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Pandemic influenza – including a risk assessment of H5N1

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Summary

Influenza pandemics and epidemics have apparently occurred since at least the Middle Ages. When pandemics appear, 50% or more of an affected population can be infected in a single year, and the number of deaths caused by influenza can dramatically exceed what is normally expected. Since 1500, there appear to have been 13 or more influenza pandemics. In the past 120 years there were undoubted pandemics in 1889, 1918, 1957, 1968, and 1977. Although most experts believe we will face another influenza pandemic, it is impossible to predict when it will appear, where it will originate, or how severe it will be. Nor is there agreement about the subtype of influenza virus most likely to cause the next pandemic. The continuing spread of H5N1 highly pathogenic avian influenza viruses has heightened interest in pandemic prediction. Despite uncertainties in the historical record of the pre-virology era, study of previous pandemics may help guide future pandemic planning and lead to a better understanding of the complex ecobiology underlying the formation of pandemic strains of influenza A viruses.

Keywords

Epidemiology; History; Influenza A virus; Pandemic

Introduction

Major influenza epidemics have apparently occurred since at least the Middle Ages, if not since ancient times (24). In addition to periodic, seasonal, and regional epidemics, there have also been occasional influenza pandemics (9,67). When pandemics appear, 50% or more of an affected population can be infected in a single year, and the number of deaths caused by influenza can dramatically exceed what is normally expected (2,60). Since 1500, there appear to have been 13 or more influenza pandemics (see ‘Past influenza pandemics’, below); in the past 120 years there were undoubted pandemics in 1889, 1918, 1957, 1968 and 1977 (47). In 1918, the worst pandemic in recorded history caused approximately 546,000 excess deaths in the United States (675,000 total deaths) (67) and killed up to 50 million people worldwide (26).

Although most experts believe that we will face another influenza pandemic, it is impossible to predict when it will appear, where it will originate, or how severe it will be. Nor is there agreement about the subtype of influenza virus most likely to cause the next pandemic. The continuing spread of H5N1 highly pathogenic avian influenza (HPAI) viruses into poultry populations on several continents, associated with a growing number of human ‘spill-over’

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infections, has heightened interest in pandemic prediction (21,73). H5N1 HPAI viruses caused an epizootic in poultry in southern China in 1996, followed within a year by an epizootic in Hong Kong that produced 18 human 'spill-over' cases and six deaths. H5N1 strains continued to circulate thereafter in China, reappearing in epizootic form in 2003, and spreading widely thereafter. Geographical extension was accompanied by the appearance and spread of genetically and antigenically different strains of H5N1 HPAI (4,5). Since 2003, dispersion of H5N1 viruses has led to epizootics in about 60 countries on three continents, and has caused 403 human cases and 254 deaths (as of 27 January 2009) (80), millions of avian deaths, and infections and deaths in several other mammalian species (77).

Despite uncertainties in the historical record of the previrology era, the study of previous pandemics may help to guide future pandemic planning and lead to a better understanding of the complex ecobiology that underlies the formation of pandemic strains of influenza A viruses. However, there has long been disagreement about which historical outbreaks were *bona fide* influenza pandemics and which were not. Before discussing past pandemics, we will present definitions and suggest criteria for categorising an historical event as an influenza pandemic.

Definitions

The Merriam-Webster Online Dictionary defines a pandemic as an 'outbreak of a disease ... occurring over a wide geographic area and affecting an exceptionally high proportion of the population' (http://www.merriam-webster.com/). In public health practice, it has become traditional to require at least that the pandemic disease in question spreads over a distinct geographical region of the world (e.g. the Caribbean), if not a continent, a hemisphere, or the entire globe. When speaking of animal diseases, the corresponding nouns/adjectives are 'epizootic' and 'panzootic'. That the most highly explosive and highly fatal epidemics of influenza-like illnesses occurring over the past 500 years have usually featured global spread within a few years has led to the expectation that influenza pandemics must necessarily be deadly and spread explosively, which has in turn affected the conceptualisation of the term 'pandemic' when applied to influenza. In reality, widespread and even global dispersion of antigenically 'drifted' seasonal influenza strains can technically lead to pandemics, although they are not usually referred to as such because they produce neither the clinical nor the epidemiological picture associated with historically recognised influenza pandemics. Nor do they produce the modern picture of the introduction of antigenically 'shifted' viruses (i.e. human influenza viruses that have acquired a novel haemagglutinin [HA] gene segment, with or without other gene segments, by reassortment) into immunologically naïve populations. Thus 'pandemic influenza' has taken on a colloquial meaning derived from old notions about severe recognised pandemics of the past. Had 'mild' pandemics occurred in the distant past they may not have been so recognised or documented; thus our perception of influenza pandemic behaviour may be biased towards those that are most severe, most explosive, and most recent, a possibility that is important to bear in mind as we anticipate and plan for future pandemics.

Influenza pandemic history: approaches and problems

Although influenza pandemics have presumably been occurring for 500 years or more (see below; references 10,11,14,23,38,39,74,79), their conceptualisation as pandemics is more recent, a fact that complicates historical determination of events occurring in the pre-virological era. While we can be reasonably certain of pandemic influenza events that occurred during the last 150 years or so, earlier outbreaks were largely (but not exclusively) documented without access to data on population vital statistics, pathology, or microbiology. Deciding what was or was not a pandemic before this time requires reliance upon non-standardised clinical, observational and anecdotal information evaluated with respect to criteria derived from the

few modern pandemics that have been studied scientifically, an obviously subjective process dependent upon circular reasoning (see below).

