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The 1918 influenza pandemic: Lessons for 2009 and the future

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Abstract

The 1918 to 1919 H1N1 influenza pandemic is among the most deadly events in recorded human history, having killed an estimated 50 to 100 million persons. Recent H5N1 avian influenza epizootics associated with sporadic human fatalities have heightened concern that a new influenza pandemic, one at least as lethal as that of 1918, could be developing. In early 2009, a novel pandemic H1N1 influenza virus appeared, but it has not exhibited unusually high pathogenicity. Nevertheless, because this virus spreads globally, some scientists predict that mutations will increase its lethality. Therefore, to accurately predict, plan, and respond to current and future influenza pandemics, we must first better-understand the events and experiences of 1918.

Although the entire genome of the 1918 influenza virus has been sequenced, many questions about the pandemic it caused remain unanswered. In this review, we discuss the origin of the 1918 pandemic influenza virus, the pandemic's unusual epidemiologic features and the causes and demographic patterns of fatality, and how this information should impact our response to the current 2009 H1N1 pandemic and future pandemics. After 92 yrs of research, fundamental questions about influenza pandemics remain unanswered. Thus, we must remain vigilant and use the knowledge we have gained from 1918 and other influenza pandemics to direct targeted research and pandemic influenza preparedness planning, emphasizing prevention, containment, and treatment.

Keywords

infectious diseases; influenza; influenza virus; pandemic; pathogenesis; pneumonia; viral diseases

The 2009 pandemic of swine-origin H1N1 influenza, the first new influenza pandemic in 41 yrs, and the decade-long circulation of highly pathogenic avian H5N1 influenza have raised interest in studying pandemics. Of these, the 1918 to 1919 "Spanish flu" pandemic was among the deadliest public health crises in human history, killing an estimated 675,000 people in the US and approximately 50 to 100 million people worldwide (1). This pandemic's explosive pattern of rapidly recurrent waves and its predilection to kill the young and healthy (2–4) have contributed an urgent element to pandemic planning today.

The entire eight-segment genome of the 1918 influenza virus was sequenced using tiny RNA fragments recovered from the lungs of several victims (5–7). This scientific milestone has spurred many important avenues of research, including investigations into the possibility that the 1918 virus may have arisen not by gene reassortment between a human and an

animal virus but by genome adaptation, a mechanism of pandemic virus generation not previously documented in humans. Despite such insights, many fundamental questions remain, including those that have implications for pandemic preparedness today (Table 1). We asked some of these questions in a 2007 review (8), and here we incorporate rapidly accumulating knowledge from the ongoing 2009 pandemic and other advances to provide additional information.

Origin of the 1918 Pandemic Influenza Virus

The 1918 to 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 avian (9), consistent with the knowledge that the enteric tracts of waterfowl, such as ducks and geese, serve as reservoirs for all known influenza A viruses (9, 10). What remains poorly understood are the mechanisms whereby avian influenza viruses can adapt to new mammalian hosts and infect very different cell types—for example, accumulating point mutations or reassortment with gene segments from a different influenza virus to enable infection of human respiratory epithelial cells rather than duck enteric cells (7, 10).

The host that served as the source of the 1918 H1N1 influenza virus has not been identified, nor is it known how the virus adapted to humans. Examination of the genome of the 1918 virus (5, 6) has not provided complete answers; however, it has posed difficult new questions and has raised the possibility of alternative mechanisms of generation (11). Whereas all eight 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 2009. The differences are primarily caused by greater-than-expected numbers of silent nucleotide changes. Furthermore, the genes of the 1918 virus apparently evolved together in parallel, possibly in an unidentified host (7). Unlike the 1957 and 1968 pandemics, each of which resulting from reassortment between circulating descendants of the 1918 human virus and circulating avian influenza strains (12), the 1918 pandemic may well have arisen by *de novo* genetic adaptation of an existing avian virus to a new (human) host (6, 7, 9).

In contrast, the 2009 H1N1 influenza pandemic virus was generated by reassortment between two well-established swine influenza virus lineages (13): one is a North American descendant of the 1918 human virus that has long-circulated in pigs, and the other is a swine virus lineage derived from complete genome adaptation of an avian virus. Reassortment importation of avian influenza and other swine influenza genes into the North American descendant before the emergence of the 2009 H1N1 pandemic further adds to the genetic diversity of this virus. Although the 2009 H1N1 virus is a multiple reassortant hybrid virus containing swine, human, and avian influenza viral genes, it has been evolving in full view of modern genetic surveillance for more than a decade. Its origin and evolution can be traced back to the 1930s and, by inference, to 1918.

