PERSPECTIVE

The 1918 Influenza Pandemic: Insights for the 21st Century

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The 1918–1919 H1N1 influenza pandemic was among the most deadly events in recorded human history, killing an estimated 50–100 million persons. Because recent H5N1 avian epizootics have been associated with sporadic human fatalities, concern has been raised that a new pandemic, as fatal as the pandemic of 1918, or more so, could be developing. Understanding the events and experiences of 1918 is thus of great importance. However, despite the genetic sequencing of the entire genome of the 1918 virus, many questions about the 1918 pandemic remain. In this review we address several of these questions, concerning pandemic-virus origin, unusual epidemiologic features, and the causes and demographic patterns of fatality. That none of these questions can yet be fully answered points to the need for continued pandemic vigilance, basic and applied research, and pandemic preparedness planning that emphasizes prevention, containment, and treatment with antiviral medications and hospital-based intensive care.

The spread of H5N1 avian influenza viruses from Asia to the Middle East, Europe, and Africa has heightened international alarm that an influenza pandemic may be imminent [1]. The World Health Organization [2] and many individual nations, including the United States [3], have developed plans to detect the emergence of pandemic influenza and to limit its effects. Because no influenza pandemic has appeared since 1967–1968, such plans rely on consideration of this and earlier pandemics. Of these, the 1918–1919 "Spanish flu" pandemic was among the deadliest public-health crises in human history, killing an estimated 675,000 people in the United States and an estimated 50–100 million people worldwide [4]. This pandemic's explosive and still-unexplained patterns of rapidly recurrent waves and predilection to kill the young and healthy [5–7] cast an element of urgency over pandemic planning today.

Lacking complete explanations for the genesis and epidemiologic behavior of the 1918–1919 pandemic [8], Taubenberger and colleagues recently took a critical step by sequencing the entire 8-segment genome of the 1918 influenza virus, using RNA fragments recovered from the lungs of several victims [9, 10]. This scientific achievement has spurred many important avenues of research, including advances such as the discovery that the 1918 virus apparently arose not by gene reassortment between a human and animal virus but by genome adaptation, a previously undocumented mechanism of pandemic-virus generation. Despite these insights, many fundamental questions remain. In this article, we discuss several issues that have implications for modern pandemic preparedness (table 1).

ORIGIN OF THE 1918 PANDEMIC INFLUENZA VIRUS

The 1918–1919 influenza pandemic was caused by an influenza A virus of the H1N1 subtype. Sequence analysis suggests that the ultimate ancestral source of this virus is almost certainly avian [10, 11]. This is not an unexpected finding: the enteric tracts of waterfowl such as ducks and geese serve as reservoirs for all known influenza A viruses [1, 11]. Waterfowl typically experience asymptomatic infection and exert little selection pressure on viral evolution. To jump to new hosts such as chickens or mammals and infect very different cell types, such as human lung cells, rather than duck enteric cells, an influenza virus may have to adapt by accumulating one or more point mutations or by reassortment with a gene segment from a different influenza virus [8, 12]. A third possible genetic mechanism, homologous recombination between gene segments of different viruses, has not yet been shown to be of importance for the evolution of human influenza viruses.

It is unclear which host served as the

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Table 1. Important questions posed by the 1918 influenza pandemic.

Question	Answer
Where did the 1918 virus originate?	Unknown; unlike H5N1, from an avian influenza lineage genetically distinct from those currently known
What was the pathogenesis, and why did so many people die?	Different pathogenesis in 1918 not documented: causes of death in 1918 similar to those during other pandemics; most fatalities had secondary pneumonias caused by common bacteria or, in a minority of cases, ARDS-like syndromes; higher proportion of severe cases at all ages; 1918 virus-virulence determinants not yet mapped
Why were there so many deaths among the young and healthy?	Unknown; unappreciated host or environmental variables possible, such as robust immunological response to the virus in younger individuals, resulting in enhanced tissue damage
Why was mortality among the elderly lower than expected?	Unknown; evidence is consistent with prior exposure to a virus—conceivably the virus associated with the 1847 pandemic—eliciting protective immunity
Why were there 3 pandemic waves during 1918–1919, and what are the implications for predicting future pandemic spread?	Unknown; at least 2 virus variants during second wave; identity of viruses during first and third waves not known; epidemiology of rapidly recurrent waves not understood
Do influenza pandemics occur in predictable cycles?	Insufficient evidence for pandemic cyclicity; steps in pandemic emergence not fully understood
Are we better able to prevent morbidity and mortality today?	Yes, in developed world with advanced medical care, antibiotics, antivirals, and effective public health; preventive vaccines would be critical if available in time; however, developing world still at great risk

NOTE. ARDS, acute respiratory distress syndrome.

source of the 1918 virus—and how the virus adapted to humans. Examination of the genome of the 1918 H1N1 influenza virus [9, 10] has not provided complete answers; indeed, it has posed difficult new questions. Although all 8 gene segments of the 1918 virus are clearly avian-like, they are genetically distinct from any of the hundreds of avian or mammalian influenza viruses collected and examined between 1917 and 2006, primarily because of greater-than-expected numbers of silent nucleotide changes. Moreover, the genes of the 1918 virus apparently have evolved together in parallel, possibly in an unidentified host [8]. Thus, unlike the 1957 and 1968 pandemics, each of which resulted from reassortment between circulating descendants of the 1918 human virus and circulating avian influenza strains, the 1918 pandemic apparently arose by genetic adaptation of an existing avian virus to a new (human) host [8, 10–12].

