How did the 2009 pandemic compare with previous pandemics?

John D Mathews

Vaccine and Immunisation
Research Group
Melbourne School of Population
Health, University of Melbourne
5th Floor 207 Bouverie St
Carlton, VIC 3053
Contact phone: 0411 021 013
Email: mathewsj@unimelb.edu.au

The pandemic spread of the novel H1N1 virus in 2009 was unusual in that the attack rates and mortality rates were often lower than in earlier pandemics[1-4]. However, most affected populations reported that morbidity and mortality were greater in younger adults than in children or older persons[1-5], reproducing the age distribution of earlier pandemics[6-10]. A small proportion of affected persons became so ill that they required intensive care or died. Aboriginality, pregnancy and obesity were risk factors for severe disease, but many patients requiring intensive care had no identifiable risk factors[1,5,11]. The pandemic features in 2009 can be explained, at least in part, in immunological terms[3,6-9,12-14]. As with earlier pandemics, older people were probably protected by specific antibodies resulting from exposure to a similar virus which last circulated when they were children[3,6,7,12]. In 2009, as in earlier pandemics, children were relatively protected against their first exposure to the new virus by the strength of their innate immune response[6], while many people of all ages were protected in whole or in part by short-lived, strain-transcending immunity resulting from their most recent exposure to seasonal influenza[9,13-15]. On this view, the individuals developing severe disease were those who were too young to be protected by specific high-avidity antibodies, too old to be well-protected by innate immunity, and unlucky enough to have missed out on recent exposures to seasonal influenza.

The behaviour of influenza, whether seasonal or pandemic, must be understood in terms of the ecological interplay between the virus characteristics, the population characteristics that determine opportunities for transmission, and levels of population susceptibility, determined principally by the history of prior exposure[8]. It is well known that seasonal influenza viruses circulate globally in partially immune populations and undergo antigenic drift as a result of immune selection pressures. In contrast, the appearance of new sub-types of influenza A, by antigenic shift, was responsible for pandemic behaviour as seen with the emergence of H1N1 in 1918, H2N2 in 1957 and H3N2 in 1968[6,8,10,15]. When a pandemic virus appeared, because of its antigenic novelty, it was able to spread rapidly in global populations which had little immune protection, causing higher rates of morbidity and mortality than seasonal influenza. Over subsequent years, as immunity to a pandemic virus accumulated in exposed populations, and as the virus itself changed, the pattern of infection was observed to change from pandemic to seasonal (Table 1).

The H1N1 virus that emerged in the Americas in April 2009[2,16] was characterised as a pandemic virus by WHO on the grounds of antigenic novelty as well as global and out-of-season spread[4] and in many ways its epidemiological behaviour was also typical of earlier pandemic viruses (Table 1). But there were also significant differences, most notably in the lower attack rate and the lower mortality in 2009. For example, only 10–20% were clinically affected in most populations, although significantly more were subsequently found to have seroconverted to the new virus[1-5]. Only 213 deaths have been directly attributable to

Table 1. Features of seasonal and pandemic influenza.

Feature	Seasonal influenza	Typical pandemic	H1N1 2009
Frequency	Usually annual	Sometimes multiple waves	Multiple waves
Cycle	Cooler months	Sometimes out-of-season onset	Out-of-season onset
Clinical attack rate	5–20%	10–70%	10–20%
Asymptomatic infection	Frequent	Less frequent	Frequent
Mortality	Low	Higher	Low
Age distribution	More deaths in elderly	More deaths in younger adults	More severe in younger adults

H1N1 2009 in Australia[17], many fewer than the excess deaths in older persons usually attributable to seasonal influenza each year[1,17]. Worldwide, the mortality from H1N1 2009 was also insignificant in comparison with the devastating pandemic of 1918–19, which killed between 0.2% and 2% of the population in most countries[18].

How do we explain the low aggregate mortality, the greater relative severity in younger adults, and the apparently limited spread of the 2009 virus? The explanation is likely to be immunological (Table 2). In particular, it seems that, as with most viral infections, children were protected from death in 2009 by innate immunity[6,8], whereas older persons were protected because of specific antibodies induced by exposure to a related H1N1 virus that had last circulated when they were children[2-8,12]. Furthermore, it is highly likely that many persons were not susceptible to infection with the 2009 H1N1 virus, because when it arrived they were protected by short-lived, strain-transcending immunity induced by recent exposure to seasonal influenza[8,9,13-15]. Indeed, in many populations, seasonal influenza strains were still circulating until driven out by H1N1 2009.

