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# 2009 H1N1 Influenza: A Twenty-First Century Pandemic With Roots in the Early Twentieth Century

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**Abstract:** A swine-origin H1N1 triple-reassortant influenza A virus found to be a distant relative of the 1918 “Spanish flu” virus emerged in April 2009 to give rise to the first influenza pandemic of the 21st century. Although disease was generally mild and similar to seasonal influenza, severe manifestations including respiratory failure were noted in some, particularly those with underlying conditions such as asthma, pregnancy and immunosuppression. Children and younger adults accounted for most cases, hospitalizations and deaths. A reverse transcriptase-polymerase chain reaction assay was superior to antigen-based rapid tests for diagnosis. All 2009 H1N1 pandemic influenza strains were susceptible to 1 or more neuraminidase inhibitors. Monovalent, unadjuvanted 2009 H1N1 vaccines were licensed in the United States in September 2009 and initially targeted to younger individuals, pregnant women, caretakers of infants and healthcare providers. The 2009 H1N1 pandemic highlights the need for modernization of influenza vaccines, improved diagnostics and more rigorous evaluation of mitigation strategies.

**Key Indexing Terms:** Pandemic; Influenza; Swine-origin; H1N1; Hemagglutinin. [Am J Med Sci 2010;340(3):202–208.]

Near the end of the 20th century, pandemic influenza planning gained global momentum after the alarming 1997 outbreak of severe human disease with H5N1 avian influenza in Hong Kong.<sup>1</sup> By 2005, >100 human cases of H5N1 influenza with approximately 50% mortality had been reported, but efficient human-to-human transmission was still lacking. H5N1 outbreaks in domestic poultry had occurred in at least 16 countries in Asia and Eastern Europe, and disease in migratory wildfowl populations was spreading along migratory paths.<sup>2</sup> The next influenza pandemic was overdue, and fears that avian influenza might adapt to human transmission were rising. In April 2009, the first influenza pandemic of the 21st century arrived with several surprising features. Instead of the predicted H5N1 avian virus emerging from Asia, a novel triple-reassortant swine-origin H1N1 virus, found to be a 4th generation descendant of the infamous 1918 influenza virus,<sup>3–5</sup> emerged in North America and quickly spread to regions throughout the world.

Here, the early experience with 2009 H1N1 pandemic influenza in the historical context of past influenza pandemics, implications for future influenza seasons and ongoing research needs highlighted by the current pandemic are reviewed.

## The 2009 H1N1 Virus

Influenza viruses, in the family Orthomyxoviridae, are single-stranded, negative strand RNA viruses. Among the 3

influenza types (A, B and C), influenza A has been responsible for all known major epidemics and pandemics. Influenza A viruses circulate in more than 18 mammalian species (including pigs and humans), but the main reservoir is aquatic wildfowl, including migratory birds.<sup>6</sup> The genome of influenza A is made up of 8 separate gene segments that may individually “reassort” with other influenza A virus gene segments to markedly shift antigenic characteristics (Figure 1).<sup>3–6</sup> The viruses are classified according to the subtypes of 2 surface proteins, hemagglutinin (HA or H) and neuraminidase (NA or N). Hemagglutinin, a surface glycoprotein that is essential for viral binding and entry into host cells, contains the primary epitopes for protective neutralizing antibodies. Neuraminidase is required for viral release and plays a lesser role in protective immunity. A subtle accumulation of changes in the HA epitopes may lead to a “drift” in protective immunity to circulating strains, prompting a yearly review of the antigenic content of influenza vaccines. Although there are 16 known subtypes of HA, only 3 have successfully adapted to human transmission resulting in pandemics—H1 in 1918, H2 in 1957 and H3 in 1968 (Table 1).

The 1918 “Spanish flu” was caused by a novel influenza A H1N1 virus of avian origin that moved almost simultaneously into human and swine populations and persisted in swine as “classical swine” H1N1 viruses with very little change for the next 80 years.<sup>13</sup> Nearly all human influenza A infections worldwide to this day are caused by descendants of the 1918 pandemic virus.<sup>8,25</sup> However, although the H1 subtype continued to circulate in humans as seasonal influenza until 1957 and later returned in 1977, accumulated antigenic drift resulted in significant divergence of seasonal H1 from the 1918 ancestor and its more antigenically stable classical swine influenza descendant.