The obscurity of the viral origin of the 1918 influenza poses a paradox. The lower-than-expected mortality among individuals who were >45 years old in 1918 (i.e., those born before 1873; see the discussion below) implies partial protection from disease and perhaps infection [5–7]. One possible explanation is previous exposure to an antigenically related virus that had circulated widely. However, evidence for such a virus is incomplete.

Further complicating the issue is the fact that at least 2 different H1N1 influenza-virus strains that had markedly different receptor-binding specificities and that were fatal to humans were circulating simultaneously in 1918 [13]. One strain contained variations in both the 190 and 225 codons (mutations E190D and D225G, respectively) of the H1 gene. These changes enable the hemagglutinin (HA) protein of the virus to bind only to α(2–6) sialic-acid receptors found on human/mammalian cells. The second circulating strain contained only the E190D change, rendering it capable of binding to both mammalian α(2–6) receptors *and* avian α(2–3) sialic-acid receptors [14, 15]. Although the 1918 virus appears to be descended from an avian virus, before the 1918 pandemic there were few if any reports of unusual die-offs of wild waterfowl or domestic poultry, as has occurred with the modern H5N1 virus, indicating that the earlier virus was not then highly pathogenic for birds. The H1N1 and H5N1 viruses thus seem to have gone down different evolutionary paths. Taken together, the information noted above is consistent with the possibility that the precursor to the 1918 virus was hidden in an obscure ecologic niche before emerging in humans.

PATHOGENESIS AND EXCESS MORTALITY IN 1918–1919

In healthy children and adults, influenza is usually an uncomplicated febrile illness that may incapacitate but rarely kills [16]. Many typical seasonal influenza infections are asymptomatic or cause only mild or vague symptoms. Others cause "classical" influenza: 4 or 5 days of fever, chills, headache, muscle pain, weakness, and, sometimes, upper-respiratory-tract symptoms and cough. Severe complications and deaths can occur, especially in infants, the elderly, and individuals with chronic conditions such as diabetes mellitus and heart disease. Among the most severe complications is pneumonia, which can be associated with secondary bacterial infection.

The first widely studied influenza pandemic occurred during 1889–1893 [17,

18]. To older physicians in 1918, obvious similarities to the 1889 pandemic included its highly contagious nature, with clinical attack rates typically in the 20%–60% range. In both pandemics, most deaths resulted from respiratory complications, such as pneumonia with bacterial invasion; however, in 1918 there also were seemingly new and severe clinical forms of disease. In 1889 many deaths due to pneumonia were attributed to familiar conditions such as subacute bacterial lobar pneumonia, whereas in 1918 this "background" influenza mortality was greatly augmented both by cases of aggressive fatal bronchopneumonia and by acute deaths associated with progressive cyanosis and collapse (figure 1).

Unlike the 1889–1893 pandemic, which made 3 or more successive annual and largely seasonal reappearances, the 1918 pandemic spread in 3 rapidly recurring waves within an ~9-month interval (figure 2*A*), before settling into a pattern of annual seasonal recurrences. Moreover, mortality during the latter 2 of the 3 1918–1919 waves was much higher, at all ages except among the elderly, than that during 1889, and it featured an enormous mortality peak in healthy young adults (figure 2*B*), an age group believed to have been at low risk of death in all other pandemics up to that time. For purposes of comparison, the 1957 and 1968 influenza pandemics, both caused by descendants of the 1918 virus, produced relatively low mortality overall, did not produce rapidly successive waves or multiple annual recurrences of high mortality, and settled more quickly into familiar patterns of annual seasonal endemic circulation [19–21].

Clinical and autopsy series [22–33] suggest that excess influenza deaths (i.e., deaths above the expected background level for influenza) during 1918–1919 seem to have been associated with 2 overlapping clinical-pathologic syndromes (figure 1). The most common appears to have been an acute aggressive bronchopneumonia featuring epithelial necrosis, microvasculitis/vascular necrosis, hemorrhage, edema, and widely variant pathology in different parts of the lung, from which pathogenic bacteria could usually be cultured at autopsy (figure 1; also see [28]). In a few autopsies, severe bronchopneumonia was seen without evidence of bacteria, but studies generally showed a close correlation between the distributions of pulmonary lesions and cultured bacteria [34, 35], identifying the major bacteria as the organisms now known as *Streptococcus pneumoniae*, *S. pyogenes*, and, less commonly, *Haemophilus influenzae* and *Staphylococcus aureus* [22, 36–40]. Scientists have long suspected that the pathogenesis of the 1918 virus was augmented by concomitant infection with the virus and with bacteria such as *S. pneumoniae* and *S. pyogenes* [41].

