

# Pandemic Influenza – Prevention and Treatment

## Past, Present and Future

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Influenza is a contagious respiratory tract infection caused by one of three influenza viruses: A, B and C. Influenza C causes mild infections in infants and young children, which may confer life-long immunity since cases in adults are rare and usually asymptomatic, whilst influenza A and B cause seasonal epidemics in people of all ages. Influenza B and C are virtually restricted to humans and, although both have been isolated from other mammals, there does not seem to be a natural animal reservoir of infection.<sup>[1]</sup> In contrast, influenza A can infect a range of avian and mammalian hosts, the key animal reservoir being migrating waterfowl. Although both A and B viruses can be responsible for the annual winter epidemics of influenza ('seasonal flu') that occur around the world, only influenza A has the potential to give rise to global pandemic disease.<sup>[2]</sup>

Influenza viruses possess two surface membrane glycoproteins, haemagglutinin (HA) and neuraminidase (NA), capable of eliciting antibody responses in the host. The B virus possesses only one HA and NA subtype, and evolves slowly and steadily, whereas the A type can possess any of 15 HA and 9 NA subtypes; mutations in these surface glycoproteins ('antigenic drift') can give rise to new viral strains to which the population has no, or reduced, immunity. Reassortment of genes between different viral strains can take place when viruses from different host species (e.g. human, avian) co-infect another host (e.g. pig) producing an antigenically novel influenza virus with the potential to cause global pandemics ('antigenic shift').<sup>[2,3]</sup>

Influenza has been a global health problem for centuries.<sup>[4]</sup> Three influenza pandemics occurred during the 20th century: the 'Spanish flu' in 1918–9 (H1N1 subtype); the 'Asian flu' in 1957 (H2N2 subtype); and the 'Hong Kong flu' in 1968 (H3N2 subtype). We are currently (January 2010) in the throes of a further global pandemic, 'swine flu' (H1N1, a linear descendant of the 1918 virus).<sup>[5]</sup>

From the British point of view, influenza has always been thought to originate in 'The East': a caricature from 1803 shows 'Mr Influenzy' wearing a French cockade; an outbreak in 1889–90 was called 'Russian influenza'; the 1918 pandemic was labelled 'Spanish'; while more recent pandemics have been

attributed to 'Asia' and 'Hong Kong'. Recent work has confirmed that seasonal influenza does indeed originate in East and South-East Asia, spreading to Europe and North America within 6–9 months and terminating in South America.<sup>[6]</sup> (An alternative hypothesis, propounded by astronomer Sir Fred Hoyle,<sup>[7]</sup> proposed that influenza viruses arrive regularly from outer space and are dispersed around the globe by meteorological phenomena. This theory failed to explain how the viruses arrived on Earth fully adapted to infect avian and mammalian cells.)

Influenza can range in severity from asymptomatic, to a mild 'common cold', to a severe systemic illness. The virus binds to receptors in the human airway;<sup>[8]</sup> replication leading to necrosis of ciliated epithelium<sup>[9]</sup> (with consequent impairment of mucociliary clearance) and release of proinflammatory cytokines,<sup>[10]</sup> which are responsible for the systemic features such as fever and muscle aches.<sup>[11]</sup> Respiratory viruses including influenza are recognized triggers for exacerbations of asthma and chronic obstructive pulmonary disease<sup>[12]</sup> and may also be associated with increased cardiovascular morbidity and mortality.<sup>[13]</sup> Myocarditis, usually asymptomatic, can occur. Infection can affect mental performance<sup>[14]</sup> and, very rarely, encephalopathy can develop.<sup>[15]</sup> Pneumonia is usually a complication in the relatively immunocompromised (including the very young and the elderly) and those with pre-existing lung disease. It can be a true viral pneumonia but is often due to bacterial superinfection, commonly with *Staphylococcus aureus*, *Haemophilus influenzae* or streptococcus species (*Streptococcus pneumoniae* and  $\beta$ -haemolytic streptococci).<sup>[16]</sup> There is evidence that influenza infection can impair innate host defences apart from mucociliary clearance, both during the presence of virus and for some weeks after the infection.<sup>[17]</sup> All-cause mortality is increased during both seasonal epidemics and global pandemics.

