

COMMENT

Influenza

TH Pennington

The big influenza question is, “When will the next pandemic start?” The answer is, “Nobody knows.” It is a question that belongs to a category defined as “trans-science”¹ – scientific questions of fact that can be stated in the language of science, but which are unanswerable by it; they transcend science. The concept was invented by the nuclear scientist Alvin Weinberg. An example he quoted was the impossibility of determining the probability of the occurrence of a devastating earthquake destroying the Hoover Dam – in other words predicting the occurrence of an extremely improbable event.

Influenza viruses are circulating all the time in humans and birds; it is reasonable to suppose that millions of individuals are infected every year worldwide. Yet human pandemics are exceedingly uncommon. Only five have occurred since 1889 (Table I) and one of them, in 1977, had features suggesting a laboratory escape of a virus rather than a natural event. So predicting the next one is like trying to tell when a major earthquake will occur in an area where they are very rare. Compounding the difficulty for influenza is that we can be as certain as we can be that the next pandemic virus will be the product of evolutionary processes, like mutation, which are by definition unpredictable because they are random events.

But being unable to predict the timing of the next pandemic does not mean that we should not be making plans to deal with it. To fail to do this would be like a householder saying that because it is impossible to predict when they will be burgled or flooded, taking out insurance is unnecessary. How much money should be spent on preventive measures is a trade-off between the improbability of the event and its consequences. For influenza the reference point is still 1918.² The official report concluded “that the mortality in England and Wales, as a whole, attributable directly or indirectly, to influenza, is without any precedent or magnitude” and “that the toll taken at the young adult ages of life is without any known West European or North American precedent”. It was the same in Scotland. The pandemic occurred in three waves. In June 1918 there were many cases but little mortality. Patients were suddenly and severely stricken but recovered quickly. However, the outbreaks in autumn (October) 1918 and spring (February) 1919 had high mortalities from pulmonary complications, with the “dreaded heliotrope cyanosis”. The clinical impression at the time was that in the second and third waves 20% of cases developed pulmonary complications, 8% being fatal. 95% of those with heliotrope cyanosis died.

Whether the next pandemic virus will have the same virulence as the one that caused the second and third waves in 1918 and 1919 is also a trans-scientific question. But even if it does not, its impact on society is likely to be severe because of the large numbers of individuals who will be simultaneously incapacitated by illness. The 1889-92 pandemic was of lower virulence (although this increased its second and subsequent waves). But it showed other properties typical of influenza. In Germany, for example, it spread rapidly across the country, lurking for a short time in Danzig in the east in October before becoming common everywhere by early and mid-December.³ Clinically, its sudden onset led to its description as “Blitzcatarrh.”

Since the discovery of the human influenza virus in London in 1933 much knowledge has accumulated about its structure, its growth in cells, its genetics, its epidemiology and its immunology. It is clear that the haemagglutinin (H) surface protein plays a key role in the early events in infection at the cellular level, as a determinant of host range and virulence, and as an antigen that stimulates protective immunity. But it does not act alone in any of these activities. Other virus gene products are involved. A dramatic demonstration of this has come from studies on the virulence of a strain reconstructed using 1918 virus genomic RNA from formalin-fixed lung autopsy material and frozen unfixed lung tissues from an Alaskan influenza victim buried in permafrost.⁴ Comparing it with recombinant viruses expressing one or more of the eight 1918 genes showed that both the haemagglutinin and polymerase genes were essential for optimal virulence (it killed mice rapidly and caused the same pulmonary pathology in them as in humans in 1918 – acute pulmonary oedema and/or haemorrhage with acute bronchiolitis and alveolitis); it was concluded that the constellation of all 1918 genes together made an exceptionally virulent virus. But testing routine clinical virus isolates in mice is not a practical proposition. There is no simple in-vitro laboratory test for virulence.

Current influenza pandemic planning round the world has been driven by the H5N1 epizootic in Asia, Europe and the Near East and Africa and the occurrence of sporadic human infections resulting from direct contact with infected poultry and/or wild birds. The first H5N1 virus was isolated from poultry in Scotland in 1959. It remained in essence a veterinary curiosity until 1997, when in March it started killing poultry in rural chicken farms in Hong Kong. It had evolved into a high pathogenicity strain. Unprecedented for avian influenza, it also infected humans; by late December 18 had fallen ill. Six died. The virus was eradicated in Hong Kong by the end of the year. It came back in 2003. By mid 2007 318 laboratory confirmed cases and 192 deaths had been recorded, most of them in Indonesia (81 deaths), Vietnam (42 deaths), Thailand (17 deaths), China (16 deaths) and Egypt (15 deaths).