The second syndrome, comprising perhaps 10%–15% of fatal cases, was a severe

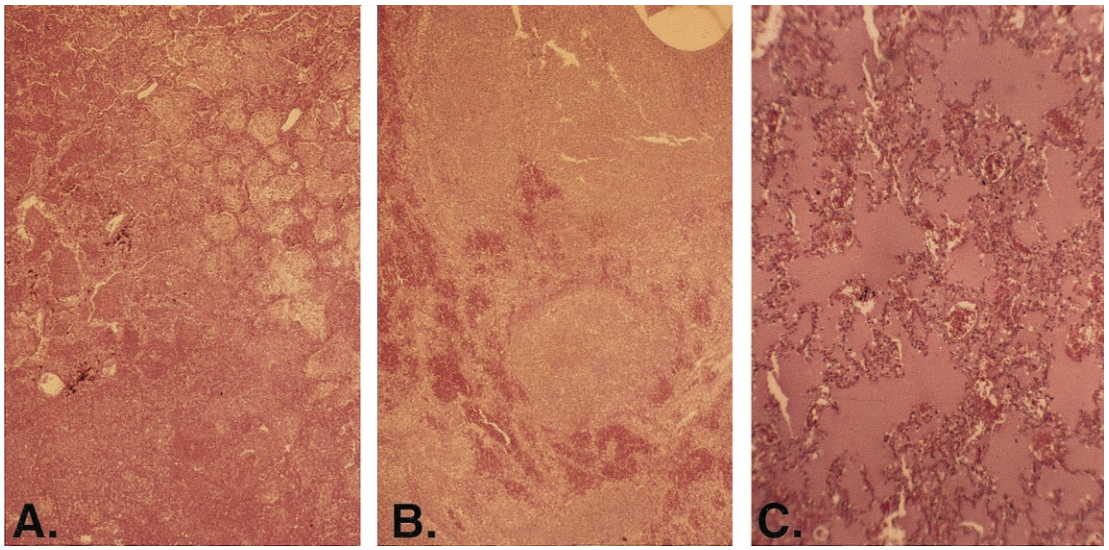

Figure 1. Histological appearance of lung sections from 3 fatal cases of influenza during 1918, showing distinct clinical-pathologic forms. *A,* Severe and rapidly progressing necrotizing/hemorrhagic bronchopneumonia, which is consistent with cytolytic viral damage and secondary bacterial invasion by respiratory-tract pathogens and which is associated with some (probably a minority of) deaths. *B,* Severe bacterial bronchopneumonia from which *Streptococcus pneumoniae, S. pyogenes, Haemophilus influenzae,* or, less frequently, *Staphylococcus aureus* could be cultured and which is associated with the majority of deaths. The extent to which secondary bacterial pneumonia may have followed primary necrotizing viral pneumonia is unclear, because early signs of viral cytolytic damage had typically been obliterated by the time of autopsy. *C,* Another clinical form of disease, which, although it had not been characterized when the culture was performed, is thought to be similar to acute respiratory distress syndrome (ARDS) [42] and appears to have been associated with a minority of fatal cases. Patients with this form experienced extremely rapid progression of the disease and may have literally drowned because of fluid-filled alveoli, often in the absence of bacteria or inflammatory infiltrate. Varying degrees of the same pathologic features seen in this ARDS-like form were also seen in many or most patients with the severe cytolytic form (see panel *A*). (Photographs courtesy of Jeffery K. Taubenberger, National Institute of Allergy and Infectious Diseases, National Institutes of Health.)