The lack of influenza virus sequence data before 1918 obscures the origin of the 1918 pandemic virus. However, at least two different H1N1 influenza strains with markedly different receptor-binding specificities, both fatal to humans, were circulating simultaneously in 1918 (14). One strain contained variations in both the 190 and 225 codons (E190D and D225G) of the H1 gene. These changes enable the hemagglutinin (HA) protein of the virus to bind only to (2–6) α -sialic acid receptors typically found on mammalian cells. The second circulating strain contained only the E190D change, rendering it capable of binding to both mammalian (2–6) α receptors and avian (2–3) α -sialic acid receptors (15, 16). The ultimate avian ancestor of the 1918 virus was likely a low pathogenicity strain, because the viral hemagglutinin lacks the polybasic cleavage site mutation characteristic of

highly pathogenic avian influenza viruses, as found in the current H5N1 lineages. Thus, even if the 1918 precursor virus had circulated widely in wild or domestic bird species before the 1918 pandemic, avian die-offs would not have been expected. The 1918 H1N1 and the current H5N1 influenza viruses thus seem to be evolutionarily quite different.

Pathogenesis and Excess Mortality in 1918 to 1919

Typical seasonal influenza infections cause classic symptoms, such as 4 to 5 days of fever, chills, headache, muscle pain, weakness, and sometimes upper respiratory symptoms and cough. Other influenza infections are asymptomatic or cause only mild or vague symptoms. Influenza usually does not kill healthy children and adults (17), but severe complications and deaths can occur, especially in infants, the elderly, and individuals with chronic health conditions, such as cardiac disease, respiratory disease, or immunosuppression. Among the most severe influenza complications is pneumonia, typically associated with secondary or coinfection with bacterial agents (18).

The 1889 to 1893 pandemic was the first influenza pandemic to be widely studied scientifically (19, 20). To older physicians in 1918, obvious similarities to the 1889 pandemic included its highly contagious nature, with clinical attack rates typically ranging between 20% and 60%. In both pandemics, most deaths resulted from respiratory complications, usually pneumonia with bacterial invasion; however, in 1918 some observers suggested new and severe clinical forms of disease. Many 1889 pneumonia deaths had been attributed to familiar conditions such as subacute bacterial lobar pneumonia, whereas this background influenza mortality was seemingly augmented in 1918 by more frequent cases of aggressive fatal bronchopneumonia and deaths associated with progressive cyanosis and collapse. Some modern scientists have theorized that such 1918 deaths might be immunopathogenic in nature (e.g., caused by “cytokine storms”), although many data from that era suggest that almost all deaths resulted from secondary bacterial bronchopneumonia of a clinical type, spectrum, course, and lethality characteristic of pneumonias not associated with influenza (18).

In a pattern remarkably different from that of the 1889 to 1893 pandemic, which made at least three successive annual and largely seasonal reappearances, the 1918 pandemic spread in one to three rapidly recurring “waves” over a 9-mo period (Fig. 1A) (21) before settling into an annual pattern of seasonal recurrence. Most countries experienced waves only in October 1918 and February 1919, but a few countries, mostly Northern European, had an additional earlier wave in summer 1918 (22). Some countries documented single waves of disease, a delay in initial pandemic detection of up to 3 yrs beyond 1918, or, in rare cases, documented no illness at all. Furthermore, mortality rates in the latter two of the three 1918 to 1919 waves were much higher than in 1889 for all ages except the elderly, and the 1918 to 1919 pandemic also featured an enormous still-unexplained mortality in healthy young adults (Fig. 1B), an age group believed to have been at low risk for death in most 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 rates 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 (23–25). Although there is some similarity in the younger age group primarily affected by the 2009 pandemic H1N1 virus and the 1918 virus, the 2009 pandemic H1N1 infection is currently more like that of the pandemics of 1957 and 1968 in its production of severe and fatal disease.

