Understanding influenza transmission, immunity and pandemic threats

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Abstract The current pandemic threat can be best understood within an ecological framework that takes account of the history of past pandemics caused by influenza A, the relationships between pandemic and seasonal spread of influenza viruses, and the importance of immunity and behavioural responses in human populations. Isolated populations without recent exposure to seasonal influenza seem more susceptible to new pandemic viruses, and much collateral evidence suggests that this is due to immunity directed against epitopes shared between pandemic and previously circulating strains of inter-pandemic influenza A virus. In the highly connected modern world, most populations are regularly exposed to non-pandemic viruses, which can even boost immunity without causing influenza symptoms. Such naturally-induced immunity helps to explain the low attack-rates of seasonal influenza, as well as the moderate attack-rates in many urbanized populations affected by 1918–1919 and later pandemics. The effectiveness of immunity, even against seasonal influenza, diminishes over time because of antigenic drift in circulating viruses and waning of post-exposure immune responses. Epidemiological evidence suggests that cross-protection against a new pandemic strain could fade even faster. Nevertheless, partial protection, even of short duration, induced by prior seasonal influenza or vaccination against it, could provide important protection in the early stages of a new pandemic.

Keywords Historical epidemiology, mathematical modelling, mortality, pandemic influenza, viral evolution.

Introduction

A pandemic is a global epidemic, usually associated with a high attack-rate, severe disease and death.[1–3] Historical influenza pandemics, dating back at least to the 12th century, could spread no faster than people could travel, so that before the 19th century they took months to spread across Asia or Europe.[1] With the advent of rail travel and steam ships, rapid spread over distances was facilitated, although it was still the case that introductions to isolated populations, including Australia, were often delayed.[4,5] By the second-half of the 20th century, the situation changed dramatically with the advent of regular intercontinental air travel; not only could infected people be conveyed rapidly into a susceptible population – they could even arrive before their own symptoms had developed. Pandemics such as influenza could now spread between continents and hemispheres within hours or days.[6]

There are records of at least 20 major historical outbreaks of 'influenza' affecting Europe and connected countries. Needless to say, there is ambiguity about the diagnosis of influenza in the earlier outbreaks, and about the precise criteria for attaching the label of 'pandemic'.[1–4] The severity of an influenza pandemic can be assessed from its attack-rate (i.e. the proportion of the population becoming ill over the entire pandemic), or from the mortality rate (i.e. the proportion of the population dying over the entire pandemic). Using these criteria, the 1918–1919 pandemic was arguably the most serious.[4,7] The attack rate in most countries ranged from 20 to 60%, and the mortality rate was estimated at between 1% and 2·5% of the world population (then 2 billion) resulting in some 20–50 million deaths with wide variations from country to country[4,7] (refer Table 1). In 1918–1919, an estimated 7% of people died from influenza in parts of India,[7] 20–30% of Western Samoans died,[4,8] and an even greater proportion of the population was lost to influenza in some isolated communities of Alaska.[4,9] Mortality was less in developed countries, with as few as 0·2% dying in Denmark,[7] 0·24–0·3% in Australia[10] and 0·55% in New Zealand whites (but 4·2% in the indigenous Maori populations).[11] An excellent review of the wide variations in 1918–1919

Table 1. Mortality impact of influenza for selected pandemics and for seasonal influenza

Year	Population	Approximate deaths per 1000 population	Influenza A subtype
1675	London	1	Unknown
1782	London	10	Unknown
1837	London	4·5	Unknown
1847	London	2·5	Unknown
1890	UK	1–2·5	
1918–1919	Worldwide	2–25	H1N1
	India	Up to 70	
	Western Samoa	200	
	Alaska	Up to 600	
	New Zealand – whites	5·5	
	New Zealand – Maori	42	
	New South Wales	3	
	Victoria	2·4	
1957	Worldwide	0·7	H2N2
	Liverpool	1	
	USA	0·35	
1968–1969	Worldwide	0·3	H3N2
	USA	0·15	
Seasonal influenza	Developed countries	0·03–0·3	H3N2, H1N1

pandemic mortality across global populations[7] showed that poverty, as assessed by per capita income, was an important predictor. The effects of poverty, most dramatically seen in parts of India, are likely to have been mediated by the effects of overcrowding and immune deficits arising from malnutrition,[12] or by higher rates of complicating bacterial infection.[13,14]

