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Historical and clinical aspects of the 1918 H1N1 pandemic in the United States

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ABSTRACT

One hundred years have passed since the 1918 influenza pandemic caused substantial illness globally, with an estimated 50 million deaths. A number of factors, including World War I, contributed to the spread of the pandemic virus, which often caused high symptomatic attack rates and severe illness. Major achievements over the last 100 years have been made in influenza prevention, diagnosis, and treatment; however, the potential for a severe pandemic to emerge remains unchanged. We provide a review of the historical context and clinical aspects of illness due to the influenza A(H1N1) virus as it emerged and spread in 1918, with a focus on the experience in the United States. Understanding the significant social disruption and burden of illness from the 1918 pandemic can help us imagine the possible impacts of a high severity pandemic if it were to emerge now.

1. Introduction

One hundred years have passed since the 1918 influenza pandemic caused substantial illness globally, with an estimated 50 million deaths (Johnson and Mueller, 2002). A number of factors, including World War I, contributed to the spread of the pandemic virus, which often caused high symptomatic attack rates and severe illness. Major achievements over the last 100 years have been made in influenza prevention, diagnosis, and treatment (Kumar et al., 2018); however, the potential for a severe pandemic to emerge remains unchanged. We provide a review of the historical context and clinical aspects of illness due to the influenza A(H1N1) virus as it emerged and spread in 1918, with a focus on the experience in the United States. Understanding the significant social disruption and burden of illness from the 1918 pandemic can help us imagine the possible impacts of a high severity pandemic if it were to emerge now.

1.1. 1918 World events

The 1918 pandemic appeared four years after World War I began. Wartime conditions included poor sanitation, overcrowding, and limited health services associated with trench warfare (Saunders-Hastings and Krewski, 2016). In addition, after a four-year period of wartime privation the European population was in poor general health (Jivraj and Butler, 2013). Although the U.S. had delayed entry into the war until April 1917, it also was experiencing wartime stress when the pandemic began.

As the U.S. entered the war, its troop strength was less than 400,000 (Byerly, 2010) necessitating a rapid military build-up. The Selective Service quickly registered over 24 million men so that, even with acceptance of only one of every six registrants (Byerly, 2005), U.S. troop strength exceeded four million by the war's end in November 1918 (Navarro, 2010). Preparing all of the new soldiers for combat required rapid construction of multiple training camps, many of which had influenza outbreaks in the spring of 1918. Recruits sometimes occupied camps before construction was complete. Camp hospitals and medical facilities were not always finished, and inadequate barrack space forced hundreds of thousands of men to sleep in tents (Barry, 2005). With the winter of 1917/1918 being the coldest on record east of the Rockies, crowding created many opportunities for transmission of respiratory viruses. The deleterious effect of crowding was later demonstrated from records of Camp Humphreys in Virginia where a regiment with 78.5 square feet/soldier experienced a 2.5% disease attack rate, while 26.7% became ill in a regiment with 45 square feet/soldier (Aligne, 2016).

Crowding was common among the civilian population as well and many cities, particularly on the east coast, also experienced influenza outbreaks in the spring of 1918 (Frost, 1919). The U.S. had become one of the most industrialized countries in the world and half of its population resided in cities filled with factories and office buildings (Rosner, 2010). The war industries pulled tens of thousands of additional

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workers into U.S. cities. Housing was inadequate for the expanding population and as many as four families shared a single apartment. In boarding houses, residents not only shared rooms, but beds as well, with many factories operating multiple shifts (Barry, 2005).

Factors other than the war however contributed to the pandemic, as most countries were not involved in the war and also experienced pandemic deaths (Johnson and Mueller, 2002). Shanks et al. described widely variable population mortality among island countries in the Pacific region, ranging from 0.1% in Tasmania to 22% in Western Samoa during 1918–21 (Shanks et al., 2018). After analyzing excess mortality occurring between 1918 and 1923 in 27 countries, Murray et al. reported large variations in excess mortality rates; ranging from 0.39% in the United States, a World War I Allied participant, to 4.39% in India, a non-participant. They reported that average individual income in the countries explained a large portion of excess mortality (Murray et al., 2006). Grantz et al. reported a similar socioeconomic effect at the city level after analyzing an historical dataset of nearly 8000 pandemic deaths in Chicago. Their data revealed that the rate of homeownership, likely a reflection of higher income and socioeconomic status, was significantly inversely related to mortality (Grantz et al., 2016). In response to this report, Shanks and Brundage noted that many infectious diseases other than influenza were more prevalent in areas of low socioeconomic areas, increasing the risk of influenza patients in those areas for acquiring secondary bacterial pneumonia. They cautioned however, that social circumstances are not necessarily causally-linked to 1918 H1N1 mortality (Shanks and Brundage, 2017).