Will H5N1 turn into the next pandemic virus? If it does, will it retain its 60% mortality? Again, these are trans-scientific questions. There are some comfort factors. There is no evidence (yet) of genetic reassortment with human viruses, and no evidence of greater transmissibility to or among humans has been found over the years. And all previous pandemics have been caused by H1, H2 or H3 viruses only; maybe H5 (and H7 and H9 which have also caused human infections on a small scale) has properties which prevent it becoming part of a pandemic virus. But the proof of these questions lies only in events yet to come.

The best policy for influenza is to hope for the best, but prepare for the worst. The current planners must be congratulated on their thoroughness (the Pandemic Plans can be accessed on Department of Health websites). But they have a difficult task. How effective will oseltamivir be? (It has never been used in a pandemic, so it is not possible to say). Will there be better

vaccines by the time the pandemic starts? (The immunogenicity of vaccines is relatively poor and has not significantly improved in the last half-century). Surveillance has been co-ordinated by the World Health Organisation since 1947 (but the overwhelming majority of influenza cases never have a virological laboratory confirmed diagnosis). And lurking at the back of at least some policymakers' minds must be the 1976 U.S. swine flu fiasco, subsequently written up as an example of how not to implement a control programme for a slippery disease.⁵ In February 1976 a US Army recruit at Fort Dix, New Jersey, died after a forced march. Influenza H1N1 of the swine subtype was isolated from him. Because swine influenza had been common in the US in 1919 it had been hypothesised that it was the precursor of the 1918-19 virus. Ten years had elapsed since the last pandemic; in 1976 there was a consensus that pandemics occurred every decade. So was the Fort Dix virus the harbinger of the next one? The experts thought it more than likely. Vaccine preparation started immediately. A memorandum went to the President in mid-March. On 24th March a "Blue Ribbon Panel" of experts met with him in the Cabinet room next to the Oval Office. A vaccination programme costing \$135M was authorised. It started in October. It was suggested that a possible complication might be the Guillain-Barré syndrome. A few cases (out of tens of millions of vaccinees) were found, and the programme was suspended on 16th December. There was no pandemic. We know now that swine flu was not the precursor of the 1918-19 virus, and that on rare occasions it can infect humans but not spread further. And thirty years have passed since the last pandemic; the ten year hypothesis was wrong.

Those who analysed the fiasco concluded that important causes were the insufficient attention paid to quantitative risk assessment and to managing television output. Easy to say, but almost impossible to do. I am glad I am not a policy maker!

References

1. Weinberg, AM Science and trans-science. *Minerva* 1972; 10; 209-222.
2. Great Britain. Ministry of Health. Report on the Pandemic of Influenza 1918-1919. (Reports on Public Health and Medical Subjects; no 4). London: HMSO, 1920.
3. Friedrich, PL Die Influenza-Epidemie des Winters 1889-90 im Deutschen Reiche. *Arbeiten aus dem kaiserlichen Gesundheitsamte* 1891; 9: 139-378.
4. Tumpey, TM, Basler CF, Aguilar PV Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science* 2005; 310; 77-80.
5. Neustadt, RE, Fineberg, HV The Epidemic That Never Was. Policy-making and the Swine Flu Affair. New York: Vintage Books, 1983.

Table 1

Influenza Pandemics in humans

Year	Colloquial Name (subtype)	Source	Impact
1889	- (?)	Unknown	Pandemic with waves
1918	Spanish flu (H1N1)	Emergence of a mutated H1N1 virus from an avian host	Pandemic, 40 million deaths globally
1957	Asian flu (H2N2)	Possible mixed infection of an animal with human H1N1 and avian H2N2 virus strains in Asia	Pandemic, H1N1 virus disappeared
1968	Hong Kong flu (H3N2)	High probability of mixed infection of an animal with human H2N2 and avian H3Nx virus strains in Asia	Pandemic, H2N2 virus disappeared
1977	Russian flu (H1N1)	Source unknown; virus is almost identical to human epidemic strains from 1950. Reappearance detected simultaneously in China and Siberia	Benign pandemic, primarily involving persons born after the 1950s. H1N1 virus has co-circulated with H3N2 virus in humans since 1977