### 1. Recent Pandemics

The 1918 pandemic, caused by an H1N1 virus, started at the end of the First World War. It has been suggested that the virus

may have originated in a large British army base in France as early as 1916, and not been widely dispersed until the time of general demobilization in 1918.<sup>[18]</sup> It is estimated to have affected one-third of the world's population, killing some 50 million people and depressing world population growth for a decade; unusually for influenza, it killed large numbers of previously healthy young adults, as well as the very young and old.<sup>[19]</sup> In the UK, 225 000 civilians and 30 000 troops died from influenza, and in Europe, as a whole, it is estimated that the pandemic caused 2.64 million excess deaths.<sup>[20]</sup> It may also have had longer-lasting health repercussions. Following on from the pandemic there was a smaller epidemic of a disorder causing Parkinsonian symptoms, which was termed Encephalitis lethargica, and thought possibly to be secondary to influenzal encephalitis, though this has never been proven.<sup>[21]</sup> More recently, it has been shown that men who were *in utero* during the peak of the pandemic are at increased risk of cardiac disease (both ischaemic and hypertensive) in their 60s–80s.<sup>[22]</sup>

In the late 1990s, both John Oxford in the UK and Jeffery Taubenberger in the US attempted to recover the original 1918 virus from preserved lung tissue in pathology collections and from the bodies of influenza victims buried in permafrost regions.<sup>[18]</sup> Eventually, Taubenberger was able to reconstruct the 1918 viral genome and showed that mice infected with the reconstructed virus exhibited exaggerated activation of pro-inflammatory and cell-death pathways compared with mice infected with contemporary human influenza A virus.<sup>[23]</sup> Macaque monkeys also showed marked rises in cytokines such as interleukin-6, but paradoxically reduced (protective) interferon responses,<sup>[24]</sup> suggesting that aberrant host defence responses may have been important factors in the high mortality caused by the 'Spanish flu'.

It is worth pointing out that at the time of the 1918 pandemic the causative organism of influenza had not been identified; it was thought to be due to infection with 'Pfeiffer's bacillus' (*H. influenzae*). There is a delightful contemporary account of attempts to induce influenza in healthy volunteers, first by instilling *H. influenzae* intranasally and, subsequently, by administering mucous secretions from cases of influenza via the same route. Eventually, intravenous injections of blood taken from influenza patients were given to the volunteers, who were finally induced to sit in front of influenza patients while they exhaled and coughed in their faces. Amazingly, not one of the 100 volunteers developed influenza – although one of the investigators did!<sup>[25]</sup> Influenza A virus was finally isolated and identified at the UK National Institute of Medical Research in 1933; influenza B was identified in 1940.

In 1957, the next pandemic began in the Far East ('Asian flu'), the virus (H2N2) being isolated in Singapore in February

and Hong Kong in April, and rapidly spread worldwide. Fortunately, the excess mortality was small compared with that seen in the 1918 pandemic, although some cases of fulminant disease were reported in young adults, particularly during pregnancy.<sup>[26]</sup> Histopathology of the lungs of fatal cases was similar to that seen in 1918, and about two-thirds had bacterial superinfection, the great majority with *S. aureus*.<sup>[27]</sup>

The last 20th century pandemic, the 'Hong Kong flu', started in 1968 with the emergence of an H3N2 virus, which also caused milder epidemics in 1970 and 1972. Overall, the excess mortality due to this strain was about half that seen during the 1957 pandemic, possibly because the N2 neuraminidase common to both viruses produced a degree of cross-immunity.<sup>[26]</sup>

## 2. The Pandemic that Hasn't Occurred Yet: 'Bird Flu'

Aquatic birds form the largest natural reservoir of influenza A viruses, including all the HA and NA variants. Until 1997, human infection with avian viruses was very rare, and was usually caused by an H7N7 subtype predominantly causing conjunctivitis, but in that year an epidemic of avian influenza (H5N1 subtype) affected poultry stocks in Hong Kong. Eighteen human cases were diagnosed, of whom six died – an extremely high death rate. Prompt action by the local authorities, who had 1.5 million poultry slaughtered throughout Hong Kong, halted the outbreak.<sup>[28]</sup> Three further cases, two fatal, occurred in a Hong Kong family in 2003, following close contact with chickens on a visit to Fujian province in China.<sup>[29]</sup> Since then, large-scale infection of wild and domesticated birds has been reported across Asia, with several hundred cases of human infection. The death rate overall has been 61%, mainly in young adults; older subjects seem to have some baseline immunity.<sup>[30]</sup> As with the 1918 virus, patients seem to show exaggerated cytokine responses<sup>[31]</sup> but, in addition, the virus appears to be relatively resistant to the antiviral effects of interferons and tumour necrosis factor.<sup>[32]</sup> Fortunately, infection seems to be due to direct avian-human transmission; human-to-human transmission appears to be very rare,<sup>[33]</sup> which has limited the risks of a pandemic so far. However, migrating birds have spread avian infection widely (it has also been detected in cats and pigs<sup>[34]</sup>), and there is still a risk that mutation could give rise to a far more readily transmitted infection with potentially devastating consequences for mankind. Endangered animals are also at risk; apart from the threat to wildfowl, H5N1 influenza has the potential to infect and kill (amongst others) falcons, buzzards, tigers, leopards, civets and seals.<sup>[35]</sup>