As suggested by clinical and autopsy series (Fig. 2) (26–37), two overlapping and closely related clinical–pathologic syndromes were associated with in excess influenza deaths in 1918 to 1919. The most common appears to have been acute aggressive bronchopneumonia featuring tracheobronchial epithelial necrosis, alveolar edema, and hyaline membrane formation, and, less frequently, small vessel thrombi, microvascular necrosis, and hemorrhage. Pathologic changes were focal and widely variant in different parts of the lung, from which pathogenic bacteria could also usually be cultured at autopsy (Fig. 2A and B) (18, 32). In a few autopsies, severe bronchopneumonia was seen without evidence of bacteria, sometimes in association with an acute respiratory distress syndrome (ARDS)-like illness; however, studies generally showed a close correlation between the distribution of pneumonia lesions and cultured bacteria (38, 39). The major bacteria identified in the pandemic were the organisms now called *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and, less commonly, *Staphylococcus aureus* and *Haemophilus influenzae* (26, 40–44).

Accumulating evidence suggests that nearly all deaths in 1918 were associated with bacterial pneumonia and that frank ARDS-like syndromes in the absence of bacterial pneumonia, and thus, conceivably attributable to primary viral pneumonia and/or cytokine storms, must have been uncommon causes of death.

It seems reasonable to propose that many excess deaths in the 1918 pandemic resulted from a disease process that began with a severe acute viral infection that spread cell-to-cell down the respiratory tract, causing severe tissue damage but normally followed by prompt tissue repair unless secondary bacterial invasion ensued. The bronchial tree appeared to be the primary organ of involvement in severe 1918 influenza cases; when bacterial invaders in the nasopharynx gained access to the peripheral bronchial tree by direct extension along denuded bronchial epithelium, bronchopneumonia could then occur (18). Such secondary bacterial infection may be a general mechanism of severe influenza pathogenesis, because it has been seen in many fatal cases of seasonal influenza since 1918. Even today, a significant number of deaths caused by the 2009 H1N1 pandemic likely can be directly attributed to this mechanism of disease (45).

Excess Deaths Among the Young and Healthy

Most excess mortality in 1918 to 1919 can be explained by two unique epidemiologic features: a high case-fatality rate at all ages and a surprising excess of mortality among those aged 20 to 40 yrs, a group at comparatively low risk for influenza mortality in pandemics. 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 (7). The 1918 to 1919 pandemic and succeeding winter epidemic recurrences in 1919 and 1920 (21) instead produced W-shaped mortality curves, which featured a third mortality peak in healthy young adults that accounted for approximately half of the total influenza deaths, including the majority of excess influenza deaths (Fig. 1B and 3) (7).

Perhaps the most puzzling mystery of the 1918 pandemic is how to explain that extraordinary excess influenza mortality in persons 20 to 40 yrs of age. These young adults were part of a cohort born between 1878 and 1898. During that 20-yr period, archaeoserological evidence suggests wide circulation of only an H3 influenza virus (46), which may have appeared as a pandemic virus in 1889 in the middle of the birth risk interval.

Among many possible explanations, host and environmental variables have not been systematically investigated as possible causes of increased mortality in the young and healthy. It is conceivable that vigorous immune responses directed against the virus in

healthy young persons could have caused severe disease in 1918. For example, a brisk and paradoxically pathogenic antiviral immune response has been observed when people with human immunodeficiency virus/acquire immunodeficiency syndrome 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) (47). Another viral cause of severe ARDS, hantavirus pulmonary syndrome (48), especially in association with the North American Sin Nombre virus, features an unexplained preponderance of cases in young adults, which appears not to be attributable solely to higher rates of exposure (49, 50). Aberrant inflammatory responses may play a role in this situation as well.

Many have questioned whether a so-called cytokine storm, a deleterious profuse release of pro-inflammatory cytokines, such as IL-6 and IL-8, and tumor necrosis factor- α , could have contributed to the high mortality in the young and otherwise healthy during the 1918 pandemic (51, 52). This hypothesis is bolstered by recent observations of fatal human H5N1 cases (53), experimental H5N1 studies in macrophages (54), and other information on immunopathogenesis (55, 56), all of which suggest that human infection with influenza viruses, including the 1918 virus (57, 58), can result in excessive cytokine release. Experimental animal studies of reconstructed 1918 influenza virus infection also have shown marked up-regulation of acute inflammatory cytokines (57–60). 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 histologic picture of necrotizing bronchitis/bronchiolitis, alveolitis, alveolar hemorrhage, and edema; and overexpression of acute inflammatory cytokines (59). Comparison of pathologic findings in 1918 to 1919, cases of fatal human H5N1 infections (53), and two unrelated viral pulmonary diseases thought to be associated with cytokine storms—severe acute respiratory syndrome (61, 62) and severe hantavirus pulmonary syndrome (48, 63)—suggest that they differ pathologically but that ARDS may be a common end point. However, it also must be remembered that most severe cases of influenza-related pulmonary disease in 1918 featured both severe bronchopulmonary tissue damage and severe secondary bacterial infection (7), and that without antibiotics such infections could not be adequately treated.