1.2. 1918 Response capabilities

Medical care for influenza and its complications was very limited in 1918. Influenza viruses had not yet been isolated, and influenza diagnostics and influenza vaccines not yet developed. Antibiotics for treatment of secondary bacterial co-infections had not yet been discovered. Advanced organ supportive technologies did not exist, and intensive care units were not available until the 1950s. Specific antiviral treatment was not available until amantadine was used during the 1968 H3N2 pandemic.

In 1914, the U.S. Supreme Court had prohibited manufacturers from labelling medicines with untrue claims intended to defraud. However by 1918 premarket approval of drugs was still not required and the “intent to defraud” standard proved difficult to verify (Milestones in U.S. Food and Drug Law History, 2018). Therefore, a number of labs, including those at New York City's Public Health Department, Tufts and Tulane Universities, and the Medical School at the University of Pittsburgh, were able to quickly create vaccines that were widely used in military camps, state custodial institutions, private practices, and among hundreds of thousands of industrial workers. Most vaccines were designed to protect against “influenza bacilli,” a rod-shaped bacteria, commonly referred to as Pfeiffer's bacillus (Eyler, 2010) purported to be the cause of influenza upon its discovery in 1892 (Pfeiffer, 1892). Although many scientists before and during the pandemic began to doubt that this organism, later identified as *Haemophilus influenzae*, caused influenza, many others did not (French, 1920; Daland, 1919; Wetmore, 1919; MacNeal, 1919; Wolbach, 1919).

Since 1912 the U.S. Public Health Service had been granted broad powers authorizing investigation into human diseases, sanitation, water supplies, and sewage disposal (U.S. Department of Health and Human Services, 2018). Concepts of surveillance, sanitation techniques, quarantine, and isolation had achieved widespread legitimacy following decades of experience with outbreaks of cholera, yellow fever, typhoid, and a host of other infectious diseases (Rosner, 2010). Of 43 US cities studied, all used community mitigation measures during the fall of 1918 in an attempt to reduce morbidity and mortality. The most popular measures included school closures, public gathering bans, and isolation/quarantine orders. The timing and duration of the measures varied between cities, allowing some comparisons. Although we cannot assume cause and effect, generally cities that implemented non-pharmaceutical interventions earlier experienced delayed and reduced peak mortality, when compared to cities that implemented interventions later (Markel et al., 2007).

Unfortunately, in 1918, demands of World War I influenced the timing and messaging of public health precautions in some cities. Many public health officials resisted and delayed community mitigation measures under pressure from civil authorities who believed morale, and subsequently wartime productivity, could suffer. For example, in Philadelphia a Liberty Loan Parade, organized to raise millions of dollars for the war effort, occurred on September 28, 1918. Hundreds of thousands of patriotic residents jammed the two-mile route to cheer for bands, Boy Scouts, women's auxiliaries, sailors, and soldiers. Many physicians and health personnel requested cancellation of the parade following ominous warning signs of the impending pandemic, including the influenza hospitalizations of 1400 sailors at the Philadelphia Navy Yard. The Director of Philadelphia's Department of Public Health and Charities however, refused to call for cancellation or to issue any warnings to the population. On September 30, two days after the parade, he did issue a statement admitting that the influenza epidemic in the civilian population had now assumed the same level as that present in the naval stations and army camps, which were completely overwhelmed with influenza cases and deaths (Barry, 2005).

2. Epidemiology

The exact extent of morbidity and mortality from the 1918 pandemic is unknown because without laboratory confirmation, influenza is indistinguishable from other respiratory diseases. Autopsy samples that have been studied are primarily from the lung tissue of victims who died during the fall of 1918 (Sheng et al., 2011). Epidemiologic data are also incomplete. Influenza was not a reportable disease nor a disease that any state or federal public health agency tracked prior to the pandemic (Barry, 2004). As the case count and fatality of the pandemic became apparent during the fall of 1918, cities began requiring physicians to report cases of influenza. However, overwhelming caseloads precluded timely and/or accurate reporting (Influenza Encyclopedia, 2012). In the January 1919 American Journal of Public Health issue, the editor wrote that data in many cases were incomplete and confused as “so great was the pressure for action, that very few were able to devote any time to observation for the sake of the future” (Anon, 1919). Additionally, in an introduction to a review of influenza affecting the American military response in WWI, the author noted that scientific accuracy of disease reports from “belligerent” countries may have been sacrificed to military or political considerations (MacNeal, 1919).