It is nevertheless possible to make educated guesses about the appearance of influenza pandemics going back to the 1500s if we are willing to accept the unproven (and possibly incorrect) assumption that they would have appeared and 'behaved', epidemiologically and clinically, as they have in the modern scientific era. Many observers have attempted to construct such pandemic chronologies, with a disconcerting level of disagreement that increases the farther back in time one goes. The problem is particularly difficult before the late 1700s, at which time there was renewed interest in cataloguing and differentiating epidemics of all kinds using nosological, clinical and proto-epidemiological means, and at which time a specialised international medical literature began to appear. Before that era, observers had to rely upon often obscure and largely uncatalogued publications, including monastery chronicles, local newspapers, general histories, and accounts of travel and exploration, to collect, assemble, and make sense of anecdotal reports in various languages and from many different locales. Often working out of single libraries with limited collections, different observers found different sources, failed to find others, and arrived at substantially different conclusions.

A recent publication has examined many older sources to arrive at a speculative list of probable and possible pandemics (47). Although the present authors strongly believe that much more scholarship is needed, this may be a helpful starting point from which to create a framework for understanding the historical occurrence of influenza pandemics.

The authors' criteria for classifying a disease event occurring before 1889 as an influenza pandemic, are as follows:

- there must be documentation of a clinical disease characterised by fever and respiratory symptoms, with relatively low population mortality (to exclude more highly fatal epidemic diseases)
- there must be evidence of high attack rates across a broad age range
- the disease must have occurred in at least two geographical regions of the world
- there should be no clear evidence that exposed regions remained unaffected
- there must be evidence of explosivity and rapid geographical spread.

When available, supporting evidence includes:

- geographical directionality of spread
- short prevalence intervals (e.g. around six weeks) in major towns
- higher than expected mortality in the elderly, the young, in pregnant women, and in debilitated persons, and evidence of miscarriages or pre-term deliveries
- evidence of multiple deaths from pulmonary conditions indicative of, or consistent with, pneumonia.

Two particularly noteworthy problems with these criteria should be pointed out. First, the requirement for geographical spread is complicated by slower modes of transportation in historical times. For example, it is difficult to be certain that an influenza pandemic in Europe in the 1700s, when the fastest ships took weeks (many serial generation times for influenza) to sail across oceans, would be capable of spreading to the American colonies. Although pandemic influenza probably reached Fiji in 1838, measles – a much more highly contagious disease with a longer incubation period – did not reach Fiji until 1875 (46). This paradox is consistent with the possibility that chance played a major role in the global spread of respiratory diseases in the eras before rapid travel. Even in the years before the first undisputed influenza

pandemic (1889), in the era of clipper ships and extremely rapid sea travel, the example of Fiji suggests that highly communicable respiratory diseases had considerable difficulty spreading to every inhabited place. Secondly, we face the problem of 'negative information' in eras in which few observers noted the occurrence of epidemics and many major epidemics probably went unrecorded or poorly recorded. Before the late 1700s, the absence of information on the regional and even the national occurrence of a respiratory epidemic cannot be taken as evidence that an epidemic did not occur. Had an earlier pandemic been as 'mild' as that of 1968 (see below), which was associated with a virus that contained a novel HA, it may not have been detected in the early 1800s, let alone earlier. Such problems prevent definitive conclusions about historical pandemic occurrence; it is only with such cautions that we proceed.

Influenza pandemic history: a framework for examining past pandemics

Application of the criteria listed above to the available historical information suggests that there may have been at least 13 pandemics over the past 500 years (1509 to 2009), or approximately one pandemic every 38 years. These pandemics may not have occurred randomly. Whether or not there has been clustering of pandemics, there is evidence that some (but not all) pandemics have been followed by periods of high respiratory disease activity, which were associated with large outbreaks and high mortality, over a number of years. It may thus be helpful to think not only about pandemics as events that occur at specific points in time, but to consider also the occurrence of 'pandemic eras'. For example, the 90 years since 1918 can be said to comprise a pandemic era, because all of the influenza A viruses circulating since that time, up to the present, are descendants of the 1918 virus, and because seasonal influenza activity has been detected continuously during that period. Yet clearly in that interval there have been three (depending on how one defines the H1N1 recurrence in 1977, see below) or four pandemics.

Whether influenza pandemics occurred before 1510 is speculative. Documentation of influenza-like illness beyond Europe in the pre-Renaissance era has to date been sparse, perhaps in part because scholars have not studied Chinese, Indian, Japanese and other non-Western sources as intensively as they have European sources. It has been said that influenza was described separately by Hippocrates or his followers and by Diodorus Siculus, but the clinical evidence is too sparse to make an identification, and in any case neither pandemics nor even large-scale epidemics were documented (79).

The first conceivable candidate for an influenza pandemic was recognised in Italy in 876 AD (CE), from where it followed the army of Charlemagne and spread all over Europe. However, its identity with influenza, though probable, cannot be confirmed and there has as yet been no evidence of it spreading beyond Europe. One curious feature is that birds and dogs were said to have been affected. It has since been frequently observed, up to the time of the 1918 pandemic, that influenza epidemics and pandemics were often preceded (or in other cases followed) at a short interval by equine epizootics, and occasionally by influenza-like illnesses in dogs and other domestic animals. Avian epizootics were apparently not recognised until modern times. It is noteworthy that in ancient Greece avian deaths were believed to be harbingers of human epidemics in general, and could well have been introduced into human disease histories for literary or other non-factual purposes. Although this practice was clearly understood by the time of the Renaissance, the extent to which 9th Century chroniclers may have appreciated it is not known.