Another possible immunopathogenetic mechanism is the effect of past exposures to different viruses at different points in time on the immune response to the new 1918 virus. 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 (64). Alternatively, the W-shaped mortality pattern could be consistent with an environmental exposure peculiar to young adults (e.g., smoking, aspirin use); however, this possibility has not been well-studied (65). Thus, the 1918 W-shaped mortality curve and the extremely high death rate in young adults remain to be fully explained.

As of November 2009, there has been considerable speculation that the new ongoing H1N1 pandemic is exhibiting a 1918-like, W-shaped mortality pattern, including increased cases of severe disease in young adults and partial protection of the elderly. However, protection of older adults in 2009 is much greater than it was in 1918, and that protection from death is attributable, at least in part, if not wholly, to protection from infection in the first place. To date, no evidence exists of increased severity/increased fatality in young adults; in fact, the risk of death to a single infected individual is higher in older persons, a group in which attack rates of 2009 H1N1 have so far been extremely low but in which higher case fatality rates have been seen in almost all influenza pandemics and seasonal influenza epidemics in the past.

Lower-Than-Expected Mortality Among the Elderly

Although the expected pattern of markedly increased mortality with advancing age was clearly present in 1918 to 1919, and both mortality and case-fatality rates were higher at most ages than expected based on previous (and subsequent) pandemics/epidemics, mortality in the elderly was less pronounced than that in other age groups (Fig. 3) (7, 8, 66, 67). This lower-than-expected mortality among individuals who were older than 45 yrs in 1918 implies partial protection from disease and, perhaps, from infection [2–4, 6]. This lower mortality rate might be attributable to previous exposure to antigenically related influenza viruses (68, 69), similar to what may be causing the reduction of attack rates of the 2009 H1N1 in the elderly (70). Yet, other than regional outbreaks (71, 72) and an 1872 American epizootic of equine influenza associated with only mild human illnesses (73, 74), there is little evidence for major interpandemic influenza events in the three decades before 1889 (75). Furthermore, none of the three pandemics in the century before 1918 (in the 1830s, 1847, and 1889) are thought to have been associated with multiple, rapidly successive waves or W-shaped mortality curves (7, 19, 20, 76–84).

The pandemics of the 1830s and of 1847 might help explain 1918 H1N1 protection in individuals older than age 70 yrs, but only if they had been caused by an H1 or, less likely, an N1 virus that was closely related antigenically to the 1918 virus. Evidence is consistent with the possibility that the influenza pandemics of 1830 to 1831, 1833 to 1834, and 1836 to 1837 could have been caused by one pandemic virus whose recurrences spanned 2-yr intervals (84), and that the restricted 1847 pandemic may have represented a return of that pandemic virus. The 1847 pandemic appears to have been inter-regional but not global, sparing the Western hemisphere, at least from 1847 to 1849 (84). The 1889 pandemic was too recent to have offered protection only for older individuals in 1918 and may have been caused by an H3 influenza virus (46). The possibility of immunoprotection mediated in 1918 by neuraminidase, rather than by HA, is intriguing (85), but few data support this possibility because the identity of the 1889 neuraminidase is unknown.

In stark contrast, the generally low attack rates in persons older than approximately 50 yrs in 2009, an increasingly well-documented pattern (86 – 88), appear to explain the lower-than-expected number of total deaths in older persons and, consequently, the proportionally greater number of cases in younger persons. Presumably, such age shifting has resulted from the widespread circulation of human H1N1 viruses after 1918 and, conceivably, also to seasonal H1N1 influenza vaccines. Although accurate data are still lacking, it would not be surprising if the current pandemic results in high case-fatality rates but low population mortality rates among older persons; that is, few older persons would have disease but those who did would still face a substantial risk of severe disease and death. Preliminary data suggest the possibility of 2009 H1N1 protection against infection in persons older than 40 yrs and, independently, against death in those older than approximately 60 yrs (89).