In 1998, triple-reassortant swine viruses (containing gene segments from human, avian and swine lineages) began to circulate in swine in North America, and there were rare reports of sporadic human disease.<sup>20,26</sup> The 2009 swine-origin H1N1 pandemic influenza A virus seems to be the result of a further reassortment of the swine triple-reassortant virus with acquisition of the neuraminidase and matrix gene segments from a Eurasian H1N1 swine virus (Figure 1) and the capacity for efficient human-to-human spread.<sup>3,4,13,26</sup> The high degree of genetic homology among all 2009 H1N1 viruses from diverse geographic locations indicates that this was most likely a single (or small number of) cross-species introductions with rapid human dissemination.<sup>26</sup> Although not the major HA subtype switch (shift) typical of the last 2 influenza pandemics, the level of antigenic mismatch of the swine-origin 2009 H1N1 virus with recently circulating seasonal H1N1 viruses likely contributed to the pandemic spread of the 2009 virus.

## Epidemiology

As of January 16, 2010, 41 to 84 million 2009 H1N1 cases were estimated to have occurred in the United States since April 2009, with an estimated 8,330 to 17,160 deaths.<sup>27</sup> Seasonal influenza is typically a disease of the extremes of age;

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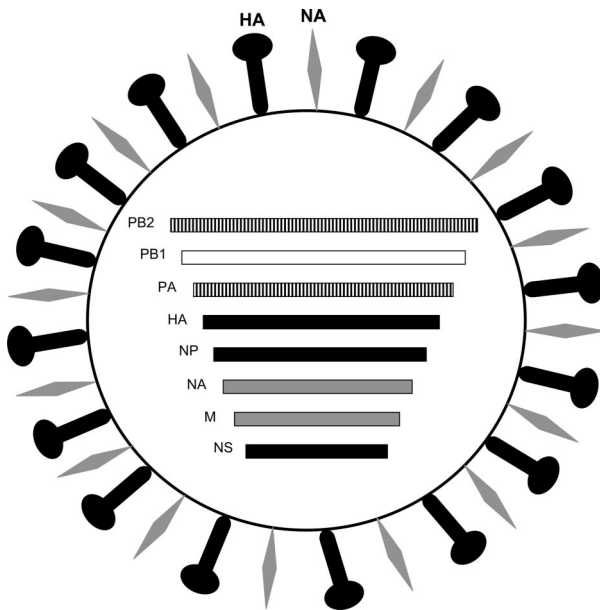


FIGURE 1. 2009 H1N1 influenza A virus. The 8 gene segments in descending order according to size are shown in the center of the virus. Gene segments with vertical hatched lines are of avian origin; the white bar indicates human origin; black bars indicate North American classical swine origin; and solid gray bars indicate gene segments of Eurasian swine origin. Hemagglutinin (HA, in black) and neuraminidase (NA, in gray) surface proteins surround the viral particle. Gene segments encode for the following proteins: polymerase PB2, polymerase PB1, polymerase PA, hemagglutinin (HA), nuclear protein (NP), neuraminidase (NA), matrix proteins (M), and nonstructural proteins (NS).<sup>3,4,26</sup>

90% of the approximately 36,000 influenza-related deaths in the United States each year occur in individuals 65 years and older.<sup>29</sup> The 1918 pandemic was distinctive in many ways, but a notable feature was the fact that almost half of all influenza-related deaths occurred in young adults aged 20 to 40 years.<sup>25</sup> Although the 2009 H1N1 influenza pandemic has thus far proven to be significantly milder than the 1918 pandemic, children and younger adults have once again suffered the heaviest burden of disease (Figure 2). In a series of 426 patients with 2009 H1N1 infection identified early in the pandemic in China, the mean age was 23 years, and nearly 94% of cases were in individuals 50 years or younger.<sup>28</sup> Although the morbidity and mortality associated with the 2009 H1N1 pandemic in the United States have been modest even in comparison with many seasonal influenza years, more than 90% of cases and 87% of deaths related to the 2009 H1N1 pandemic have been in those younger than 65 years, and the median age of patients who died was 26 years in 1 study.<sup>29</sup>