Many historians believe that a European-wide epidemic of 'a certain evil and unheard of cough' that appeared in December 1173 was pandemic influenza, but evidence of spread beyond Europe is again lacking (10). Some historians believe the first 'true' pandemic of influenza began in either 1293 or 1323. The 14th and 15th Centuries featured repeated influenza-like illnesses and epidemics, including a major European-wide epidemic in 1386−1387 followed

by other European-wide epidemics over the next 30 years, but without documentation of pandemic spread beyond Europe. Irish documents introduced the term *creatan* to describe a specific epidemic chest disease in the 14th Century; the term *influenza* was first used in Italy to describe a disease prevailing in 1357, and was again applied to the epidemic in 1386−1387 that preferentially killed elderly and debilitated persons. This is probably the first documentation of a key epidemiological feature of both pandemic and seasonal influenza (14). The 15th Century brought increasing documentation of influenza-like epidemics, as well as features we now recognise as characteristic. For example, an epidemic of coughing disease associated with spontaneous abortions was noted in Paris in 1411, and increased mortality in young children and in the elderly was noted in epidemics of influenza-like disease in 1427, 1438, and 1482.

Past influenza pandemics

Pandemic 1: 1510

The first recognisable influenza pandemic invaded Europe from Africa in the summer of 1510 and proceeded northward to involve all of Europe and then the Baltic States. Attack rates were extremely high, but fatality was low and said to be restricted to young children. The lack of mention of mortality in the elderly and debilitated is curious, and there is no evidence one way or the other of protection provided by previous illnesses.

Pandemic 2: 1557 to 1558

The pandemic of spring 1557 is the first in which global involvement and westward spread from Asia to Europe was documented. Unlike the pandemic that appeared 47 years previously, this one was highly fatal, with deaths recorded as being due to ‘pleurisy and fatal peripneumony’. High mortality in pregnant women was also recorded. Examination of Parish registries in England showed a high frequency of excess deaths from 1558 to 1560, representing the first documentation of excess influenza deaths in a defined population, and suggesting that the disease prevailed for at least two years, conceivably having exhibited one or more recurrences.

Pandemic 3: 1580

The pandemic that appeared in 1580 again swept over the entire globe, spreading east to west from Asia, and was notable for its extremely quick progression, evolving and disappearing entirely between spring and autumn 1580. Like the 1557 pandemic, it was apparently highly fatal, and was also associated with severe complications. Finkler (14) believes that in England it appeared in two successive waves, in August to September and October to November, but documentation is sparse.

After the 1580 pandemic, pandemics of influenza-like illness were not documented again for almost 150 years, although localised and even non-European epidemics, some of them severe, were seen episodically. Large-scale European outbreaks were documented at relatively short intervals (e.g. 1610, 1658 to 1659, 1675, and 1709 to 1710), but most of these outbreaks had limited, non-directional geographical spread. Among the most interesting feature of this apparently long non-pandemic period is the development of influenza-like epidemic activity in the Americas, which appeared to be independent of European activity. The 1557 pandemic is said to have reached the sparsely populated Americas, which were at that time isolated from Europe by long ocean voyages, but documentation is weak. The 1580 pandemic apparently did not reach the New World. Decades later (in 1617), at a time when there was no major influenza activity in Europe or elsewhere, influenza-like illness broke out in Chile, possibly having been imported from Spain. It quickly spread throughout South and North America and the

Caribbean. This epidemic seems to have initiated a period of semi-autonomous American influenza activity, which is discussed separately below.

Pandemic 4: 1729 to 1730, 1732 to 1733

The pandemic that appeared in 1729 was first detected in Russia and it spread westward and southward into Europe in the winter of 1729. A 'second invasion' also began in Russia three years later, in 1732, and it again spread widely, even reaching the Americas. Whether these were two pandemics separated by a very short interval or one pandemic with a long-delayed recurrence is not known. Both occurrences were associated with high attack rates and high mortality, but there are no reliable data to answer the question of whether illness in the first appearance protected against illness in the second. Webster and Finkler both believed that the 1732 pandemic began in America and spread from there to Europe (14,74), but this seems questionable. An equine epizootic (featuring lassitude and nasal discharge) was documented before human involvement in 1732. After 1733 there was pronounced global influenza activity for a number of years, especially in 1737 to 1738, when America and Europe were invaded in the same month, and in 1742 to 1744, when European deaths associated with influenza-like illnesses reached extraordinary peaks. Some observers have counted the 1737 to 1738 epidemic as a pandemic rather than a recurrence. Whatever happened, the period 1729 to 1747 remains one of the more remarkable and epidemiologically chaotic eras in the history of pandemic influenza.

Pandemic 5: 1761 to 1762

The 1761 pandemic is remarkable for the fact that it is said to have begun in the Americas in the spring of 1761 and to have spread from there to Europe and around the globe in 1762. Coming in the midst of Enlightenment fervour, the pandemic of 1762 was the first to be studied by multiple observers who communicated with each other in learned societies and through medical journals and books. Influenza was characterised clinically to a greater degree than it had been previously, as physicians carefully recorded observations on series of patients and attempted to understand what would later be called the pathophysiology of the disease. For example, the sites of inflammation were determined to extend to the larynx and trachea and, in severe cases, to the lungs. Recurrences in subsequent years were sometimes severe; for example, in 1775, an epidemic that spread widely was associated with equine epizootics, and had many features of an actual pandemic.

Pandemic 6: 1780 to 1782

The 1780 pandemic, which began in Southeast Asia and spread to Russia and eastward into Europe, was remarkable for extremely high attack rates but negligible mortality, although there were excess deaths in the London bills of mortality, perhaps in part due to excess blood-letting by some physicians. It appears that in this pandemic the concept of influenza as a distinct entity with characteristic epidemiological features was first appreciated (47).

Pandemic 7: 1788 to 1790

Although the 1788 pandemic is generally regarded as being separate from that of 1782 (largely because of its by now typical genesis in Asia, its rapid global and directional dispersion, and its extremely high attack rates), Creighton (10) contends that persons who became ill in the 1782 pandemic were protected not only in 1788 but through 1802. Whatever the case, the 1788 pandemic initiated another pandemic era, in which global influenza activity appears to have been heightened for almost 20 years (1788 to 1806); some observers have postulated additional pandemics in this interval.