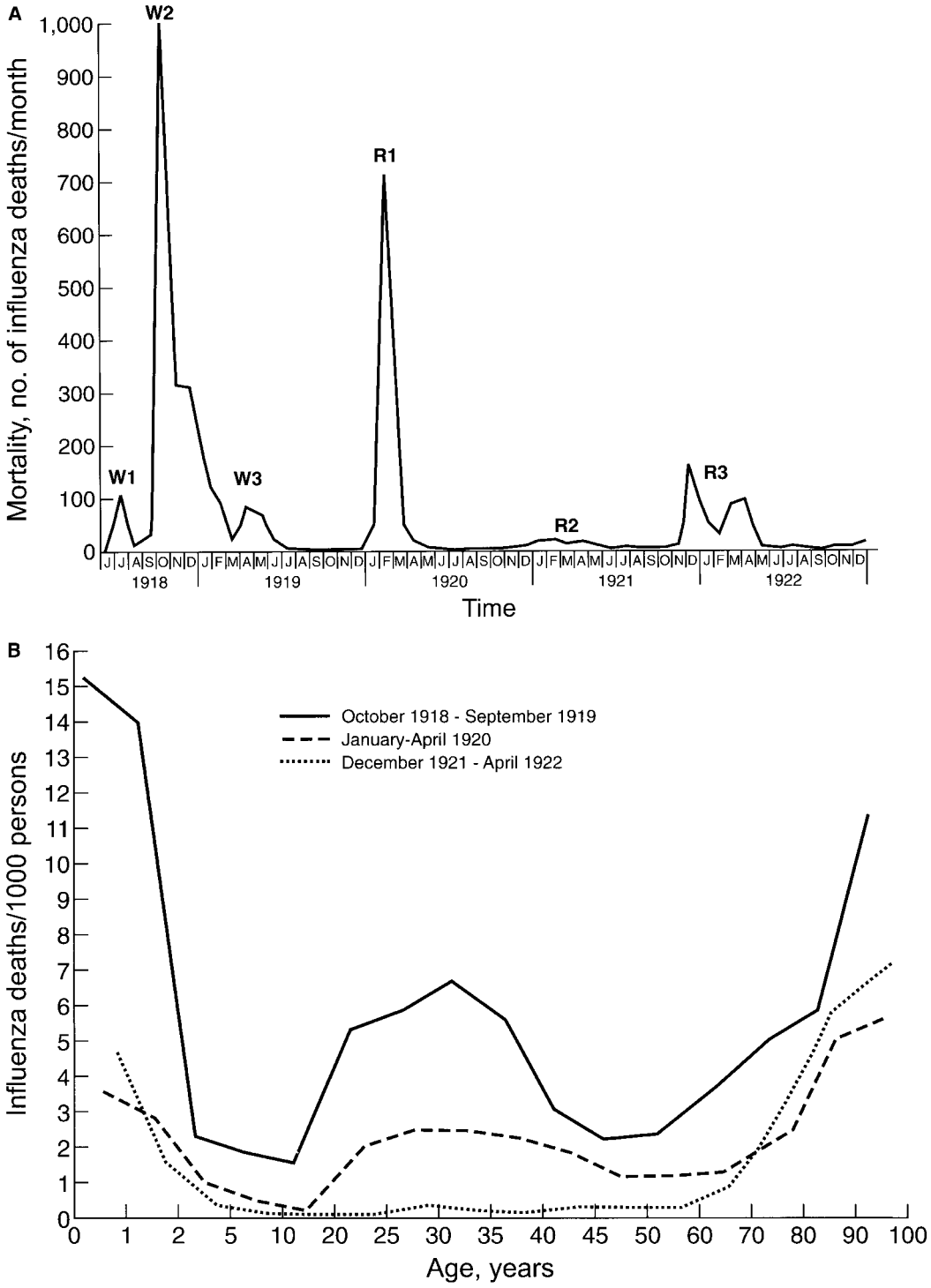

Figure 2. *A,* Monthly influenza-associated mortality in Breslau, Silesia (now Wroclaw, Poland), from June 1918 through December 1922. On this graph, reproduced on the basis of data reported by Lubinski [44], we have superimposed indications of the 3 waves (W1, W2, and W3) of the 1918–1919 pandemic, as well as the first 3 annual winter postpandemic recurrences during 1919–1920 (R1), 1920–1921 (R2), and 1921–1922 (R3). During 1918–1919, many locales experienced these 3 waves. *B,* Age-specific influenza-associated mortality in Breslau, from July 1918 to April 1922. The unbroken line combines influenza-associated mortality during waves W2 and W3 of the 1918–1919 pandemic; the dashed line denotes influenza-associated mortality during the first winter recurrence, from January to April 1920 (R1); the dotted line denotes influenza-associated mortality during the R3 winter recurrence, from December 1921 to April 1922. The peak young-adult mortality, documented worldwide, is evident in the W2+W3 and R1 curves of 1919–1921 but has completely disappeared by 1922.

acute respiratory distress–like syndrome (ARDS) [42] in which patients developed a peculiar "heliotrope cyanosis" characterized by blue-gray facial discoloration and essentially drowned from "huge [amounts of] … thin and watery bloody exudates in the lung tissue and bronchioles" [24, p. 650]. There are few if any representative data to document these percentages exactly, and there are marked differences between various published series and between military and civilian populations. Nor is it certain that deaths due to either the ARDS-like syndrome or bronchopneumonias lacking massive bacterial invasion represented primary viral pneumonias. Although these 2 pathologic pictures may not be unique to the 1918 pandemic [43], they clearly occurred with significantly greater frequency than they had during other known influenza pandemics. It seems reasonable to propose that in the 1918 pandemic many excess deaths resulted from a disease process that began with a severe acute viral infection that spread down the respiratory tree, causing severe tissue damage that often was followed by secondary bacterial invasion. More-definitive answers regarding disease pathogenesis may be fostered by a comprehensive reexamination of 1918 autopsy series.

EXCESS DEATHS AMONG THE YOUNG AND HEALTHY

Two unique epidemiologic features account for most excess mortality in 1918–1919: a high case-fatality rate at all ages, and a surprising excess of mortality among 20–40-year-old individuals, an age group at comparatively low risk for influenza mortality in pandemics before and since. Curves of influenza mortality by age at death are typically U-shaped, reflecting high mortality in the very young and the very old, with low mortality at all ages between [8]; in contrast, the 1918–1919 pandemic and succeeding winter epidemic recurrences in 1919 and 1920 [44] produced W-shaped mortality curves, which featured a third mortality peak, in healthy young adults, which was responsible for approximately half of the total influenza deaths, including the majority of excess influenza deaths [8] (figure 2*B*).

Explaining the extraordinary excess influenza mortality in persons 20–40 years of age in 1918 is perhaps the most important unsolved mystery of the pandemic. These young adults were part of an age cohort born during 1878–1898; evidence suggests that, during that 20-year time span, there was wide circulation only of an H3 influenza virus [45], which appeared as a pandemic in 1889, in the middle of the birth-risk interval.