Meanwhile, the avian H7N7 subtype is still prevalent and caused a major outbreak of disease in poultry in the

Netherlands in 2003; there were 89 confirmed human cases, with one death.<sup>[36]</sup>

### 3. The Current Swine Flu Pandemic

Despite the dictum that influenza epidemics originate in China and end in South America,<sup>[6]</sup> the swine flu epidemic started in Mexico in March 2009 and spread both north and south. By May, cases had been reported as far afield as the UK, Australia and China: in June, the WHO declared a pandemic. By September, 296 471 cases had been reported from all six WHO regions, with 3486 (1.2%) deaths.<sup>[37]</sup> The causative virus was identified as an H1N1 subtype of swine origin.<sup>[38]</sup> As in previous pandemics, incidence was shifted from the elderly to younger adults. Cross-reactive antibodies have been demonstrated in 34% of adults born before 1950, presumably due to previous exposure to H1N1 viruses, which circulated widely prior to 1957.<sup>[39]</sup> Symptoms of infection are typical of mild-to-moderate influenza, although gastrointestinal effects (nausea, abdominal pain and diarrhoea) seem more common than usual. Despite initial suggestions of high mortality rates in South America, overall mortality worldwide now appears to be <1%. As usual, patients with chronic underlying disease (including asthma) or immunosuppression are most at risk. Infection during pregnancy seems to pose a particular hazard, 11 of 34 cases in one report requiring hospitalization, of whom 6 died.<sup>[40]</sup> In fatal cases, there is again evidence of aberrant host defence responses<sup>[41]</sup> and bacterial pneumonia (mainly *S. pneumoniae*).<sup>[42]</sup>

Governments worldwide implemented pandemic influenza preparations (put in place primarily against a putative 'bird flu' pandemic), ordering stocks of antiviral agents (mainly oseltamivir) and specific vaccines. Most countries have now experienced a 'second wave' of infection, which, thankfully, has been relatively mild. At the time of writing (January 2010) it seems that the present pandemic will be classified with those of 1957 and 1968, rather than that of 1918, but there is still time to be proven wrong.

### 4. Prophylaxis and Treatment of Influenza Pandemics

During the 1918 pandemic the population was advised to limit exposure to contagion by avoiding unnecessary contact with outsiders such as workmen and washerwomen, unventilated public transport and enclosed spaces of public entertainment. 'Influenza masks' (some made by former manufacturers of First World War poison gas respirators) were popular, as were fumigants such as carbolic acid vaporized by means of a Vapo-Cresolene or Clarke's Fairy Inhaler. Patients

were advised to take a nourishing and stimulating diet (including alcohol) and antipyretics such as quinine or salicin.<sup>[43]</sup> Other widely promoted commercial remedies were the Carbolic Smoke Ball (subject of a landmark court case<sup>[44]</sup>) and 'Cigars de Joy' (tobacco was considered antiseptic; but they also contained arsenic).

A recent review<sup>[45]</sup> confirmed that simple physical measures, including frequent handwashing, wearing masks and gloves, and probably social distancing, can be highly effective in preventing the spread of epidemic respiratory viruses.

First attempts at vaccination against influenza were made (with live cultured virus) in 1937 and continued throughout the Second World War. An effective vaccine against 'Asian flu' was reported in 1958. Current practice is for manufacturers to produce supplies of vaccine annually, directed against the predicted strains of virus. However, this strategy fails when a major antigenic shift occurs. It is to the manufacturers' credit that four different vaccines (both live and attenuated) against the H1N1 swine flu were approved by the US FDA within 6 months of the start of the current pandemic. Three of these are given by injection, one as a nasal spray.<sup>[46]</sup> The sublingual route of administration has also shown potential in a mouse model.<sup>[47]</sup> Initially, it was thought that two doses of vaccine would be required to confer full protection, but it has now been shown that a single dose is sufficient.<sup>[48]</sup> It has also been demonstrated that some cross-protection against swine flu is given by the existing 2008–9 seasonal flu vaccine.<sup>[48]</sup> Unfortunately, the public continue to be wary of flu vaccines, prompted by personal experiences of mild 'flu-like' reactions and also by events such as the 1976 swine flu debacle, when 43 million Americans were vaccinated against an anticipated swine flu pandemic that failed to materialize; there were numerous reports of ensuing Guillain-Barré syndrome, although this was never definitively linked to the vaccine.

Vaccines against the H5N1 bird flu (for both human<sup>[49]</sup> and avian<sup>[50]</sup> use) have been developed and tested.

The anti-influenza activity of amantadine was first reported in 1964; both amantadine and rimantadine have been shown to be effective in prophylaxis and treatment of influenza A infection (but not of influenza B, which lacks the M2 protein, which is the target of the adamantane drugs). Unfortunately, resistance to both drugs develops rapidly during their use.<sup>[51]</sup> Although most strains of seasonal H1N1 influenza A remain sensitive, seasonal H3N2 and, more importantly, H1N1 swine flu are resistant.