Pandemic 8: 1830 to 1831, 1832 to 1833, 1836 to 1837

A similar phenomenon was observed with the next pandemic to appear (1830). It began in Southeast Asia and spread through Russia to Europe and the rest of the globe, causing extremely high attack rates but low mortality. A recrudescence in 1832 and 1833 spread with almost the same directional pattern and was associated with higher mortality. Noting the intense period of global influenza activity that followed the 1830 pandemic, Leichtenstern postulated 'two or three' possible successive pandemics separated by short intervals (39), but it is difficult to determine whether the events of the 1830s represent three separate pandemics or three recurrences of one pandemic virus. Curiously, one observer noted that persons over 45 years old were relatively spared (14), suggesting the possibility that a virus that circulated before 1782 (e.g. the 1761 pandemic virus) could have been antigenically similar. Such observations on protective immunity have not been systematically sought for influenza pandemics in the pre-virology era, an obvious target for historical research. The 1837 recurrence in Europe led to some of the first attempts to understand pulmonary pathology in influenza.

A so-called pandemic in 1847 is among the more problematic epidemic influenza events to have occurred because of its limited explosivity, progression, and fatality. Beginning in Europe in the winter of 1847, it took several years to spread to the Western Hemisphere (1850 to 1851); this was clearly uncharacteristic behaviour for an influenza pandemic. Moreover, after causing high attack rates in United Kingdom in the first year after its appearance, it promptly disappeared, exhibited a recrudescence in 1857 to 1858 and then vanished almost completely. It is therefore curious that lower than expected mortality in elderly persons in the 1918 pandemic (see below) seems to be associated with birth around 1850. Was the 1847 virus an entirely new pandemic virus that protected against the 1918 virus, or was it a descendant of earlier viruses such as the 1830 virus? The 1847 'pandemic-like' epidemic remains one of the more mysterious events in the history of influenza pandemics.

Pandemic 9: 1889 to 1893

The great pandemic of 'Russian flu' was probably the most explosive up to that time and the first to have its progression 'tracked' in real time. Like most others before it, it spread east to west from Asia and quickly reached almost every region of the globe. Unlike previous pandemics, it returned in up to five successive and largely seasonal annual recurrences, although some locales had fewer and less substantial recurrences. The pandemic occurred in the very early years of virology, but its cause was at the time attributed by many to a newly characterised bacterium, *Bacillus influenzae* (now *Haemophilus influenzae*). Based on epidemiological studies conducted in the 1930s and subsequently, which examined sera obtained from persons born before and after the 1889 pandemic, it has been hypothesised that the virus responsible contained an H3 subtype HA. Specimens from the pandemic and post-pandemic period have not yet been identified and studied to identify the agent further.

Pandemic 10: 1918 to 1919

The 'Spanish influenza' pandemic, which stands as the single most fatal event in human history, killed an estimated 50 million or more people (26). Reconstruction of the ribonucleic acid (RNA) genome from the tissues of several victims, conducted in the laboratory of co-author J.K. Taubenberger, has demonstrated that the causative agent was an avian-descended H1N1 virus that appears to be a direct progenitor of all of the influenza A viruses circulating in humans today (66,67). The high mortality associated with the 1918 virus appears to have been a result of bacterial pneumonia, but the co-pathogenic mechanisms responsible for such fatal bacterial diseases remain unknown (48). Epidemiological features of the pandemic were also unprecedented, including its appearance in up to three waves within the first year, and a 'W-shaped' (tri-modal) age-specific mortality curve that featured an unexplained peak in healthy young adults. Evidence for a lower than expected mortality elevation in persons over about 65

years old (see above) is consistent with a protective effect that ended around 1855, corresponding to the period of the apparent circulation of the 1847 epidemic virus or perhaps an earlier virus. The place of origin of the 1918 virus is obscure and there is little evidence of directionality of spread other than chaotic multi-directionality during the second of the three major waves. By about 1920 the virus had begun to settle down into a pattern of seasonal endemic recurrences and remained so as it 'drifted' for nearly 40 years. When the next pandemic appeared in 1957 (see below), the H1N1 virus disappeared from circulation. However, 20 years later, in 1977, it returned to circulation (possibly after accidental release from a freezer) and caused a (low grade) pandemic that disproportionately affected persons under the age of 20 (see below). The virus continues to co-circulate globally today, along with H3N2 influenza A viruses descended from the 1968 pandemic (see below).

As data have accumulated, evidence has emerged to indicate that the genome of the 1918 H1N1 strain may have had a novel origin that has not been seen in strains responsible for subsequent pandemics. Viral sequence data now suggest that the entire 1918 virus was novel to humans in, or shortly before, 1918, and therefore that it was likely not to have been a reassortant virus produced from previously circulating human influenza strains that acquired one or more new gene segments by reassortment, like those that caused the 1957 and 1968 pandemics (29,58). On the contrary, data suggest that the 1918 virus was an avian-like influenza virus that was derived *in toto* from an unknown source (56,68).

Pandemic 11: 1957 to 1958

The pandemic virus that emerged in 1957 was a lineal descendant of the 1918 H1N1 pandemic virus that had somehow acquired three novel gene segments. The gene segments encoding the two surface proteins, HA and neuraminidase (NA), were replaced by an avian-like H2 subtype HA and an N2 subtype NA (59), respectively. The gene segment encoding the PB1 polymerase was also replaced with an avian-like gene segment (29,59). Even though this pandemic occurred in the era of influenza virology, it is not known in what animal host (possibly including humans) the reassortment event(s) occurred. It is also not known how long it took from the initial reassortment event(s) for the virus to evolve into the efficiently transmissible, human-adapted influenza A virus that caused the pandemic.