Host and environmental variables have not been systematically investigated as possible causes of increased mortality in the young and healthy. It is possible that vigorous immune responses directed against the virus in healthy young persons could have caused severe disease in 1918; for example, an unusually brisk and paradoxically pathogenic antiviral immune response has been observed when patients with AIDS respond to treatment with antiretroviral drugs; return of immune function leads to severe inflammatory responses to viruses and microorganisms infecting the patients (the immune-reconstitution inflammatory syndrome [46]). Another viral cause of severe ARDS—hantavirus pulmonary syndrome [47], especially in association with the North American Sin Nombre virus—features an unexplained preponderance of cases in young adults, a preponderance that appears not to be due solely to higher rates of exposure among this age group [48, 49]. It is conceivable that aberrant inflammatory responses play a role in this situation.

The notion that a so-called cytokine storm, a deleterious overexuberant release of proinflammatory cytokines such as interleukin-6 and -8 and tissue necrosis factor–α, could have contributed to the high mortality and excessive number of deaths among the young and otherwise healthy during the 1918 pandemic has been frequently proposed [50, 51]. This theory is bolstered by recent observations of fatal cases of H5N1 infection in humans [52], experimental studies of H5N1 in macrophages [53], and other information on immunopathogenesis [54, 55], which suggests that human infection with influenza viruses, including the 1918 virus [56, 57], can result in excessive release of cytokines. Experimental animal studies of reconstructed 1918 influenza-virus infection have also shown up-regulation of acute inflammatory cytokines [56–59]; for example, intranasal challenge of mice with the reconstituted 1918 virus led to a highly lethal and rapidly progressing pulmonary disease characterized by high viral growth, a histological picture of necrotizing bronchitis/bronchiolitis, alveolitis, alveolar hemorrhage and edema, and overexpression of acute inflammatory cytokines [58]. Comparison of pathologic findings during 1918–1919, cases of fatal human H5N1 infections [52], and 2 unrelated viral pulmonary diseases—namely, severe acute respiratory symdrome [60, 61] and severe hantavirus pulmonary syndrome [47, 62]—thought to be associated with cytokine storms suggests that, although they differ in pathologic features, ARDS may be a common end point. However, it must also be remembered that in 1918 many or most severe cases of influenza-related pulmonary disease featured both severe bronchopulmonary tissue damage and severe secondary bacterial infection [8].

Immunopathogenesis may also differ between various age groups because people of different ages have been exposed to different viruses at different times and because response to a new virus may depend on the history of previous exposures. In this regard, antibody-dependent enhancement of infection, which has been suspected as a cause of dengue hemorrhagic fever in association with second dengue infections, has been demonstrated in vitro with influenza viruses [63]. Alternatively, the W-shaped mortality pattern could be consistent with an environmental exposure peculiar to young adults (e.g., smoking or aspirin use); however, data ex-

amining this possibility have not been reported, and thus the 1918 W-shaped mortality curve and the extremely high mortality in young adults remain to be fully explained.

LOWER-THAN-EXPECTED MORTALITY AMONG THE ELDERLY

Although both mortality and the case-fatality rate in 1918–1919 were higher, at all ages, than would be expected on the basis of prior (and subsequent) pandemics/epidemics, and although the expected pattern of markedly increased mortality with advancing age was clearly present, it is noteworthy that, although increased, mortality in the elderly was less pronounced than that in the other age groups (figure 3). It has been speculated that this might be due to previous exposure to an antigenically related influenza virus [64–66]. Yet, other than regional outbreaks [67, 68] and an 1872 American epizootic of equine influenza, which was associated with only mild human illnesses [69, 70], there is little evidence for major interpandemic influenza events during the period before 1889 [71]. Moreover, none of the 3 pandemics during the century before 1918 (in 1830, 1847, and 1889) are thought to have been associated with multiple, rapidly successive waves; W-shaped mortality curves; a predominance of aggressive bronchopneumonias; or marked hemorrhagic features characteristic of the 1918 pandemic [8, 17, 18, 72–79]. The 1889 pandemic, which occurred too closely in time to have offered protection only for older individuals in 1918, appears to have been caused by an H3 influenza virus [45]. The possibility of immunoprotection mediated by neuraminidase (NA), rather than by HA, during 1918 is intriguing [80], but there are few data bearing on this possibility: the identity of the 1889 NA is not known with certainty, although serologic data from 2 independent sources are consistent with an N8 virus appearing in approximately 1889 and circulating until some time before 1918 [81, 82], suggesting that the 1889 pandemic virus could have been of H3N8 identity. The 1847 pandemic might explain 1918 H1N1 protection in individuals >70 years old, but only if it was caused by an H1 or, less likely, N1 virus that was closely related antigenically but much less pathogenic.