Later pandemics (i.e. the Asian flu – H2N2 from 1957, and Hong-Kong flu H3N2 from 1968) were less serious in terms of both attack rate and mortality rate. Best estimates were that the 1957 pandemic caused some 2–3 million excess deaths, while the 1968–1969 pandemic caused about 1 million deaths, corresponding to 0·7 and 0·3 per 1000 respectively.[6,15,16]

Even today, it is difficult to assess the mortality impact of influenza. Some deaths are coded to influenza itself, and others are coded to pneumonia or other causes. However, during an influenza outbreak, there is usually an increase in all-cause deaths, over and above those that are coded to influenza and/or pneumonia.[15–17] Thus a common method of assessing the mortality impact of influenza is to count the total number of excess deaths that occur in an influenza pandemic or during the influenza season, compared with the non-influenza period.[7] For example, in the 1837 pandemic, mortality was increased two- to threefold in London over a 6 week period, corresponding to an approximate 18% increase in annual mortality. At that time, mean life expectancy was short (some 40 years), so by extrapolation, approximately 18% of 2·5% (roughly 4·5 per 1000) Londoners died during the 1837 pandemic. Only 15% of

these deaths (2·7% of annual deaths) were attributed to influenza.[1]

Table 1 presents estimates of the mortality impact of influenza for a number of historical and recent pandemics, and for seasonal influenza, using this total mortality method. Figures in the table are derived from a number of the publications cited in this text and from the authors' calculations based on publicly accessible data resources.

Virus evolution and selection

Virus evolution continues during a pandemic, or indeed during any influenza outbreak.[18,19] Emergence and persistence of novel variants will be more likely during a pandemic because the greater biomass of virus offers more opportunity for mutation and selection. One form of selection can occur in a partially immune host population, with antibody directed against epitopes of the infecting virus that were shared with a previously circulating virus. A virus with a random mutation in a relevant epitope may be better able to escape the relevant antibody; this will give the mutant virus a selective advantage over the original infecting virus. This process of 'antigenic drift' helps to explain how the transmissibility of a virus can increase in the early phases of an outbreak.[6,20] Moreover, as the population becomes progressively infected and immunized, selective pressure from antibody becomes more important, so that by the time an outbreak in a large population is declining, there is a greater chance that the viruses still being transmitted are drifted mutants.

Environmental factors and host behaviours can also exert selective pressures upon influenza virus. For example, if persons with the most severe symptoms are isolated at an early stage, or if people become more successful in avoiding contact with symptomatic persons, this may reduce the fitness and transmission of viral genes that contribute to more severe illness. This mechanism could help to explain how the severity of symptoms can decrease over the course of an influenza pandemic or outbreak. On the other hand, if it is difficult to avoid people with the most severe symptoms, there would be no negative selection against increasing virulence; as a consequence, any mutant that reproduces more rapidly will have a selective advantage, leading to a possible increase in virulence over time.

The apparent virulence of influenza can also change over time as a result of non-genetic mechanisms. For example, there is strong animal evidence to show that the severity of illness increases with the dose of the infecting virus,[21,22] presumably because this gives the virus a head-start in its battle with the immune defences of the infected individual. All the measures designed to reduce transmission (quarantine of cases, avoidance of crowds, hand-washing, face masks etc)[23–25] will also have the effect of reducing the viral dose, and the risk of severe illness, for those who eventually become infected.[26] Indeed, some people infected with a low dose of the virus are likely to be infected without developing symptoms, but still develop at least temporary immunity towards the new virus.[26] Contrariwise, if overcrowded living conditions and poor hygiene lead to larger doses of infecting virus, attack-rates and mortality rates are likely to increase.