The pandemic followed the by now typical pattern of appearance in Southeast Asia and subsequent global spread, although its movement and mortality rate were not as impressive as those of the two previous pandemics, in 1889 and 1918. Emergence of the H2N2 'Asian' influenza virus was first detected in April 1957, when it was reported that the strain responsible for epidemic outbreaks throughout Southeast Asia was antigenically distinct from the prevailing H1N1 strain. Predictions that the virus would spread through the Southern Hemisphere during the summer but cause widespread outbreaks in the Northern Hemisphere only in the autumn proved correct. The virus spread through the tropics during May and June, causing outbreaks in the Southern Hemisphere during July and August. While there were limited outbreaks in institutional settings in the United States of America (USA) and Europe as early as June, large-scale epidemics did not begin until September. Japan was the only country in the Northern Hemisphere to experience widespread epidemics during the spring. Contemporary observers noted the easily traceable geographical spread of the epidemics, a characteristic that was shared with the pandemic of 1889 (see above), but was not readily apparent during inter-pandemic influenza epidemics (36). As the first pandemic to occur in the era of modern virology, the 1957 to 1958 pandemic was studied scientifically with the latest virological and bacteriological methods. Its pathology and clinical appearance were similar or identical to those of the 1918 virus, although the unusual epidemiologic features of the 1918 pandemic noted above were not seen in 1957. As was true for the 1918 pandemic, after about

two years the virus became seasonally endemic and sporadic, disappearing entirely within 11 years. To date (2009) it has not returned.

Pandemic 12: 1968

Like the pandemic that preceded it, the 1968 pandemic of H3N2, 'Hong Kong flu', was caused by a virus that had been 'updated' from the previously circulating virus by reassortment of avian genes, in this case two of them, to create yet another new generation of 1918 viral descendants. Spreading again from Southeast Asia, the 1968 pandemic was so mild in its mortality impact that in some locales fewer influenza deaths occurred than in certain non-pandemic years. As had been the case in 1957, the virus quickly became endemic and sporadic in its appearance, and it has now (in 2009) circulated globally for 41 years.

The 1968 H3N2 pandemic virus replaced the H2N2 type virus that had been circulating since the 1957 pandemic. A molecular analysis of the H3N2 virus demonstrated that the H2 HA had been replaced by reassortment with an avian-like H3 HA (59) and that the PB1 polymerase gene segment had also been replaced, again by reassortment with an avian-like PB1 (29). The other six gene segments, including the NA gene segment, were retained from the 1957 H2N2 virus. Antibodies to NA, while not preventing infection, have been shown to reduce the duration and severity of illness. It has been suggested that the relative mildness of the 1968 pandemic in comparison with previous pandemics was the result of the retention of the previously circulating NA (31).

Pandemic 13: 1977 to 1978

The re-emergence in 1977 of a descendant of the 1918 H1N1 virus that had been absent from circulation for 20 years, constitutes a pandemic by definition (see above), but it is usually regarded as a 'technical' pandemic that represents an unusual coda to the 1918 pandemic. The issue is partly a semantic one, which nonetheless disarms because it upsets attempts to find patterns in natural pandemic recurrence. It is curious that the same virus that disappeared on its own in 1957 has, after reintroduction, been able to survive for over 30 years in the face of immunity pressures thought to be as great or greater than those associated with its disappearance (i.e. high population immunity from natural infection and additional immunity from annual vaccination, which is much more common now than it was in 1957). The 1968 H3N2 and the 1977/1918 H1N1 pandemic viruses have been co-circulating endemically for over 30 years, in the face of high population immunity, with no evidence of imminent extinction.

The exact place of origin of the 1977 H1N1 virus is uncertain. In May to June 1977 an influenza outbreak occurred in northern China (35). The epidemic spread rather slowly, in marked contrast to the pandemics of 1957 and 1968. The H1N1 viruses were detected between June and October 1977 in other parts of China. The H1N1 strains did not replace the H3N2 strains then circulating in China, but co-circulated with them during that first year, with more H1N1 circulation in northern China than in the south of the country (35). By November 1977, H1N1 viruses were causing limited outbreaks in the far eastern Union of Soviet Socialist Republics (USSR) (81), followed by cities in Siberia and the European portions of the USSR. Infection was limited predominantly to young adults (below the age of 25) and school-age children.

During the next winter influenza season (1978 to 1979) H1N1 viruses caused limited outbreaks throughout the world. In the USA, the first H1N1 outbreaks occurred in schools and on military bases in January 1978. Some of these outbreaks were associated with clinical infection rates of up to 70%, but with few cases in individuals over 26 years of age (19). As in other countries, the H1N1 viruses co-circulated with the H3N2 strains without replacing them, but unlike the H3N2 outbreaks, H1N1 outbreaks were associated with little or no excess mortality.

The H1N1 strains isolated in 1977 and 1978, as represented by the A/USSR/90/77 strain, were antigenically similar to H1N1 viruses that had circulated widely between 1947 and 1956 before being replaced by the H2N2 pandemic strain in 1957. The isolates were also antigenically uniform, which suggests a single source. It is considered unlikely that influenza viruses could have been maintained in nature for 25 years without accumulating mutations, suggesting that the 1977 epidemic resulted from the release of a frozen strain from the 1950s (30,75). Molecular genetic techniques confirmed that the USSR/77 strain was very similar to early 1950s H1N1 strains in all eight gene segments (49,59). Because the post-1977 H1N1 strains did not replace the previously circulating H3N2 strains, co-circulation of influenza viruses of both subtypes has continued up to the present time (2008), and co-infection with both subtypes has been reported (62), together with the circulation of reassortant H1N2 viruses (20,50).

Unanswered questions and conclusions

Interpandemic events: seasonal influenza versus undocumented and/or 'low level' pandemics?