Death statistics are also incomplete. At the time, only three quarters of U.S. states and territories reported mortality data to the U.S. Census Bureau (Glezen, 1996). Global death statistics of the time suffered from missing records, misdiagnosis, and frequent underreporting. Underreporting occurred as a result of both missed recording deadlines and inconsistent coverage/reporting of specific population segments (Johnson and Mueller, 2002).

Some health professionals attempted to capture data demonstrating the effects of the pandemic. Immediately following the fall disease wave, the US Public Health Service surveyed 146,203 persons from households in twelve localities across the US in an effort to describe age and sex characteristics of the affected (Collins, 1931). In a thorough accounting of the pandemic among U.S. military personnel, the medical officer assured readers that he was presenting only known facts in regard to the disease without any regard for censorship, as he anticipated his paper would not receive publicity until the necessity for military or political censorship ceased to exist (MacNeal, 1919).

3. Pandemic waves

Despite many limitations in available data, epidemiologic findings

and anecdotal reports support the occurrence of three waves of pandemic influenza disease occurring in 1918 and 1919 (Simonsen et al., 2018). Based on census statistics, Frost reported in 1919 that there had been a sharp and general rise in influenza and pneumonia mortality during the spring of 1918, with deaths in April "sufficient to constitute an unmistakable departure from normal" (Frost, 1919). Historic analysis of available death statistics from select US cities also suggest the appearance of an initial "herald" wave surfacing in the spring of 1918. Findings include a distinct influenza and pneumonia mortality age-shift with increasing deaths in young adults occurring in New York City (Olson et al., 2005), St. Joseph, Missouri (Hoffman, 2011), and the state of Arizona (Dahal et al., 2018). Opie (Opie et al., 1919) reported on an explosive spring outbreak of influenza and pneumonia at Camp Funston, with over 1000 men hospitalized from a population of 30,000.

Spring outbreaks disrupted the operation of some training camps, as well as a few factories (Crosby, 2004). American Forces in Europe also recorded outbreaks, albeit later, from May through July 1918. At the time however, most spring/summer outbreaks did not attract significant attention. Prompt recovery was common and complications were rare (MacNeal, 1919). In a detailed report on the pandemic in England and Wales, the first wave was described as one with numerous cases, but little or no pulmonary complications and mortality; patients being stricken but recovering speedily (Newman, 1920). However, there were exceptions. One physician in Haskell, Kansas was sufficiently concerned about a respiratory outbreak in his small town that he reported 18 cases of severe influenza and 3 deaths in the April 1918 issue of *Public Health Reports* (Anon, 1918). This may be one of the earliest reports of what was later called the 'Spanish Influenza'.

What is generally agreed to be the second wave of the pandemic, surfacing in the fall of 1918, proved much worse. Unprecedented numbers became ill. The severe disease and resultant mortality devastated available capabilities of both military and civilian medical resources. For example, Camp Devens in Massachusetts was one of the first camps to see cases in the fall, beginning on September 8, 1918. By the end of the month, influenza had affected more than 30% of the camp population of 45,000. The camp hospital admitted more than 10,000 soldiers in September, over 1000 on each of three days: September 16–18. Nineteen percent of cases developed pneumonia, and camp medical officers reported a pneumonia case fatality proportion of 27.9% (Woolley, 1918). Whereas the incidence of pneumonia is typically highest in the very young and very old, an unusually high incidence of pneumonia among young adults was seen during the 1918 pandemic. Most deaths at Camp Devens were attributed to pneumonia (Shanks et al., 2016). However, Britten noted that case fatality of influenza patients among adults aged 20–39 years in cities across the U.S. was lower than for those aged < 5 years and ≥ 60 years, and that pneumonia case fatality in adults was similar until increasing substantially for those aged ≥ 60 years (Britten, 1932). High mortality observed in young adults, including in soldiers at Camp Devens, was therefore due to the high incidence of pneumonia. Although crowded barracks and tents could have facilitated high spread of respiratory bacterial colonization among soldiers, Shanks and Brundage suggested that during the course of recuperation from pandemic influenza on crowded, open-base wards in military hospitals, soldiers were exposed to a range of respiratory bacterial strains, resulting in high incidence of secondary bacterial pneumonia (Shanks et al., 2016).