THE 3 PANDEMIC WAVES IN 1918–1919: IMPLICATIONS FOR PREDICTING FUTURE PANDEMIC PATTERNS

Understanding patterns of pandemic spread is important in planning prevention strategies and anticipating public-health and medical burdens. Unlike all previous and subsequent pandemics, the 1918–1919 pandemic seems to have spread in at least 3 distinct waves within an ~9-month interval. Not all influenza pandemics have had such prominent recurrences, and those that did have tended to return at yearly intervals (e.g., 1889–1893), making them difficult to distinguish, in kind if not in impact, from normal seasonal influenza [8, 83]. Globally, the first wave of the 1918 pandemic, W1, occurred during spring-summer 1918 (as recognized in the Northern Hemisphere) and was associated with high morbidity but low mortality. The 2 following waves, in summer-fall 1918 (W2) and winter 1918–1919 (W3), were both deadly [7, 44] (figure 2).

It is difficult to make epidemiologic

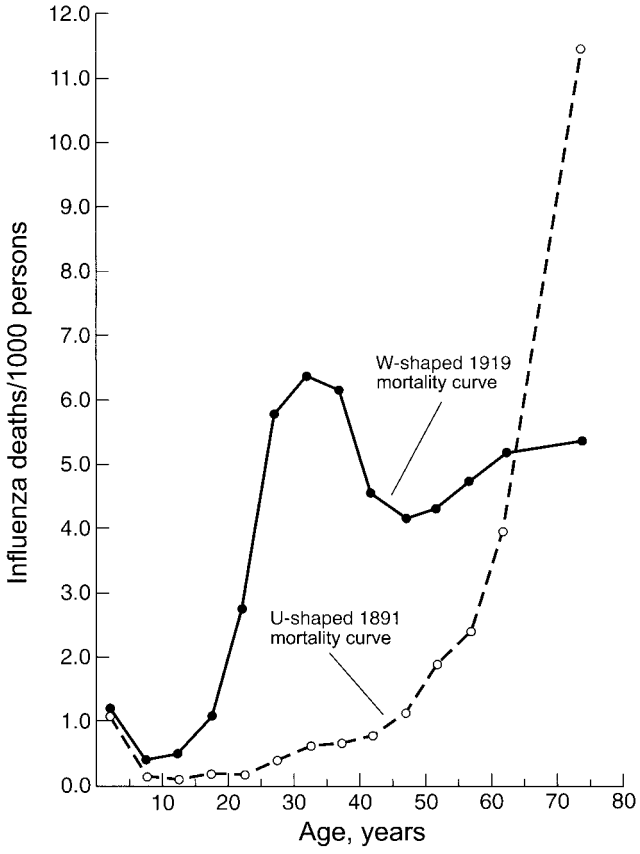

Figure 3. Influenza-associated mortality in New South Wales, Australia, during the 1891 and 1919 influenza pandemics [65]. The severe waves of the 1918–1919 pandemic in Australia were delayed until (the Southern Hemisphere) winter of 1919. Because population data by age in 1891 were not available, and because the mortality in males was similar to that in females, the 1891 data are based on published male/female mortality-rate means. In all age groups except persons >65 years old, the mortality per 1000 persons per age group during 1919 (●—●) were higher than those during 1891 (○ — ○), and the age-specific mortality curve was W-shaped, featuring a middle peak of mortality in young adults.

sense of this pattern. If some combination of rising population immunity and unfavorable seasonality had reduced W1 circulation during the spring of 1918, it is hard to explain how W2 could have begun almost immediately thereafter—and in the summer, normally the least favorable time for influenza-virus circulation. Also, it is difficult to explain why, at least in some locales, the early-summer end of W1 was largely free of mortality whereas the late-summer/early-fall onset of W2, appearing so soon thereafter, was associated with extraordinarily high mortality.

The question arises whether different influenza viruses caused the different waves. In this regard, all of the viruses so far identified by the Taubenberger laboratory are from W2 [8]. It would be useful to know whether illness during W1 protected against illness during W2 and W3, which would imply viral antigenic similarity or identity. However, there are few good data addressing this issue, and those which exist are both imperfect and contradictory [84]. Although the most reliable data demonstrate W2 protection against W3, they also suggest that W1 protection against W2 or W3 illness was minimal at best [85]. It is also possible that mutation of the pandemic virus, leading to greater pathogenicity, was occurring during mid-1918; however, this possibility does not in itself explain generation of apparently low protective immunity after high attack rates in W1. The implication that 2 H1N1 phenotypes were circulating during the fall wave (W2), discussed above, also remains to be explained, given (1) that W2 did appear to protect against illness in W3 and (2) that, after several years had passed, influenza mortality declined to baseline levels, a finding consistent with powerful population immunity and emergence of less pathogenic viruses. Thus, the 3 waves of the 1918–1919 pandemic remain unexplained, and there is, thus far, little basis for predicting the recurrence pattern of the next pandemic.