As noted above, a major problem in the interpretation of the historical evidence of past pandemics is the possibility that significant information may have been either not recorded or not yet identified. For example, what are we to make of the 149-year interval between 1580 and 1729 in which there was much evidence of major influenza activity, including Europe-wide and Western Hemispheric epidemics of influenza-like illness, sometimes associated with high mortality, but little evidence for pandemic activity? It is difficult to decide whether true pandemics may have been missed during this long era, or whether this interval represented a prolonged period of seasonal influenza, analogous to our current 52-year interval in which moderately severe influenza outbreaks associated with directional global spread have not been recognised since 1957 (i.e. the H2N2 pandemic). Additional historical research may shed light on these uncertainties.

Avian and swine influenza

At the time of the 1918 influenza pandemic, no one suspected that the cause of human influenza was derived from an avian infectious agent capable of infecting multiple mammalian species. Strong associations between some human influenza epidemics/pandemics and equine epizootics in previous centuries (15) had been noted, but a human–swine influenza link had not been established, and indeed was not to be noted until the detection of swine epizootics in China and the USA during the autumn 1918 pandemic wave (7,33). Highly pathogenic avian influenza ('fowl plague') had been recognised as a disease entity since 1878 (54), but was not well known to physicians or biomedical researchers. Between 1901 and 1903 Italian and Austrian researchers, working independently, identified filterable agents as the cause of fowl plague (3,40,42), but it was not until 1955, more than 20 years after the identification of swine and human influenza viruses, that Schäfer identified fowl plague virus as influenza A (57). Additional avian influenza A viruses were identified in the 1960s (52). Webster and colleagues proposed in 1967 that pandemic influenza viruses might be related to avian influenza viruses (53). Slemons *et al.* isolated influenza A viruses from the cloacae of wild ducks in 1974 (61), and it is now generally believed that wild aquatic birds are the natural reservoir for influenza A viruses (reviewed in Webster *et al.* [75]).

Given that pigs can be infected with both avian and human strains of influenza, and that various influenza virus reassortants have been isolated from this species, pigs have been proposed to be an intermediary in the process of viral reassortment (41). In 1976, a classical swine (H1N1) influenza A virus caused severe respiratory illness in 13 soldiers in the USA (Fort Dix, New Jersey) resulting in one fatality (18). This outbreak was thought to pose a significant threat for the development of a pandemic. Public health officials in the USA initiated a large-scale

vaccination programme, but no further spread occurred (34). In 1979, an avian-like H1N1 virus began infecting swine in northern Europe and established a stable novel H1N1 viral lineage (41) that was unrelated to the swine H1N1 lineage descended from the 1918 virus. Until 1997 there was little evidence that a wholly avian influenza virus could similarly infect humans directly; in that year eighteen people were infected with avian H5N1 influenza viruses in Hong Kong and six died of complications (8,64). Although these viruses were very poorly transmissible, if at all (28), between humans, their detection reinforces the knowledge that under poorly understood circumstances humans and other mammals can be infected with wholly avian influenza strains of either high or low pathogenicity for poultry. Since 2003 there have been 403 documented human infections with H5N1 viruses, associated with 254 deaths (as of January 27, 2009; [80]; see below). Therefore, it may be unnecessary to invoke pigs as the intermediary in the formation of a pandemic strain because reassortment could conceivably take place directly in humans or other mammals. It is also of note that there are no data that link pigs (or other intermediate hosts) with the formation of the human/avian reassortant influenza pandemic viruses of either 1957 or 1968.

The origins of pandemic influenza viruses

The occurrence of three influenza pandemics in the 19th Century (47) and another three in the 20th Century has led some experts to conclude that pandemics occur in cycles, and that we are currently overdue (78). Belief in influenza cyclicity can be traced to epidemiological efforts in the mid-19th Century. Following the 1889 pandemic, interest was renewed in examining the recurrence patterns of influenza (13). By the 1950s, cumulative historical information (14,27,47,71,72) appeared to suggest that pandemics appear in regular cycles. This seemed to make biological sense: the most recent pandemics (in 1889, 1918 and 1957) had apparently been caused by different viruses with novel HA genes imported from a large naturally existing avian pool. It was becoming clear at about the same time that high population immunity led post-pandemic viruses to drift antigenically, and that genes encoding surface proteins could potentially mix with other HA and NA genes to which humans lacked immunity (22). It was reasonable to assume that such an intimate viral–immunological relationship would have a predictable life span.

Around the time of the 1957 and 1968 pandemics, the prevailing view was that pandemics tended to recur as frequently as every 10 to 11 years, an idea that was first proposed in the 1830s. The swine influenza outbreak in 1976 (see above) further strengthened this hypothesis (18,34). One year later, after 20 years of natural ‘extinction’, an H1N1 descendant of the 1918 virus suddenly re-emerged to re-establish post-pandemic co-circulation, along with one of its own further descendants, the H3N2 influenza virus (51), which set up nearly three decades of endemic co-circulation of former pandemic viruses that has continued until today (2009) (55). Influenza expert Edwin Kilbourne has recently concluded that: ‘... there is no predictable periodicity or pattern of major influenza epidemics and ... all differ from one another’ (32). Without pandemic cycles there can be little basis for predicting pandemic emergence.

It now appears likely that pandemic emergence can result from at least two very different mechanisms: *de novo* emergence of a completely unique avian-descended virus (as in 1918), or modification of a circulating human-adapted virus by importation, via genetic reassortment, of a novel HA, either with concomitant importation of a novel NA (1957 H2N2 pandemic) or without a novel NA (1968 H3N2 pandemic) (67). The possibility that a pandemic could result from viral acquisition of a novel NA alone, or from a distinctive HA that is of the same serotype as a circulating virus but antigenically remote from it, has not been disproven.