The pandemic severely affected many cities as well. Philadelphia serves as a prime example of a city hit hard with influenza in the fall of 1918. The first reported case occurred on August 27, 1918 with the peak of weekly estimated death rates seven weeks later (Markel et al., 2007). During this time, the annual all-cause death rate was more than twice as high as in 1917 (Rogers, 1919). On November 30, 1918 the Philadelphia Evening Bulletin reported the city had experienced 150,000 cases of influenza with 13,000 deaths (150,000 "Flu" Cases Here, 1918).

Sadly, there was still more to come after the fall wave had run its course. A third wave of disease surfaced in many locations during the winter of 1918–1919, with the period between second and third waves so brief it was nearly undetectable in some locales (Taubenberger et al., 2006).

The question remains however why respiratory outbreaks in the spring, if caused by the pandemic virus, did not result in a discernable increase in disease during the summer months. An autopsy series of 68 fatal influenza/pneumonia cases in the US military that occurred between May and October of 1918, indicate that the pandemic virus was circulating for four months before the severe fall wave (Sheng et al., 2011), reminding us there remains much to be learned about the 1918 pandemic.

4. Mortality curve

A unique hallmark of the 1918 pandemic was the unexpected number of deaths in young adults. Typically, seasonal influenza epidemics are characterized by a U-shaped mortality curve, with most deaths occurring in the very young and very old. In 1918 however, the mortality curve was W-shaped with large numbers of deaths occurring in young adults (Shanks, 2015). Influenza pneumonia death rates for 15–34 year olds during the 1918 pandemic were more than 20 times higher than in previous years and 99% of excess influenza-related deaths occurred in individuals less than 65 years of age (Taubenberger et al., 2006).

In addition to the incidence of pneumonia in young adults referenced above, other hypotheses have been proposed to explain the high young adult mortality. One relates to the concept of "original antigenic sin," in which the initial subtype of influenza A virus infection experienced at a young age induces immunologic memory and influences susceptibility to influenza A viruses in the future by conferring protection against the same subtype, but not to other subtypes (Worobey et al., 2014; Gagnon et al., 2015; Luk et al., 2001). Gagnon et al. (2013) used historical data from the U.S. and Canada to determine that the numbers of deaths and the mortality rate in 1918 peaked at age 28 years. It was suggested that young adults might have been more susceptible to the pandemic H1N1 virus because their initial influenza virus exposure early in life would likely have been to an influenza A(H3N8) virus that emerged during 1889–1890. Exposure to a novel influenza A(H1N1) virus could have resulted in a dysregulated innate immune response, leading to poor outcomes (Gagnon et al., 2013; Shanks and Brundage, 2012). Others have noted that multiple host immunological factors may have contributed to excess mortality in young adults, including cross-reactive or non-neutralizing humoral immunity, abnormal cellular immunity, and dysfunctional innate immune response (McAuley et al., 2015).

Viboud et al. analyzed death certificate data from Kentucky and identified that the maximum excess mortality risk during the fall 1918 pandemic wave was highest in adults aged 24–26 years, but declined substantially during the 1918–1919 winter pandemic wave (Viboud et al., 2013). Recently, Gagnon et al. reported that excess mortality in the U.S. and Mexico during the 2009 H1N1 pandemic was highest among persons who were born during the 1957 H2N2 pandemic, consistent with the hypothesis that immunity conferred early in life can increase susceptibility and mortality risk against a heterosubtypic pandemic virus in the future (Gagnon et al., 2018).

It has also been proposed that as the 1889 pandemic A(H3) virus evolved through antigenic drift to be less virulent, the cytotoxic T-cell memory response was attenuated and resulted in less severe disease in persons aged < 20 years (Gagnon et al., 2015). Gagnon et al. have also suggested that exposure to a pandemic virus before approximately age 20 years can "reprogram" or confer "immunologic refocusing" such that in survivors a robust immune response is mounted that can be recalled during infection at later periods.