Thus there are plausible mechanisms to explain how the severity of influenza could be changed over the course of an outbreak, both by the direct effects of host responses, both behavioural and immunological, and by their consequential selective effects on virus genotype. What is the empirical evidence? In the 1918–1919 pandemic, there was an early phase when the virus circulated in unremarkable fashion, with low mortality.[4,6,27] This changed most dramatically in August 1918, with high attack-rates and high mortality in military camps in the USA and on troop-ships, and in disembarkation camps in Europe.[4,5,28] This apparent increase in virulence was mirrored in the United Kingdom: mortality in the summer wave was low, but much higher in the autumn wave from September, and in the winter wave from December 1918.[29,30] The difficulties in implementing quarantine and case isolation with overcrowded military camps would have resulted in little negative selection to limit viral evolution towards increasing virulence. The evolution of high virulence mutants because of selective pressure in the military provides a very natural explanation for the emergence of our most virulent pandemic during the closing stages of WW1.

However it was also observed that some populations affected later in the pandemic had lower attack-rates and lesser mortality, suggesting that virulence had decreased. For example, mortality rates in Australia, first affected in January 1919,[10] were lower than in New Zealand, affected from October 1918.[11] Most dramatically, after Western Samoa was infected in November 1918, via a ship from New Zealand, some 20–30% of the population died. In contrast, because of strict quarantine, the virus did not reach nearby American Samoa until a year later, when its impact on mortality was negligible by comparison.[4]

Competition between viruses

In an immunologically naïve host population, competition between different influenza strains will depend solely on their rate of reproduction and spread. These characteristics are synthesized in the basic reproduction number (R_0), which is a measure of the number of secondary infections arising from a single index case in a fully susceptible population.[18,19,31] In a partially immune population, protection afforded by exposure to related strains will reduce the likelihood of spread of a given virus, reducing R_0 to the population-specific parameter $R_{effective}$. New antigenic variants, arising from antigenic drift, tend to replace their ancestor strains, at least in the next influenza season.[18,19,32] Detailed analysis of the phylogeny of influenza A suggests that there is considerable cross-immunity, albeit short-lived, between antigenic variants within a sub-type such as H1N1 or H3N2.[31] Even more compelling is the tendency for each new pandemic sub-type to replace the sub-type that was previously circulating as seasonal influenza.[6,18,19] For example, H2N2 replaced H1N1 in 1957, which was in turn replaced by H3N2 in 1968. H1N1 returned in 1977, and has since circulated with H3N2 as seasonal influenza, although in any one season only one or the other tends to dominate. These observations suggest that there is also immunologically mediated competition between influenza A viruses of different sub-types, again reflecting sharing of epitopes based on common ancestry.

Pandemic influenza is influenced by age and isolation

In the 1918–1919 pandemic, attack-rates were very high when the virus reached *isolated* Alaskan villages that were probably not exposed to seasonal influenza in the preceding years. Surprisingly, children survived, likely due to robust innate immune responses, while most of their parents and grandparents died.[4,9] The high death rate in adults was likely due to altered immune regulation, combined with an absence of antibody, which may have unfavourably

influenced the delicate balance between protection and pathogenesis.[9]

In contrast, the mortality pattern in *urbanized* populations in 1918–1919, was somewhat different, in that older adults (born before about 1890) had a lower death rate than younger adults,[4,6,27,29] arguably because they still had protective antibody from a related virus that had circulated prior to 1890, and then disappeared.[9,33] Furthermore, the influenza death rate at all ages in urbanized populations was much less than in those immunologically naïve Alaskan villages.[4,7,29]

An attack-rate of 96% was seen on the isolated island of Tristan da Cunha when the H3N2 virus first arrived in 1971, although only 1% died; the population had not been exposed to any form of influenza for 8 or 9 years.[34,35]

Explaining variations in pandemic attack-rates and mortality

Mortality from pandemic influenza in 1918–1919 varied dramatically from place to place; some of this mortality differential can be explained by poverty,[7] and some by isolation.[34,35] Other variation was not so easily explained. For example, there was wide variation between military camps,[28,29] and between ship-board outbreaks[5] in the proportion of cases that were fatal. Some of these differences could reflect genetic differences in the virulence of the infecting strain,[18,19] effects of inoculum dose, or different risks of complicating bacterial infection in different locations.[13]

As viral multiplication is likely greaters when immunity is less, the viral burden and transmitted dose would also be greater in isolated populations. If a higher dose contributed to a higher viral burden and to disease severity in the next infected host, as is seen in animal experiments,[21,22] this would also contribute to the higher case fatality in remote populations. Furthermore, with larger doses of virus, mutants could more easily by-pass the evolutionary bottleneck[18,19] involved in case-to-case transmission, raising the possibility of rapid evolution towards virulence in populations with low levels of immunity.