The Three Pandemic Waves in 1918–1919: Implications for Predicting Future Pandemic Patterns

To plan prevention strategies and anticipate public health and medical burdens, it is important to understand patterns of pandemic virus spread. Unlike all previous and subsequent influenza pandemics, the 1918 to 1919 pandemic seems to have spread in up to three distinct “waves” within a 9-mo period. Not all influenza pandemics have had such prominent recurrences, and those that did 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 (7, 90). Globally, the first wave of the 1918 pandemic (W1), as measured by pneumonia and influenza mortality, occurred in only a few mostly Northern European

countries in the summer of 1918 (as recognized in the Northern hemisphere), largely in July and August, and was associated with modest mortality. The two following waves in summer to autumn 1918 (W2) and winter 1918 to 1919 (W3) were seen in most of the world. Both were more deadly than the first wave (Fig. 1A) (4, 21, 22), perhaps because of higher attack rates or higher case-fatality rates. As noted, almost all countries experienced only one or two waves (approximately October 1918 and February–March 1919), although several other confusing patterns also were seen, including summer to autumn 1918 epidemics with very low mortality and fatal waves delayed for several years beyond 1918.

Making epidemiologic sense of these patterns is difficult; increased viral virulence has been invoked, but without evidence and despite the historical record of other pandemics. Unfavorable environmental conditions (summer temperature and humidity) might have slowed the initial appearance of the virus until the autumn, a phenomenon consistent with the 1957 and the current 2009 pandemic, as seen in the Western hemisphere. However, the effect of season on pandemic virus transmission is incompletely understood. Conceivably, viral, host, and environmental factors may interact in complex ways, e.g., a changing balance between aerosol vs. droplet/contact/fomite transmission during different seasons, expressed in the context of gradual virus evolution and growing population immunity.

Predicting Influenza Pandemics

Long ago, experts concluded that influenza pandemics occur in cycles, with accepted intervals varying from as long as 31 yrs (as articulated in 1792) (91) to as short as 10 yrs (as articulated in 1841) (92). After the 1889 to 1893 pandemic, interest in examining such influenza recurrence patterns was renewed (93) but the unexpected emergence of the 2009 H1N1 pandemic has again demonstrated difficulties in prediction of cycles. By the 1950s, cumulative historical information (2–4, 71, 72, 76–83) seemed to confirm the notions of early 18th and 19th century observers that pandemics appear in regular cycles. At that time, this seemed to make biological sense. Before the current pandemic, 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, high population immunity seemed to pressure postpandemic viruses to drift antigenically, and surface protein-encoding genes potentially could mix with other HA and neuraminidase genes, to which humans lacked immunity (94). Given these facts, it was reasonable to assume that such an intimate viral–immunologic relationship would have a predictable life span.

The prevailing view during approximately the 1957 and 1968 pandemics was that they tended to recur as frequently as every 10 to 11 yrs, exactly as predicted in 1841, at which time a clear distinction between influenza pandemics and epidemics had not yet been made. However, in 1976, a fatal H1N1 “swine flu” outbreak raised considerable alarm without causing a predicted pandemic (95). A year later, after 20 yrs of natural “extinction,” an H1N1 descendant of the 1918 virus suddenly re-emerged to reestablish post-pandemic co-circulation, along with one of its own descendants, the H3N2 influenza virus (96), setting up nearly three decades of endemic co-circulation of former pandemic viruses that has continued up until today.

The events of 2009 have complicated the picture even further. We now find ourselves in an era in which a direct descendant of the 1918 H1N1 virus circulates endemically, along with two of its progeny: the postpandemic 1968 H3N2 reassortant virus, which had been updated at least twice by avian influenza genes before reaching humans, and the 2009 swine-origin pandemic influenza virus, which apparently jumped from pigs to humans after “triple” reassortment-associated updating by avian, other swine, and human influenza genes (13, 97).

Influenza authorities now express fading belief in pandemic cycles. For decades, noted influenza expert Edwin Kilbourne, Sr, articulated the widely held conviction about pandemic cyclicality and its scientific rationale. However, examination of more recent evidence led Kilbourne to conclude that "... there is no predictable periodicity or pattern of major influenza epidemics and ... all differ from one another" (98). Without pandemic cycles, there can be little basis for predicting pandemic emergence.

