occurred [85]. In contrast, only about 1000 excess deaths occurred in the very next season. However, roughly 20,000 excess deaths also occurred in 1976–1977, some 8 years after the pandemic [85]; and in 1989–1990, 26,000 excess deaths occurred [76]. These latter data demonstrate that the mortality experience in the 1968–1969 pandemic was similar to that in subsequent seasons when ‘severe’ inter-pandemic influenza activity occurred.

7. Age-specific mortality of pandemics

In inter-pandemic years, the vast majority of influenza-related deaths occur in the elderly, although deaths are also reported in infants and young children [67,75]. A similar pattern of age-specific mortality occurred in the first quarter of 1918 in England and Wales (Fig. 1) [78]. During this period, the death rate in children aged 0–4 years was about 80 per 1000, falling to <40 per 1000 in older age groups before rising sharply after the age of 50 years to peak at >130 per 1000 in those aged 70–74 years. However, in the fourth quarter of 1918, during the second wave of the pandemic, this pattern changed radically. Although mortality among children aged 0–4 years rose considerably (120 per 1000), death rates in all other age groups <40 years rose much more dramatically, peaking at almost 150 per 1000 in persons aged 25–29 years. Above the age of 50 years, death rates in the fourth quarter were lower than before and were especially low in persons aged 80 years and over. Earlier, between 1890 and 1917, deaths among females aged 0–35 years had accounted for 7–11% of all female influenza deaths; during the pandemic, however, girls 0–14 and 15–35 years in age accounted for 25 and 45% of all female influenza deaths [78].

The complete reversal in the pattern of age-specific mortality in the 1918–1919 pandemic was extremely dramatic and is still without precedent. However, a similar trend was observed in 1957–1958 during the H2N2 pandemic and again in 1968–1969 during the A/H3N2 pandemic, albeit to a far lesser extent on both occasions [83,86–88]. In both of these pandemics, most excess deaths occurred among

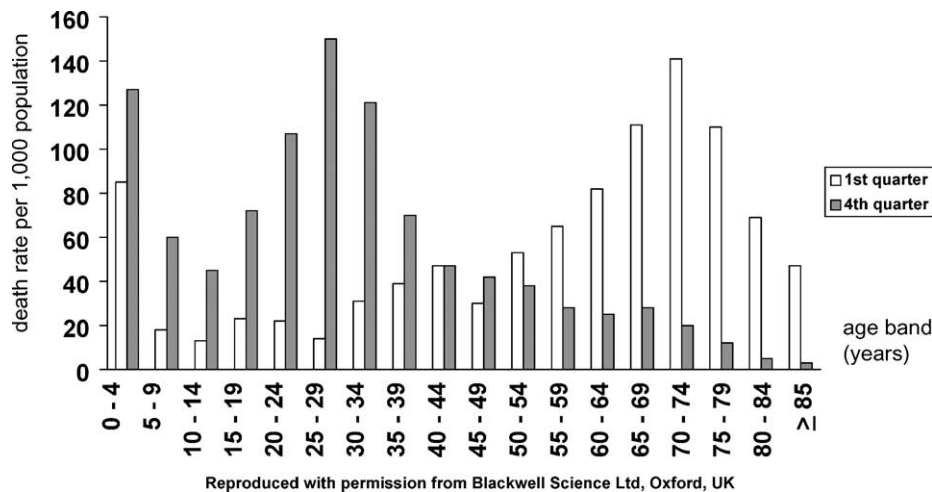


Fig. 1. Age-specific influenza death rates among females in England and Wales during first and fourth quarters of 1918 (source: Ministry of Health, 1920) [78].

elderly persons, but the relative increase in excess deaths was still greater among young adults. There is also evidence that the very elderly were partially protected in the pandemics of 1957–1958 and 1968–1969, as they had been in 1918–1919 [89,90]. This may well relate to the fact that many persons in this age group had been exposed to similar antigens as children or young adults (in keeping with serological evidence on antigenic recycling), and retained partial immunity in later life.