PREDICTING INFLUENZA PANDEMICS

The occurrences of 3 influenza pandemics during the 19th century and of another 3 during the 20th century [1] have led some experts to conclude that pandemics occur in cycles and that we are now overdue. Belief in influenza cyclicity can be traced to epidemiologic efforts during the mid 19th century; after the 1889–1893 pandemic, interest in examining the patterns of influenza recurrence was renewed [86]. By the 1950s, cumulative historical information [5–7, 67, 68, 72–79] seemed 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. At approximately the same time, it was becoming clear that high levels of population immunity pressured postpandemic viruses to drift antigenically and that surface protein–encoding genes could potentially mix with other HA and NA genes to which humans lacked immunity [87]. It was reasonable to assume that such an intimate viral-immunologic 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 10–11 years; however, in 1976 a fatal H1N1 "swine flu" outbreak raised considerable alarm without causing a predicted pandemic [88], and, a year later, after 20 years of natural "extinction," an H1N1 descendant of the 1918 virus suddenly reemerged to reestablish postpandemic cocirculation with one of its own further descendants, the H3N2 influenza virus [89], setting up nearly 3 decades of endemic cocirculation of former pandemic viruses that has continued until today (2006).

Fading belief in pandemic cycles has been acknowledged by influenza authorities. For decades, noted influenza expert Edwin Kilbourne, Sr., articulated both the widely held conviction about pandemic cyclicity and its scientific rationale. Examination of more-recent evidence, however, leads Kilbourne to conclude that "there is no predictable periodicity or pattern" of major influenza epidemics and that "all differ from one another" [90, p. 9]; without pandemic cycles there can be little basis for predicting pandemic emergence.

It has become clear that pandemic emergence can result from at least 2 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 (e.g., the 1957 H2N2 pandemic) or without such concomitant importation (e.g., the 1968 H3N2 pandemic) [8]. There is no reason to suppose that these 2 different pandemic mechanisms should be capable of producing the same cyclic intervals—or that other, competing adaptational mechanisms, such as reassortment with closely related HAs [91] 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 catalog of naturally occurring influenza surface-protein genes theoretically capable of causing new pandemics by reassorting themselves into human-adapted strains, only 3 of 16 known HAs (i.e., H1, H2, and H3) and 2 of 9 known NAs (i.e., N1 and N2) are known to have done so during the past 117 years [87, 92].

Drawing on the earlier theories proposed by Thomas Francis, Jr. [93], and others, Maurice Hilleman attempted to reconcile these complications by proposing a form of "macrocyclicity" in which reappearances of H1, H2, and H3 (approximately every 68 years) are driven by cycles of waning population immunity that have approximately the same dura-

tion as does the mean human life span [87]. Because scientific evidence of viral identity extends backward for only 117 years, it will take many future generations to fully test Hilleman's hypothesis.

Historical evidence of pandemic occurrences provides no obvious cyclic patterns during the past 3 centuries [67, 68, 72–79, 94–97] (figure 4). Presumably, mutable viruses producing high population immunity will eventually drive their own evolutionary changes; however, if pandemic cycles do occur, they must be so irregular as to confound predictibility.

PREVENTING MORBIDITY AND MORTALITY IN FUTURE PANDEMICS

The weight of evidence, supported by mathematical modeling data [98], suggests that if a novel virus as pathogenic as that of 1918 were to reappear today, a substantial proportion of a potential 1.9 million fatalities (assuming 1918 attack and case-fatality rates in the current US population) could be prevented with aggressive public-health and medical interventions. In an age of frequent air travel, we might expect global spread to proceed rapidly and to be difficult to control, but hardly much more so than the 1918 pandemic, in which most of the world was affected by W2 within a matter of a few weeks.

Almost all "then-versus-now" comparisons are encouraging, in theory. In 2007, public health is much more advanced, with better prevention knowledge, good influenza surveillance, more trained personnel at all levels, established prevention programs featuring annual vaccination with up-to-date influenza and pneumococcal vaccines, and a national and international prevention infrastructure. Also important for pandemic response are 2 classes of antiviral drugs (adamantanes and neuraminidase inhibitors), one or both of which have proven effective, in culture, against most of the currently circulating H5N1 viruses. However, antiviral resistance might appear fairly quickly, and circulating H5N1 strains in several countries have already been shown to be adamantane resistant [99]. We also have antibiotics to treat pneumonias caused by all of the major bacteria implicated in the 1918 pandemic; hospital-based intensive care and supportive therapy, including ventilatory support for patients with severe ARDS; and a biomedical research ca-