Although other scenarios have been suggested, pandemic emergence can probably result from at least three very different mechanisms: *de novo* emergence of a unique avian-descended virus (as perhaps occurred in 1918), modification of a circulating human-adapted virus by importation via genetic reassortment of a novel HA (7), and adaptation to humans of nonhuman mammalian adapted viruses (2009 H1N1). There is no reason to suppose that these three different pandemic mechanisms could produce the same cyclic intervals or that other competing adaptation mechanisms, such as reassortment with closely related HA (99, 100) or viral drift caused by changing population immunity induced by natural infection and increasing use of immunologically complex vaccines, could not disrupt cycles that might otherwise occur. Several "pseudopandemics" (pandemics by definition as applied to other infectious agents) have occurred by these mechanisms (97). Despite a large catalog of naturally occurring influenza surface protein genes theoretically capable of causing new pandemics, only three of 16 known HA (H1, H2, and H3) and two of nine neuraminidases (N1 and N2) are known to have done so in the past 120 yrs (7, 8, 94, 101).

Maurice Hilleman attempted to reconcile these complications by drawing on the earlier theories of Thomas Francis, Jr (102), and others to propose a form of "macrocyclicality" in which reappearances of H1, H2, and H3 (approximately every 68 yrs) are driven by cycles of waning population immunity of approximately the same duration as the mean human life span (94). Because scientific evidence of viral identity extends backward only 120 yrs, many future generations will be needed to fully test Hilleman's hypothesis.

No obvious cyclic patterns have occurred over the past three centuries (Fig. 4) (71, 72, 76–84, 103–106). 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 predictability. Therefore, vigilance is prudent, and continuous pandemic preparation is important to reduce the overall burden of morbidity and mortality of current and future pandemics.

Preventing Morbidity and Mortality in Future Pandemics

Advances in public health, medical technology, and medical care have had a major impact on influenza mortality. The weight of evidence, supported by mathematical modeling data (107), 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.

In both pandemic and seasonal influenza, a small number of previously healthy individuals will die in all age ranges, but those with chronic or acute underlying illnesses/conditions are always at greatly increased risk for influenza-related complications and death. Cardiopulmonary diseases, diabetes, immunocompromised states, and pregnancy are just a few of the many conditions that predispose to influenza complications (108). At the time of the 1918 pandemic, the underlying cause was unknown and thus there was little scientific basis for specific treatment. Convalescent plasma was tried (109), as were immune serums against known serotypes of complicating secondary bacterial invaders, including anti-*Pneumococcal* and anti-*Streptococcal* serums, but neither demonstrated conclusive evidence of efficacy.

Treatment of influenza in 1918 consisted largely of supportive nursing care, which by all accounts did decrease mortality rates. Today, a robust combination of pharmaceuticals, technology, and treatment algorithms are available to identify and treat patients at high risk and those who are severely ill. This level of medical care was unavailable in 1918, and much of it was unavailable in 1957 and 1968 as well. Today, we have increased public awareness, preventive strategies, and better/earlier diagnostic and treatment modalities of many chronic diseases in general. We can now identify patients at high risk for severe or complicated influenza and target them for early prevention, prophylaxis, or treatment, including administration of vaccines and antivirals.

When a patient with influenza seeks medical attention, rapid antigen testing for influenza and the timely availability of imaging and laboratory data (e.g., radiographs, computed tomography scans, arterial blood gases, sputum Gram stains, chemistry, and blood counts) allow emergency room and clinic physicians to determine whether the patient is at high risk for complications or requires further evaluation. Respiratory and pulmonary complications of influenza remain the most common causes of severe/fatal outcomes; many of the aforementioned techniques assist physicians in determining the presence or likelihood of complications, such as viral pneumonia, bacterial pneumonia, respiratory failure, and ARDS.

As noted, careful examination of autopsy tissue of fatal influenza cases from the 1918 pandemic indicates that bacterial pneumonia played an extremely important role in most deaths (23). Antibiotics, which became widely available after 1942, have over the past 70 yrs reduced the mortality rate of community-acquired pneumonia from 30% to 40% to approximately 15% (110–112). Severely ill patients and those with respiratory complications receive early empirical antibacterial therapy with any of a number of broad-spectrum antibiotics to treat infectious complications of influenza and mitigate bacterial pneumonia. In the antibiotic era, excess influenza mortality quickly declined from 15 to 50 per 100,000 persons in 1942 to <10 per 100,000 since 1951 (113–115).

Respiratory failure is a severe influenza complication that can result from induced bronchospasm, viral and bacterial pneumonia, or general systemic inflammatory response syndrome. The advent of mechanical ventilation has revolutionized supportive care of these patients. Modern intensive care units and mechanical ventilation matured after 1952, when invasive positive pressure ventilation was used during a Scandinavian polio epidemic. Additional significant advances in respiratory care followed in the 1960s. Noninvasive positive pressure ventilation has been shown to reduce mortality in patients with hypoxemic respiratory failure (116, 117), and invasive methods of mechanical ventilation are used with some success to support the most severely ill, including such advanced invasive modalities as extracorporeal membrane oxygenation (118). Advances during the past 30 yrs have been significant and may partly explain further decreases in excess influenza mortality since the 1970s to today's level of less than five per 100,000 persons annually (115).