The final piece of the puzzle is to understand why it was that only a small minority of middle-aged adults became severely ill from H1N1 2009, even in the absence of risk factors such as obesity, Aboriginality and pregnancy[1,2,5,11]. Again the answer may be immunological. For such adults, innate immune responses would have been less active than in children, but they were too young to have specific immunological memory and protection dating from the last circulation of an H1N1 virus similar to that of 2009. A recent report[19] has suggested that low-avidity cross-reacting antibody to H1-2009 antigen, forming immune-complexes *in vivo*, could help to explain the severity of disease in a minority of middle-aged adults.

As in 1918-19[13,20], we suggest that young or middle-aged adults were most susceptible to severe infection if they also lacked the short-lived, strain-transcending immune protection that would have been boosted by recent prior exposure to seasonal influenza. In other words, those with the most severe infections in 2009 were likely to be younger adults who by chance had escaped recent infections with seasonal influenza. This conjecture is quantitatively plausible, in the light of modelling that indicates a half-life of serological protection against seasonal influenza of perhaps four–eight years[21], and data from the island of Tristan da Cunha, suggesting a very high degree of susceptibility to influenza following isolation for a period of at least nine years[8,9,22]. Indeed, it seems possible that the lesser severity of H1N1 2009, particularly when compared with 1918–19, is partly due to the increasing connectedness of the modern world, which helps to ensure that most people are regularly exposed to seasonal influenza, and hence partly protected, perhaps even against a novel pandemic strain.

The effect of seasonal influenza vaccines in modifying the human response to H1N1 2009 infection is still controversial. Some reports have suggested that pandemic symptoms were more frequent in persons previously vaccinated against seasonal strains of H1N1 and H3N2[23]. Such an effect was predicted earlier[9], on the grounds that by preventing infection with seasonal virus, seasonal vaccine could also prevent the induction of strain-transcending immune protection against any new virus.

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Biography

John D Mathews is an epidemiologist and professorial fellow in the School of Population Health at the University of Melbourne. He was foundation director of the Menzies School of Health Research in Darwin (1984–1999), and senior adviser in population health to the Australian government in the Department of Health and Ageing (1999–2004).

Table 2. Overview of protective immune mechanisms following human influenza infection[13].

Category	Duration of effectiveness	Suggested mechanisms	Antigenic specificity	Importance
Innate immunity	Days[a]	Interferons, other cytokines & cellular responses	Very low	Early defence & viral clearance
Temporary strain-transcending immunity	Months[b]	? IgM or IgG or IgA antibody ? Cytotoxic T cells	Broad specificity e.g. to B-cell or T-cell epitopes shared between different sub-types & strains	Broad protection for the host; mediates competition between viral strains
Longer-lived immunity	Years[c]	B-cell-dependent IgG and IgA antibody, particularly to specific HA epitopes of the infecting strain	High antigenic specificity	More permanent strain-specific protection

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Footnotes

a The occurrence of second infections after a mean latency of 12 days (95% confidence interval 9–17 days) suggests[9] that the innate response clearing the first infection is switching off once viral clearance has occurred – typically by seven days in most influenza infections.

b See Table 3 for various estimates of the mean duration of strain-transcending temporary immunity.

c After full recovery from influenza, it is usually at least several years before the same serotype is able to cause a repeat episode of symptomatic influenza. The interval between repeat attacks can be shorter in children, suggesting that longer-lived immunity is incremental – that is to say, that it may depend on repeated exposures. Modelling studies[9, 21] suggest that longer-lived immunity has an average duration of perhaps 4–8 years, although in certain circumstances it may be life-long.

d Although their model helps to explain the slow rate of evolution of influenza A, the authors did not report confidence intervals for their estimate.

Table 3. Estimates of the mean duration (95% credibility intervals) for strain-transcending temporary immunity.

Estimate (days)	Basis of estimate	Authors
187[d]	Arbitrary (six-month) duration to explain restricted rates of infection for a novel strain following earlier infection with wild-type strain	Ferguson *et al.* (2003)
68 (56–95)	MCMC-based estimate from modelling of symptomatic influenza in air-force personnel in the 1918–19 pandemic	Mathews *et al.* (2007)
67 (36–135)	MCMC-based estimate from modelling of symptomatic influenza amongst English schoolchildren in the 1918–19 pandemic	Mathews *et al.* (2010)
130(64–219)	MCMC-based estimate from modelling of symptomatic influenza amongst predominantly adult populations in the 1918–19 pandemic in England.	Mathews *et al.* (2010)
125(101–158)	MCMC-based estimate from modelling of Slepushkin data using methods similar to those in Mathews *et al.* (2010).	Mathews (in prep.)