However, there are many clues to suggest that prior immunity played an important role in reducing pandemic attack-rates and mortality. For example, in the UK some persons sleeping in the same room or bed as a sick person remained symptom free.[29] Many people lived through all three waves of the 1918–1919 pandemic without reporting symptoms.[29] Preliminary results of work in progress suggest that the low attack-rates in 24 706 persons across the three waves may be explained by protection attributed to prior immunity, by many asymptomatic infections, and by the induction of more specific immunity after exposure to the pandemic virus. We also estimated a greater level of prior immunity in a local school population (Finchley Elementary School in London), than in the sequestered populations of two private boarding schools (Haileybury and Clifton College). Attack-rates were greater in the boarding schools (Mathews, JD, personal communication), as we previously reported for the Saffron Walden boarding school.[35] There are other supportive observations; for example, in US military camps, attack-rates when the pandemic virus arrived were greater amongst those recruits who had been in the camps for shorter periods of time,[29] suggesting that those in the camp for longer periods had been protected by prior exposure to (non-pandemic) influenza. On a different continent, the mortality rate from pandemic influenza in Spain decreased with population size of affected cities,[29] suggesting that cities of a larger size had been more regularly visited by seasonal influenza, and thus had higher levels of protective immunity when the pandemic virus arrived.

What happens after a pandemic?

After a pandemic, the virus subtype responsible, albeit changed by antigenic drift, tends to return annually to cause seasonal influenza in temperate zones.[6,18,19] Recent molecular evidence suggests that large populations in the tropics can serve as reservoirs of influenza infection throughout the year, with re-seeding of drifted viruses into populations at higher latitudes giving rise to outbreaks in the cooler months.[36,37] The seasonality of outbreaks is arguably determined by the time it takes for immunity induced by the last seasonal virus to wane (and for new susceptibles to be born), and for the drifted viruses to become sufficiently different to re-invade the population.[6,18,19,31,38] It also seems that influenza virus transmits more readily in cooler weather, possibly because people spend more time indoors. Some have postulated that the virus survives better in cool and drier air or when levels of ultraviolet radiation are less. Further, experience of symptomatic infection may be influenced by immuno-modulatory effects of climate, possibly mediated by UV light and/or vitamin D.[18,19,38–40]

However, the change from pandemic to seasonal (interpandemic) behaviour is by no means abrupt. For example, some pandemic features of the 1918–1919 virus, such as the characteristically greater mortality in young adults (Table 2) persisted into the 1920s, albeit with diminishing effect in later years. Similar patterns were observed after the 1957 and 1968 pandemics.[6,41]

Why is pandemic influenza different from seasonal influenza?

One part of the answer is straightforward – simply that pandemic viral strains are antigenically novel – because of an 'antigenic shift', involving the jump into the human

Table 2. Comparison between pandemic and seasonal (inter-pandemic) influenza

Characteristic	Pandemic	Seasonal
Onset	Any season	Colder months
Waves	Multiple waves	One wave each season
Attack-rate	High (20–60%)	Lower (5–30%)
Ages attacked	All ages	Children preferentially
Mortality rate	High (0·2–20%)	Low (0·003–0·03%)
Highest death rate	Young adults	Older persons

population of a virus containing gene segments from a different animal host.[6,18,19,41] For example, the H1N1 virus of 1918–1919 evolved from an earlier avian virus; evolutionary changes, involving transit through pigs, were apparently required in other viral genes to allow H1N1 to spread efficiently in human populations. Once this had happened, the H1N1 virus could cause devastating outbreaks in humans because there was little specific immunity against those H1N1 antigens,[6] and because the virus carried other gene segments conferring high virulence. However, the factors that allowed H1N1 to survive and evolve while it was adapting to human populations are not fully understood. As in the 1918 pandemic, the new H1N1 virus detected in 2009 in Mexico has inherited some of its gene segments from swine influenza; other genes have come from bird influenza and from an earlier human influenza, through a process known as gene re-assortment or shuffling.[42] This new virus is likely a single 'lucky' survivor of such a gene reshuffle, probably occurring in a pig coincidentally infected with influenza viruses from different species. Such re-assortments, although rare, tend to occur in places where there are large numbers of humans and animals in potential contact, as in Asia where most past pandemics originated,[1,6] and now it seems, Mexico.[42]

How does pandemic influenza kill people?