5. Epidemiologic parameters

Another unique epidemiologic feature of the 1918 pandemic was the overall estimated case fatality proportion. Estimates of the case fatality proportion are difficult to compare because it was not always clear if the denominators included only symptomatic individuals, both asymptomatic and symptomatic infected persons, or the overall population at risk. Although denominators were not well-defined, the estimated attack rate of 28% (Frost, 1919), serial generation time of 4.5 days (Sheng et al., 2011), and basic reproduction number of 1.8 (Biggerstaff et al., 2014), were similar to that for subsequent pandemics in 1957 and 1968. The case fatality proportion however, was at least ten times higher than in other pandemics. In 1931, Collins analyzed the 1918 U.S. Public Health survey results and concluded the case fatality proportion was 1.7% (Collins, 1931). Since that time, others have reported case fatality proportions as high as 2.5% (Taubenberger et al., 2006). This larger estimate is consistent with reports from the American Expeditionary Forces that chronicled nearly 200,000 cases of influenza from July 1917 through April 1919, with pneumonia complications appearing in 5–10% of the cases, and death occurring in 44% of pneumonia cases (MacNeal, 1919). An English physician suggested an even larger case fatality proportion based on his treatment of thousands of patients. He approximated 200 of each 1000 patients developed a severe form of influenza and 80 of the severe cases tended to be fatal (French, 1918).

6. Clinical manifestations

Many physicians recognized a variety of influenza presentations and attempted to classify 1918 pandemic influenza into syndromes or "types." Some physicians described four influenza types (rapid spreading, simple, mild catarrhal infection, "true" influenza without complications, influenza with respiratory distress, and influenza with progressive and fatal pulmonary edema), (Friedlander et al., 1918) while others distinguished only two (mild nasopharyngitis and influenza complicated by pneumonia) (Woolley, 1918). Signs and symptoms identified also varied somewhat between those chronicling their experiences. Still, there was overwhelming consensus that many patients experienced mild respiratory illness while others suffered from a more virulent form of the disease, especially during the fall wave. This more virulent form had not previously been associated with influenza.

Mild uncomplicated illness that had predominated in the spring herald wave included upper respiratory tract symptoms such as nasopharyngitis, sore throat, and cough, as well as systemic manifestations of fever, malagia, and prostration. Epistaxis was reported in both mild and severe cases (Navarro, 2010). A physician reporting on 3000 cases at Camp Fremont noted that epistaxis was a common feature throughout the pandemic. He postulated that some blood dyscrasia may have been a feature of the disease as blood often gushed from the patient's nose and mouth (Brem et al., 1918). The duration of mild disease was often limited to three days. Cough was typically non-productive. Fevers up to 104 °F were common (MacNeal, 1919). Prostration was often sudden and severe. One description depicted a patient as "seized rapidly, or almost suddenly, with a sense of such prostration as to be utterly unable to carry on with what he might be doing" (French, 1918).

Patients with severe illness exhibited marked respiratory distress. Their constellation of symptoms included a strikingly intense cyanosis, air hunger, reduced consciousness, and diffuse, bubbling rales indicative of acutely progressive pulmonary edema (Friedlander et al., 1918). The cyanosis, labeled 'heliotrope cyanosis' after the deep blue or purple color of the heliotrope flower, was observed in some patients prior to death (Friedlander et al., 1918; Shanks, 2015). Physicians often initially noticed the deep blue discoloration on the lips and ears before it spread over the rest of the face. Some described the color as purplish-black (Lucke et al., 1919) and one Scottish physician working at Camp Deven noted in a letter to a fellow physician that it was difficult to "distinguish the colored men from the white" (Byerly, 2005). When repeated spectrographic examination of patients' blood found no abnormal pigment, one physician concluded the cyanosis was caused by extensive exudate in the alveoli precluding adequate oxygenation (French, 1918).