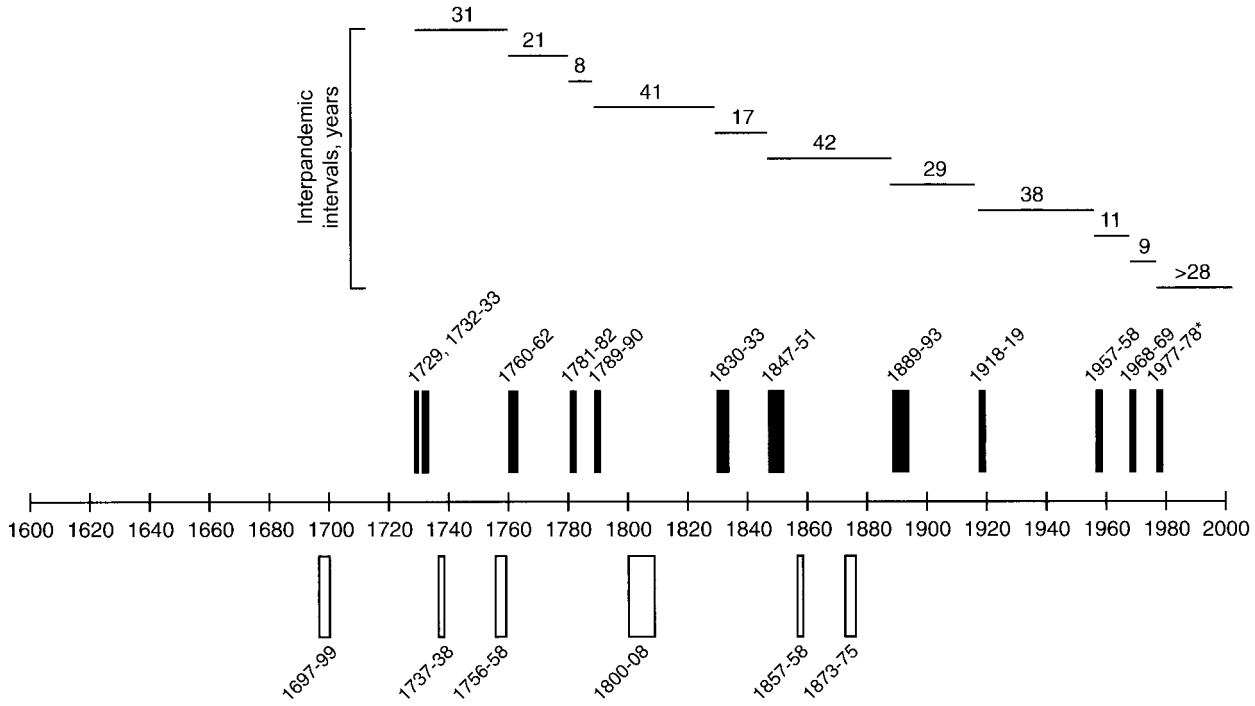

Figure 4. Influenza pandemic occurrence, 1600–2000. Information was compiled from historical references [67, 68, 72–79, 94–97] and from scientific publications from 1889 to the present (not cited). Interpandemic intervals are noted at the top of the graph. Pandemics are associated with (1) abrupt and widespread epidemicity in multiple locales in 2 or more geographic regions, (2) rapid progression through large open populations, (3) high clinical-illness rates affecting a broad range of ages, and (4) no other pandemic activity within 5 years (to adjust for the possibility of slow and interrupted pandemic spread before the mid 19th century). Especially before 1697, pandemics may be difficult to verify and track, because of slower spread [87] as a result of slower and less frequent human travel. Some cited sources suggest different interpretations than those presented here (see text and references [67, 68, 72–79, 89–92]). The black bars (■) denote pandemics; the white bars (□) denote major widespread epidemics that do not meet pandemic criteria. The 1977 reemergence and global spread of an "extinct" descendant of the 1918 pandemic virus, denoted by the asterisk (*), is included here as a pandemic emergence, although it might also be considered as reflecting the continuing spread of the original pandemic virus.

pacity rapidly compiling critical knowledge about many aspects of influenza.

The most difficult challenge would probably not be to increase medical knowledge about treatment and prevention but to increase medical capacity and resource availability (e.g., hospital beds, medical personnel, drugs, and supplies) and public-health and community-crisis responses to an event in which 25–50% of the population could fall ill during a few weeks' time. Health-care systems could be rapidly overwhelmed by the sheer volume of cases; ensuring production and delivery of sufficient quantities of antivirals, vaccines, and antibiotics, as well as providing widespread access to medications and medical care, particularly in impoverished regions, would be a sobering challenge. And the just-in-time nature of our supply chain of necessary medications and equipment for medical care could easily be disrupted by such a global public-health catastrophe.

Moreover, because most of the world would not have access to the same level of prevention and medical care as is available to developed countries, the greatest burden of pandemic influenza would fall on those least privileged. The best hope for everyone may rest on the future development and stockpiling of vaccines that are more broadly efficacious—for example, "universal" influenza vaccines based on either immunogenic antigens shared by all influenza viruses [100] or multivalent HAs and NAs [101], both of which are currently being developed. In the meantime, efforts must be directed toward prevention based on improved understanding of pandemic risks, increased surveillance, development of countermeasures, logistical planning, and an aggressive and broad research agenda.

It is noteworthy that influenza research during the past decade has simultaneously looked both forward and backward in time, not merely to connect the dots but to identify slowly unfolding patterns that can only be revealed when examined in their entirety—for example, the remarkable evolution of the several related pandemic influenza viruses that have appeared and circulated during the past century. The more that we learn about these viruses and about what they are capable of doing to maintain their deadly relationship with the human species, the more remarkable they seem. The challenge for us humans is to learn as much about influenza viruses as they have already learned about us. Arguably, we have not yet done so, but we are clearly gaining ground, and there is good reason to believe that the next decade will yield significant advances in fundamental knowledge and, more importantly, in prevention and control. Today, nearly a century after the event, mysteries surrounding the 1918 influenza pandemic remain largely unexplained. However, we must continue to examine and investigate this long-ago tragedy, allowing it to stand clearly before us as a challenge to complacency, as a modern problem with future implications, and as a grim reminder of the importance, to humanity, of continuing the fight against emerging and reemerging infectious diseases.

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