In 1918–1919, early deaths occurred within 1–4 days of infection; these were associated with rapid inflammation of the lung (viral pneumonia), cyanosis and acute respiratory failure.[14,27] It has been suggested that the inflammatory response[43] in the lung was triggered by influenza virus interacting with T-cells, macrophages and respiratory epithelium, in the absence of protective antibody. If the acute inflammation was less severe, complicating bacterial pneumonia could supervene to cause death later in the illness (e.g. from day 3 to 21). In the modern era, the severity of viral pneumonia would be reduced by early treatment with antivirals,[44] most cases of bacterial infection would be treated effectively by antibiotics, and many more cases of respi-

ratory failure would survive because of the availability of oxygen, respirators, and other supportive measures.

Explaining the differences between pandemic and seasonal influenza

Seasonal influenza occurs in the cooler months in temperate climates, affecting only a small minority of individuals in any one season; children are more often symptomatic than adults. Death is uncommon, but the risk of death by age in seasonal influenza is typically U-shaped.[6,41,45] Deaths in infants and young children are typically rare and arguably due to immunodeficiency of genetic origin, or to lack of antibody from the mother or from prior exposure.[6] During outbreaks of seasonal influenza, the risk of death from all causes rises with age amongst the elderly, presumably because of immuno-senescence.[46] Although pneumonia is a frequent terminal illness amongst the frail elderly, influenza is mentioned on the death certificate in only a minority.

In contrast to seasonal influenza, the 1918–1919 influenza pandemic was unusual, with out-of-season onset and multiple waves. The novelty of the H1N1 virus in 1918 could help to explain the out-of-season onset,[47] while the multiple waves, most clearly seen in well-demarcated summer, autumn and winter waves in England,[29] could be due to loss of short-term immunity or antigenic drift of the virus,[6,35] social distancing,[48] and/or seasonal effects.[6,38] In most urban populations, mortality rates from pandemic influenza were the greatest for young adults,[4,7,27] arguably because children were protected by innate immunity while older persons were protected by immunity to a related virus, previously circulating, which had disappeared by 1890.[9,33]

Summary

In terms of both morbidity and mortality, the impact of influenza A virus is highly variable over populations and regions, due to a complex and difficult to predict interplay between immunity resulting from past exposure, climate, age-susceptibiltiy and social well-being. With human swine-like H1N1 influenza rapidly spreading, and seemingly destined to be the source of the world's next pandemic, it is essential that we return to the historical record, to make informed decisions in international and national pandemic responses and be aware of the full spectrum of possibilities.

The 1918–1919 pandemic was remarkable for high mortality,[29,49] which was most marked in remote or isolated populations,[4,34,35,49] at least in part because prior immunity was lacking in places that had not been recently affected by any form of influenza. These observations provide a timely warning as countries around the world prepare for the

inevitable importation of the newly emergent human swine-like H1N1 strain. Attack-rates and severity of infection in one location cannot be assumed to predict behaviour of the virus in another time and place, as the susceptibility of host populations may vary, with both location and age-cohort effects observed.

We have further postulated that the selective pressures acting on the virus under different circumstances lead to a diversity in virulence and pathogenicity. For example, overcrowding, as seen in Alaskan huts in winter and army camps at the tail of World War 1, could have contributed to higher viral doses and thus to higher mortality.[4,27] While not currently displaying the high virulence characteristic of the 1918–1919 virus, we cannot discount the possibility that increasing virulence of human swine-like H1N1 influenza may occur. If we are correct in inferring an association between viral dose and virulence, strict attention to measures being proposed by governments to reduce ongoing transmission such as case isolation, antiviral therapy, quarantine of contacts and closure of schools and workplaces may help to select against severe disease over time.

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