Arrhythmia, myocardial infarction, and cardiopulmonary failure are also common causes of death in influenza. Continuous cardiac monitoring and electrocardiography are widely available to evaluate and monitor patients for cardiac events and changes. Echocardiography and other modalities are available to diagnose less common complications, such as myocarditis/cardiomyopathy. Loss of cardiac vascular tone attributable to sepsis and shock can also contribute to cardiopulmonary failure, and a wide array of vasopressors and cardiac inotropes are available to support patients during treatment of the infection and to reverse the process of systemic inflammation.

Since the 1918 pandemic, pharmaceutical advances in both antibacterial and antiviral therapy (119) have included two classes of antiviral drugs (adamantanes and neuraminidase inhibitors) proven clinically effective against most influenza viruses. However, antiviral resistance has appeared fairly rapidly in both seasonal and pandemic viruses, and development of resistance during the 2009 pandemic is possible. Almost all severely ill and hospitalized patients are treated with antivirals, but the clinical effects have been modest, and their utility in reducing mortality in a pandemic is unclear. Because studies are still ongoing to determine the optimal doses and the effect on outcome, decisions about antiviral prophylaxis or treatment need to be individualized based on a variety of factors, including the patient's risk status for influenza illness, complications, and transmission to others at risk.

The care of severely ill patients continues to evolve. Hospital and critical care have improved greatly since 1918, but many aspects of such advanced care are controversial, including studies evaluating the treatment of systemic inflammatory response syndrome with drug interventions such as steroids and activated protein C (drotrecogin alfa), ventilator management strategies such as limited use of sedation and low tidal volumes, and other interventions such as tight glucose control and newer modes of ventilation such as extracorporeal membrane oxygenation. The continued ongoing careful evaluation of critical care medicine techniques will likely have a further positive impact on future patients in whom severe disease develops.

Aside from medical technology, public health is more advanced than in 1918, with better medical and scientific knowledge about prevention, good influenza surveillance, more trained medical and public health 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. It is often said that there is little role for early pandemic detection and early public health intervention, but such recent events as the 2003 severe acute respiratory syndrome outbreak and the current 2009 influenza pandemic make this notion untenable. Although it is true that in an age of high-volume air travel, global spread of a pandemic influenza virus can proceed rapidly and can be impossible to control, even in 1918, before the age of commercial air travel, the virus was transmitted rapidly during the second wave, affecting most of the world within a matter of a few weeks. Today, the most difficult challenge is not pandemic detection or medical knowledge about treatment and prevention, but medical capacity, resource availability (hospital beds, medical personnel, drugs, and supplies), and public health and community crisis responses to an event in which up to half of the population could become ill within a few weeks.

Because of concern about the spread of H5N1, efforts over the past decade by both the US government and international health agencies have improved pandemic preparedness with stockpiles of antivirals, vaccines, and antibiotics, as well as increasing surge capacity of hospitals and emergency medical facilities. We are better-prepared than we ever have been, but providing widespread access to medications and medical care, particularly in impoverished regions, is still a sobering challenge. So far, the 2009 pandemic has been neither as explosive nor as fatal as many earlier pandemics. Furthermore, the age distribution of cases, concentrated in children and young and middle-aged adults, has spared the elderly.

Because most of the world does not have access to the same level of prevention and medical care as developed countries, the greatest burden of any influenza pandemic can be expected to effect those least privileged. Globally, environmental issues such as cold climates, lack of sewage systems, and lack of quality housing with amenities such as central heating are likely to contribute to excess mortality (120).

Undoubtedly, improved standards of living and quality health care constitute the best hope for lowering global pandemic influenza deaths, especially for persons in developing regions of the world, and more so when supplemented by the development and stockpiling of broadly efficacious vaccines. Truly universal influenza vaccines based on either immunogenic antigens shared by all influenza viruses (121) or multivalent HA and neuraminidases (122), both currently undergoing development, would provide broad protection. In the meantime, multidisciplinary approaches that include preventive medicine, treatment of acute and chronic disease, and good public health measures remain important components of any pandemic preparedness strategy. Furthermore, efforts must be directed toward prevention based on improved understanding of pandemic risks, increased surveillance, development of countermeasures, logistic planning, and an aggressive and broad research agenda.