Two overlapping clinical syndromes, an acute respiratory distress syndrome (ARDS) resulting in rapid death, and bronchopneumonia have been described for fatal cases (Morens and Fauci, 2007). It is generally believed that except for those who died within a few days after 1918 H1N1 illness onset, secondary bacterial infection resulting in bronchopneumonia caused most pneumonia deaths (Morens and Fauci, 2007). Initial leukopenia was followed by a leukocytosis in those with bronchopneumonia (Daland, 1919). Brundage and Shanks reported that for most affected populations, the median time from illness onset to death was reported to be 7–10 days, and many deaths occurred > 2 weeks after onset, consistent with secondary bacterial pneumonia (Friedlander et al., 1918; Brundage and Shanks, 2008; Brem et al., 1918). Klugman et al. noted that a median of 10-days from onset to death in soldiers during 1918 was consistent with the time course of fatal untreated *Streptococcus pneumoniae* pneumonia in the 1920s–1930s (Klugman et al., 2009a). *Streptococcus pneumoniae* was the most commonly isolated bacteria from blood, pleural fluid, and lung culture from 1918 H1N1 cases with pneumonia (Klugman et al., 2009b; Chien et al., 2009). Testing of lung tissue specimens from U.S. Army soldiers who died of influenza and pneumonia in 1918 identified a predominance of *Streptococcus pneumoniae* and other Gram positive bacteria (Sheng et al., 2011).

Pathologists of the time were familiar with the post mortem appearance of lungs from pneumonia victims. However, the congested and hemorrhagic pulmonary findings in fatal 1918 H1N1 cases were very different from classic lobar pneumonia. Lungs were described with adjectives such as livid, swollen, sodden, and distended (Byerly, 2005). Examination often revealed a thin and watery bloody exudate in the lung tissue and bronchioles. One pathologist described the condition as the "lungs of the drowned" (Lucke et al., 1919), a description more reflective of severe acute respiratory distress syndrome than of classic lobar pneumonia. Findings of hemorrhagic trachea-bronchitis, bronchiolitis, diffuse alveolar damage, pulmonary hemorrhage, pulmonary edema, and hyaline membrane formation, along with detection of influenza viral antigens in bronchiolar and alveolar cells, suggest the contribution of 1918 H1N1 virus infection of the lower respiratory tract to fatal outcomes (MacNeal, 1919; Sheng et al., 2011). A subset of victims likely died from primary viral pneumonia and ARDS (Cunha, 2004; Morens and Fauci, 2007), particularly those who died after a short illness course (U.S. Department of Health and Human Services, 2006). In-vivo studies in mice, ferrets, and non-human primates have demonstrated that 1918 H1N1 virus triggers cytokine dysregulation that results in extensive pulmonary and extrapulmonary inflammation (Tumpey et al., 2005; Kash et al., 2006; Kobasa et al., 2007; de Wit et al., 2018; Cilloniz et al., 2009). Inflammation is also consistent with the reports of pericarditis, myocarditis, and hepatitis associated with some 1918 H1N1 patients (Britten, 1932). Hsieh, for example, found reports of pericarditis, myocarditis, hepatitis, and splenomegaly (Hsieh et al., 2006). Salicylate toxicity from the high doses of aspirin recommended for treatment of 1918 H1N1 pandemic influenza resulting in Reye syndrome has also been proposed to account for the high mortality experienced in the U.S (Starko, 2009).

7. Conclusions

The 1918 pandemic appeared during a period of unique wartime stresses. Although health professionals had learned to successfully prevent a number of other infectious diseases by that time, the cause of the 1918 H1N1 pandemic remained an unknown etiologic agent for nearly two more decades. Lacking specific treatment, public health officials relied on community mitigation measures to contain the

disease. The politics of a nation at war however, often stymied their efforts. Hospitals and medical staff were insufficient to care for victims, many of whom were in the prime of their lives with severe disease.

Times have changed and 100 years after the 1918 pandemic we are more prepared for the next influenza pandemic, with global influenza surveillance, molecular diagnostics, influenza vaccines, vaccines for some respiratory bacterial infections, antiviral and antibacterial drugs, infection control, intensive care and ventilatory support. Gaps, nonetheless, remain for prevention and control of seasonal influenza, including needed improvements in the performance of influenza vaccines and in the clinical management of influenza patients (Uyeki et al., 2018; World Health Organization, 2017). Clinicians, researchers, and public health officials today might attribute the impact of the 1918 pandemic to the expected outcomes in the pre-antibiotic, early years of modern medical science; however, that view would fail to recognize the historic magnitude of illness and death from the H1N1 virus that emerged in 1918. Despite the significant gains over the last 100 years, influenza viruses continue to cause substantial disease every year and have ample opportunities to co-mingle, reassort, and emerge to cause a very severe pandemic. Examining the events in 1918, and using that knowledge to envision 'worst case' scenarios, can inform influenza pandemic preparedness activities and can help to prepare for the possible impact of other pathogens that might emerge for which no vaccine or treatment is available.

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