The alternative anti-influenza agents are the neuraminidase inhibitors oseltamivir (given orally) and zanamivir (given by inhalation). Although some strains of seasonal influenza have

developed resistance to oseltamivir<sup>[52]</sup> (but not zanamivir), H1N1 swine flu was initially fully sensitive to both agents, although cases of oseltamivir resistance have subsequently been reported.<sup>[53]</sup> Recently, the FDA approved the investigational intravenous neuraminidase inhibitor peramivir<sup>[54]</sup> for emergency use in certain critically ill swine flu patients.<sup>[55]</sup>

## 5. Discussion

In a review article in 2004, following the Severe Acute Respiratory Syndrome (SARS) epidemic, I wrote: "It is very likely that in the next 5 years we will experience another major epidemic, or even pandemic, due to a respiratory viral pathogen."<sup>[56]</sup> At the time, the likely candidates seemed to be the H5N1 avian flu or some unexpected new pathogen like the SARS virus. In the event (and right on time), the world endured an influenza pandemic caused by a well known viral subtype, H1N1. Fortunately (to date), this has proved to be relatively mild; we may not be so lucky next time.

Avian influenza viruses continue to pose a major potential threat.<sup>[57]</sup> Once they infect humans, they can cause a high mortality that is currently limited only by very inefficient person-to-person transmission. However, the conditions for further mutation, re-assortment and transmission of avian viruses persist in the Far East, with domestic poultry being kept in close proximity to humans and live animal markets ('wet markets') providing a ready source of potential pathogens.<sup>[58]</sup> There is also the possibility of bioterrorism involving an influenza virus,<sup>[59]</sup> a possibility that is not so remote now that we have witnessed the complete reconstruction of the 1918 pandemic virus genome.<sup>[60]</sup>

The world has the capacity to produce specific vaccines against novel influenza viruses in about 6 months. However, just three pharmaceutical companies (GlaxoSmithKline, sanofi-aventis and Novartis) account for most of the world's manufacturing capacity. Even if this were turned over fully to producing the new pandemic vaccine, it would not nearly suffice to vaccinate the global population at risk; access to vaccination would probably be determined by the wealth of a country rather than its need.<sup>[61]</sup>

With regard to antiviral agents, we currently have only the adamantanes and the neuraminidase inhibitors. Resistance to the adamantanes and a few cases of oseltamivir resistance have been seen during the current H1N1 pandemic. Perhaps more worryingly, resistance to adamantanes and oseltamivir has also been reported with the avian H5N1 virus.<sup>[57]</sup> In the case of the adamantanes this may have developed due to widespread use of

amantadine by Chinese farmers to prevent avian flu in poultry.<sup>[62]</sup> The efficacy of the neuraminidase inhibitors was recently brought into question in one of the odder episodes of the current pandemic, when the *British Medical Journal* devoted most of an issue to an attack on the manufacturer of oseltamivir, Roche, for failing to release complete clinical trials data to independent researchers who were attempting to write a systematic review of the efficacy of neuraminidase inhibitors.<sup>[63]</sup> They published their (restricted) findings anyway,<sup>[64]</sup> which told us nothing we didn't know already – that neuraminidase inhibitors only shorten the duration of seasonal flu by about 1 day or less,<sup>[65]</sup> and that we do not have sufficient data yet to know how effective they are against pandemic influenza. There have also been recent concerns about the safety of oseltamivir in children and adolescents, with reports of abnormal behaviour and confusion.<sup>[66]</sup> Novel drug targets in the influenza A virus have been identified<sup>[67,68]</sup> and new drugs are under investigation. It has also been reported that combination therapy with amantadine, oseltamivir and the broad-spectrum antiviral ribavirin<sup>[69]</sup> may have synergistic action against influenza virus resistant to amantadine or oseltamivir.<sup>[70]</sup>

One should also bear in mind that deaths from pandemic influenza may be due to an exaggerated cytokine cascade or to bacterial superinfection, rather than the viral infection *per se*. Unlike 1918, we now have highly effective antibacterials available to us; we also have an array of anti-inflammatory and immunomodulatory agents<sup>[71]</sup> including statins, which have shown protective effects in patients hospitalized during the 2007–8 flu season.<sup>[72]</sup> In addition, we have the availability of intensive care and cardiopulmonary support. All these factors suggest that the 1918 influenza mortality rates should not be duplicated in future pandemics. Nonetheless, it is worth noting that it has recently been estimated that the economic impact of severe pandemic influenza in the UK could equal the drop in gross domestic product experienced during the current recession.<sup>[73]</sup>

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