There is no reason to suppose that the two different known pandemic mechanisms should be capable of producing the same cyclic intervals, or that other competing mechanisms of adaptation, such as reassortment with closely related HAs (25), or changing population

immunity induced by increasing use of immunologically complex vaccines, could not disrupt cycles that might otherwise occur. It has also become clear that despite a large catalogue of naturally occurring genes for influenza surface protein that are theoretically capable of causing new pandemics by reassorting themselves into human-adapted strains, only three of the sixteen known HAs (H1, H2 and H3) and two of the nine NAs (N1 and N2) are known to have done so in the past 120 years (44,67).

Drawing upon earlier theories of Thomas Francis, Jr (17), and others, Maurice Hilleman attempted to reconcile these complications by proposing a form of 'macrocyclicity' in which reappearances of H1, H2 and H3 (roughly every 68 years) are driven by cycles of waning population immunity that last approximately the same duration as the mean human lifespan (22). Because scientific evidence of viral identity only extends backwards for 120 years, it will take many future generations to fully evaluate Hilleman's hypothesis. Historical evidence of pandemic occurrence provides no obvious cyclic patterns over the past three centuries (47). Presumably, mutable viruses that induce high population immunity will eventually drive their own evolutionary changes; however, if pandemic cycles do occur they must be so irregular as to confound predictability.

H5N1 avian influenza and the risk of a future pandemic

The continuing spread of H5N1 HPAI viruses into poultry populations on several continents, associated with a growing number of human 'spill-over' infections, has heightened interest in pandemic prediction (21,73). H5N1 HPAI viruses initially caused a 1996 poultry epizootic in southern China, followed within a year by an epizootic in Hong Kong that produced 18 human cases and six deaths. H5N1 strains continued to circulate thereafter in China, and they reappeared in epizootic form in, and spread widely after, 2003. This geographical extension was accompanied by the appearance and spread of genetically and antigenically different H5N1 HPAI strains (21).

Although overshadowed by the spread of H5N1, during the past decade at least eight other major poultry epizootics have occurred, caused either by emergence of novel H5 or H7 subtype HPAI viruses unrelated to Asian H5N1 viruses, or in one case by an H9N2 low pathogenic avian influenza (LPAI) virus. Some of these epizootics have featured human infections and, rarely, human deaths (1). Since the mid-1990s, strains of H9N2 LPAI viruses have become enzootic in domestic poultry populations on several continents (1,6), leading to a small number of human infections. Like those of H5N1, different genetic lineages of H9N2 have been established, some of which share with H5N1 viruses closely related gene segments that encode internal proteins. Some H9N2 viruses have even acquired enhanced specificity for the human form of the HA receptor (45). In 2003 an H7N7 HPAI virus caused a poultry epizootic in the Netherlands and spread regionally. Before the epizootic was contained, at least 86 poultry workers and three of their contacts had become infected and developed conjunctivitis with or without an influenza-like illness; one of them died (16). Similarly, two persons developed influenza conjunctivitis during an outbreak of H7N3 HPAI in Canada in 2004 (69). The H5N1 epizootics are unique, however, in causing infections and deaths in a large number of wild bird species, occasional infections in wild and domestic mammals, more frequently severe and fatal human spill-over infections, and in rare instances possible 'dead end' human-to-human transmission (70).

Do these unique features of epizootic H5N1 viruses predict an impending pandemic? There is little consensus among experts. Despite significant research, fundamental questions about how influenza A viruses switch hosts from wild avian species to domestic poultry and mammals, and subsequently to human hosts, remain unanswered. Also incompletely understood are the viral genetic changes that underlie human adaptation; even less well understood are those genetic changes that would allow human-to-human transmissibility, and the viral, host, or

environmental cofactors that may contribute to human pathogenesis (67). Given the potential for high morbidity and mortality, an approximation of the risk of the H5N1 virus becoming adapted to efficient human-to-human transmission would be extremely helpful for pandemic preparedness planning. In this regard, even though historical observations support the inevitability of future pandemics, data accumulated over the past decade may not strongly point to emergence of an H5N1 influenza pandemic. Examination of current and historical information leads us to the following reflections.

Evidence suggests that H5N1 viruses are evolving rapidly; however, the direction of this evolution, which is driven by incompletely understood selection pressures, is unclear. While current strains of Southeast Asian H5N1 HPAI viruses are descendants of the 1996 Chinese epizootic virus, significant genetic and antigenic evolution has since occurred, involving drift in the H5 HA, mutations in other genes, and reassortment with other avian influenza viruses (5). It is not yet clear which of these many changes are associated with lethality in wild birds, or with pathogenicity and transmissibility in poultry or other species. At the same time, adaptation of H5N1 HPAI strains associated with asymptomatic, endemic infection of domestic ducks is probably contributing to continuing spill-over into poultry, leading to the maintenance of a pool of pathogenic viruses to which humans will be continually exposed (63). Nevertheless, there are limited data relating to whether or not any H5N1 influenza strain is evolving in the direction of human adaptation.

Given that only H5 and H7 viruses have been shown to acquire the requisite polybasic insertional mutation at the HA cleavage site that makes them highly pathogenic to poultry, the last three human pandemic viruses, which contained avian-like HA genes of H1, H2, and H3 subtypes, were by definition not HPAI viruses. Neither is there evidence that a human pandemic or even an epidemic has been caused by any of the many other HPAI viruses. Furthermore, while HPAI outbreaks have been described in poultry for over 130 years, none of the last three pandemics is known to have been temporally associated with an epizootic in poultry or wild birds, leaving no historical data to support the possibility that poultry are capable of serving as intermediate hosts in the development of a pandemic.