CONCLUSION

Influenza research over the past decade has looked both forward and backward in time to identify virus transmission patterns, e.g., the remarkable evolution of several related pandemic viruses that have circulated during the past century (97). The more we learn about these viruses and their deadly relationship with the human species, the more remarkable they seem. The next decade should 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 and pandemics continue to emerge. We must continue to examine 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 of continuing the fight against emerging and re-emerging infectious diseases.

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Figure 1.

A, Three pandemic waves were observed in many locales in 1918 to 1919, as in these data from Breslau, Silesia (now Wrocław, Poland), documenting monthly influenza mortality from June 1918 through December 1922. The figure is reproduced from data of Lubinski (21), on which we have superimposed indications of the three 1918 to 1919 “waves” (W1, W2, and W3) and the first three annual winter postpandemic recurrences of 1919 to 1920 (R1), 1920 to 1921 (R2), and 1921 to 1922 (R3). B, Age-specific influenza mortality, Breslau, October 1918 to April 1922. The dark blue line combines influenza mortality in W2 and W3 of 1918 to 1919. The light blue line reflects influenza mortality in the first winter recurrence of January to April 1920 (R1). The orange line reflects influenza mortality in the R3 winter recurrence of December 1921 to April 1922. The young adult mortality peak, documented worldwide, is evident in the W2 + W3 and R1 curves of 1919 to 1921 but has completely disappeared by 1922.

Figure 2.

Histologic appearance of lung sections from two fatal cases of 1918 influenza, showing distinct clinical–pathologic forms. *A*, Some deaths, probably a minority, were associated with a severe and rapidly progressing clinical form thought to be similar to acute respiratory distress syndrome (8), which had not been characterized at that time. These patients had rapid progression and fluid-filled alveoli, although they also frequently had concomitant bacterial bronchopneumonia in other sections of the lungs. *B*, The majority of deaths in 1918 to 1919 appear to have been associated with severe bacterial bronchopneumonia from which *Streptococcus pneumoniae*, *Streptococcus pyogenes*, or, less commonly, *Staphylococcus aureus* could be cultured. The extent to which secondary bacterial pneumonia may have followed primary viral pneumonia is unclear, but most cases with histologic evidence of bacterial pneumonia also showed focal areas consistent with primary viral changes, as in (*A*). Hematoxylin & eosin stain; original magnifications 200×.

Figure 3.

U-shaped and W-shaped combined influenza and pneumonia mortality, by age at death, per 100,000 persons in each age group, US, 1911 to 1918. Influenza/pneumonia-specific death rates are plotted for the years before the pandemic, ie, 1911 to 1917 (blue line), and for the pandemic year 1918 (red line) (7, 66, 67).

Figure 4.

Influenza pandemic occurrence, 1500 to 2009. Information was compiled from historical references (69, 70, 74–82, 101–104) and scientific publications from 1889 to the present (not cited). Interpandemic intervals are noted on the top of the figure. Pandemics are associated with abrupt and widespread epidemicity in multiple locales in two or more geographic regions, rapid progression through large open populations, high clinical illness rates affecting a broad age range, and no other pandemic activity within 5 yrs (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 (86) as a result of slower and less frequent human travel. Some cited sources suggest different interpretations than those presented here (see text) (71, 72, 76–84, 98–101). *The 1977 re-emergence and global spread of an “extinct” descendant of the 1918 pandemic virus is included here as a pandemic emergence, although it might also be considered to reflect continuing spread of the original pandemic virus.

Table 1**Important questions posed by the 1918 pandemic**

Where did the 1918 virus originate?	An unknown source; unlike H5N1, from an avian influenza-like 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 other pandemics; most fatalities had secondary pneumonias caused by common bacteria, ARDS-like syndromes in a minority of cases; higher proportion of severe cases at all ages seen; 1918 virus virulence determinants not yet fully mapped
Why were there so many deaths among the young and healthy?	Unknown; unappreciated host or environmental variables possible, such as a robust immunologic 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 previous exposure to a virus eliciting protective immunity, conceivably the virus associated with the 1847 pandemic
Why were there three pandemic waves in 1918 to 1919, and what are the implications for predicting future pandemic spread?	Unknown; at least two virus variants in second wave; identity of viruses in 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, but developing world still at great risk

ARDS, acute respiratory distress syndrome.