8. The morbidity impact of pandemics

In the late 19th and early part of the 20th centuries, access to healthcare was limited for the majority of persons and most countries had poorly developed healthcare systems; thus, morbidity data from this period are limited. Nevertheless, the estimated clinical attack rates in all four pandemics since 1889–1892 were remarkably similar. The clinical attack rate during the 1889–1892 pandemic was estimated to be 25–50% [91]. In the 1918–1919 pandemic, it is estimated that 50% of the world's population became infected, of whom half suffered clinically apparent illness: an overall clinical attack rate of about 25% [58,82]. Again, in 1957–1958, clinical attack rates were estimated to be 25–30% [38,58,83,89,92,93]. In England, Miller et al. reported a clinical attack rate of 25% during the 1968–1969 pandemic [84]. In Portland, OR, USA, ambulatory care visits during the 1968–1969 pandemic occurred at a rate of 20 per 100 persons compared with 13 per 100 in 1970–1971, a non-epidemic year [94]. However, hospitalisations for pneumonia and influenza occurred at a rate of 144 per 1000 compared with 58 per 1000 in 1970–1971; an excess rate of 150%. The incidence of hospitalisation increased dramatically with age, peaking at about 500 per 1000 in those aged 65 years and over [94]. Thus, experience in Oregon in

1968–1969 showed that with a clinical attack rate of around 20%, there was a large increase in demand for secondary care, especially among the elderly.

The estimates of excess morbidity associated with pandemic influenza should be judged in the context of the ability of modern health services to deal with sudden increases in demand during times of inter-pandemic influenza activity. For example, in England and Wales in 1975–1976, an epidemic widely associated with severe health service disruption, it is estimated that 4.9% of the population (2.4 million persons) consulted a primary care physician with influenza [47]. In 1989–1990, although only 1.5% of the population (755,000 persons) consulted with a physician [46], health services were again placed under considerable strain [53]. Few hospital services could nowadays absorb an increase in hospital admissions similar to the one in Oregon during the 1968–1969 pandemic [95].

9. The clinical features of infection in pandemics

Data also exist on the clinical features of pandemic influenza. In 1918–1919, patients presented with the sudden onset of severe but typical influenza symptoms: high fever, headache, myalgia/arthritis, anorexia, nausea, vomiting and cough lasting 2–4 days. Epistaxis was also a frequent but unusual feature [96]. Although most patients recovered, some died very quickly, being rapidly overwhelmed by a tracheobronchitis associated with dyspnoea and the appearance of mahogany spots around the mouth, which coalesced into a violaceous heliotrope cyanosis [97–100]. After initial recovery, up to 18% of patients subsequently developed pneumonia [101–103]. The case fatality rates ranged from 0.6% in children, to 2% in young adults and 3% in the elderly [75]. Post-mortem findings in rapidly fatal cases revealed haemorrhagic lungs with an absence of

pus [104]. In contrast, patients who died from secondary pneumonia showed the classical changes associated with bronchopneumonia [104].

The incredibly virulent clinical picture of pandemic influenza from 1918 to 1919 does not seem to have been repeated in 1957–1958 or 1968–1969 when, on both occasions, the clinical picture appears to have been rather more typical [75]. However, a higher than normal incidence of primary viral pneumonia was widely observed in 1957–1958 [75,105]. In both 1918–1919 and 1957–1958, maternal mortality was also noted to increase [106–109]. These features may be significant in future pandemics.

10. Conclusions

The three influenza pandemics of the 20th century indicate what can be expected when the first pandemic of the 21st century makes its appearance. The pandemic virus may emerge in China or a nearby country and could include surface antigens or virulence factors derived from animal influenza viruses, much like the avian A/H5N1 virus that emerged in Hong Kong in 1997. Once the new virus acquires the ability to be transmitted efficiently from person to person, it will spread rapidly throughout the world. Several waves of infection will occur. Morbidity will be extensive in all age groups, and there will be widespread disruption of social and economic activity in all countries. Excess mortality will be evident in most if not all age groups. It is unlikely that health care systems in even the most economically developed countries will be able to adequately cope with the demand for health care services. Although modern medical care will offer life-saving treatment to some individuals who in earlier pandemics would not have survived, the principle determinants of the severity of the next pandemic will be the virulence and transmissibility of the virus and the susceptibility of human populations to infection. There is little that people can do to change or control these variables. What they can do, however, is prepare their societies for managing the consequences of the pandemic and ensure that there are adequate supplies of vaccines and antiviral agents to lessen if not control its impact.

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