Biological barriers to the fitness of viruses with various gene segment combinations are still poorly understood; however, virulence/pathogenicity, host adaptation, and host-to-host transmissibility are likely to be independent properties that are associated with different, and possibly competing, mutational changes. The role of virulence and pathogenicity in evolutionary virus–host relationships is therefore unclear; pandemic viruses of comparatively low (e.g. 1968), intermediate (e.g. 1889 and 1957), and high (e.g. 1918) pathogenicity have all adapted to humans and exhibited efficient pandemic transmissibility.

To cause a pandemic, an avian virus would have to adapt at least to human HA receptors and separately acquire human transmissibility properties. This appears to be a difficult challenge that is rarely met by influenza A viruses. Despite the likelihood that humans and other mammals have been exposed to countless avian viruses over many centuries, the last two pandemics have resulted from reassortment of pre-existing human-adapted viruses with imported genes derived from avian influenza viruses, not from *de novo* adaptation of avian viruses to humans. When genes from a 1997 H5N1 virus were experimentally reassorted in various combinations with those from a human H3N2 virus, some reassortant combinations resulted in viral replication in ferrets, but none was efficiently transmitted between animals (43), prompting critical questions about whether H5N1 viruses may be limited in their potential to adapt to, and be transmitted between, humans.

The mutational changes that are associated with the binding of H5N1 viruses to receptors in different hosts are proving to be complex (65). Adaptation of the viral HA receptor-binding

site from a form optimised for binding the 'avian' receptor to a form binding efficiently to the 'human' receptor seems to require some loss of specificity for α2,3-linked sialic acids in favour of increased specificity for α2,6-linked sialic acids. Experiments suggest that only two mutations in the receptor-binding site converted the H1, H2, and H3 HAs of the past three influenza pandemic viruses from avian receptor-binding patterns to human receptor-binding patterns. Several mutations have been reported to enhance the binding of H5 to the human form of the receptor; however, none has been reported to induce a complete switch in specificity. While it is possible that additional unknown mutations could result in such a complete switch, there is no evidence that this has happened after at least 11 years of exposure of thousands of humans to H5N1, and no evidence that this has happened after human exposure to other HPAI or LPAI viruses of the H5 subtype over many decades. Changes in HA receptor binding during host adaptation must therefore be extremely complex, and must differ from subtype to subtype. The H5 viruses and other subtypes may well face unappreciated biological barriers in achieving efficient binding to human receptors.

The next pandemic

Although we can be reasonably confident that a pandemic will eventually occur, we are currently unable to predict the details of a future pandemic, including when or where it will occur, what subtype it will be, and what morbidity/mortality impact it will have. While concern over the emergence of an H5N1 pandemic is clearly warranted, if for no other reason than its current high case fatality rate, many other possibilities for pandemic emergence must also be anticipated and planned for.

The majority of the world's population (those under the age of 41) has no protective immunity to the H2 subtype-bearing influenza viruses that circulated between 1957 and 1968. Isolates of H2N2 viruses from that era are still maintained in countless freezers, while circulating human-adapted H3N2 viruses presumably remain susceptible to importation of avian H2 by reassortment; this suggests obvious potential origins of future pandemics. Current H9N2 viruses, some with the ability to bind to human receptors, and already capable of causing human disease, are another potential source of a future pandemic.

Since 1977, H1N1 and H3N2 viruses have co-circulated globally to produce seasonal epidemics, which cause approximately 36,000 deaths annually in the USA. Moreover, recent data have made it clear that evolution of circulating human influenza viruses occurs not just by gradual antigenic drift but also by intra-clade reassortment resulting in the importation of new HAs to which there is a lesser degree of population immunity, and which creates, at the same time, novel constellations of viral gene segments (25). It is unclear whether continued co-circulation and accelerated evolution of different post-pandemic viruses, coupled with the growing use of influenza vaccines against them, will increase or decrease pandemic risk or influence the HA or NA subtype of the next pandemic virus. The co-circulation of post-pandemic H1 and H3 viruses for three consecutive decades seems to be unprecedented over the past 125 to 160 years. If only H1, H2, or H3 viruses have pandemic potential, the question arises whether such co-circulation limits, in the near future, the next pandemic to only H2 viruses. At present there are no data to answer such a question; however, over the past several decades the dogma regarding pandemics has been so radically overturned that it is now important to rethink and restudy all aspects of this issue.

The past decade has demonstrated how difficult it is to contain HPAI outbreaks, given high intensity poultry production and the movement of poultry between countries. The H5N1 viruses are likely to remain enzootic in domestic bird populations in many countries indefinitely. This poses numerous agricultural and economic problems. While it might provide an opportunity for H5N1 viruses to acquire efficient human-to-human transmission (if such a change is in fact possible), it might, on the other hand, provide a better opportunity for viruses to adapt to poultry

and wild birds, the chief spill-over hosts. The use of antiviral drugs in agricultural settings has made many H5N1 viruses resistant to adamantanes, while there has also been evidence for H5N1 resistance to neuraminidase inhibitors (37). The evolution of H5N1 into antigenically distinct clades, probably driven in part by the use of poultry vaccines, greatly complicates the situation and makes it more difficult to predict where H5N1 evolution is going, what to expect next, and how to plan for it (76).

Understanding and predicting pandemic emergence is a difficult challenge that we are far from being able to meet in 2009. As our understanding of influenza viruses has increased dramatically in recent decades, we have moved ever further from certainty about the determinants of, and possibilities for, pandemic emergence. Planning efforts must consider a range of possibilities that cannot yet be prioritised in terms of their likelihood, and must also deal with unpredictable ranges of pandemic morbidity and mortality impacts. As a prescient editorial noted more than 75 years ago (12), it is still not possible to make any scientifically based prediction about the emergence of future pandemics. Until such time as ‘universal’ influenza vaccines or better drug treatments become available, there remains a need for strong basic public health approaches to pandemic control.

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