Surveys of serum collected before 2009 demonstrated that only 4% of U.S. residents born after 1980 had preexisting neutralizing antibody reciprocal titers of 40 or greater against the pandemic H1N1 strain; in contrast, 34% of those born before 1950 and 57% born before 1940 had neutralizing titers of 80 or greater.<sup>30</sup> Similarly, in the United Kingdom, a substantial number of older adults but not children had preexisting antibody to 2009 H1N1.<sup>31</sup> Recent seasonal flu vaccines were found to provide minimal protection against the 2009 pandemic virus.<sup>30</sup>

The 2009 pandemic influenza virus spread rapidly from person to person worldwide. It emerged early in the southern

hemisphere's winter flu season (May to September) and became the predominant circulating influenza virus in most southern hemispheric locations by mid-season. In the United States, after the initial wave of cases in April to June 2009, an unusually early onset of the influenza season ensued, with cases reaching a peak in early September 2009 in some areas in the southern United States, where children return to school in mid-August, and peaking in October and November in most of the rest of the United States. The presence of underlying conditions was common among hospitalized patients.<sup>29,32</sup> Up to 60% of children and 83% of adults admitted with 2009 H1N1 infection had 1 or more underlying conditions, including asthma, diabetes, immunosuppression, cardiovascular disease (more common in adults) and neurologic and developmental disorders (more common in children).<sup>29</sup> Eleven percent of hospitalized adults with 2009 H1N1 were pregnant.<sup>29</sup> Preliminary reports of an association of obesity, particularly in adults with morbid obesity,<sup>33,34</sup> with more severe 2009 H1N1 disease will require further analyses, controlling for any relevant associated risks (eg, type 2 diabetes) to determine the significance of the association.

### Clinical Features

Symptoms of 2009 H1N1 infections were generally mild and closely resembled seasonal influenza. Initial symptoms primarily included fever, sore throat and cough.<sup>3,28,29,32</sup> Less typical of seasonal influenza, vomiting and/or diarrhea were reported in 39% of hospitalized cases. Although less than 1% of estimated U.S. 2009 H1N1 cases resulted in hospitalization, a quarter of those hospitalized required intensive care unit admission, and more than half of these required mechanical ventilation for respiratory failure, refractory hypoxia, acute respiratory distress syndrome or shock. Reports of concurrent pneumonia (viral, bacterial or unknown) ranged from 10% to 50% of hospitalized patients.<sup>3,29,32</sup> A small number of specific bacterial coinfections have been reported including *Streptococcus pneumoniae*, group A streptococcus and staphylococcal infections.<sup>29,32</sup>

The significance of bacterial coinfections, particularly *S pneumoniae*, in the morbidity and mortality of influenza has been well documented.<sup>35–38</sup> Decades before the 1918 pandemic and the subsequent identification of the influenza virus, Pfeiffer<sup>39</sup> reported that he had found the etiologic agent of influenza, after repeatedly isolating the bacterium now called *Haemophilus influenzae* from the respiratory tract of patients with clinical influenza. In fact, in Richard Shope's<sup>11</sup> original report of the identification of a filterable virus (the influenza virus) associated with swine influenza in 1931, he also noted that "it is permissible to interpret these experiments as indicating that swine influenza is due to a filterable virus and the bacteria *Haemophilus influenzae suis* acting together."

### Diagnostics

Although antigen-based rapid influenza testing has been widely embraced in clinical settings in recent years, it became quickly apparent that the rapid tests had inadequate sensitivity to monitor the 2009 pandemic. The first 2 cases were detected within 2 collaborative enhanced surveillance networks established by the Department of Defense's Global Emerging Infections Surveillance and Response System and the Center for Disease Control (CDC) Border Infectious Diseases Surveillance Project in California. When testing a new point-of-service diagnostic device, 2 nonsubtypable influenza A strains were identified from unrelated cases and subsequently confirmed to be identical swine-origin H1N1 viruses at CDC in April 2009.<sup>40</sup>

TABLE 1. Timeline of key events in the modern history of influenza

Date	Event
1918–1919 Pandemic	Emergence of “Spanish flu” H1N1 virus derived from avian-like source; pandemic kills >500,000 people in United States and 20–50 million worldwide; the influenza virus etiology not yet recognized <sup>7,8</sup>
September 30–October 5, 1918	Cedars Rapids Swine Show, influenza outbreak in swine: first recognition of influenza disease in swine <sup>9,10</sup>
1931	Richard Shope described influenza virus in pigs; finds it to be related to the 1918 “Spanish flu” in humans; later termed “classical swine influenza”; proposed a role for bacterial coinfection <sup>11,12</sup>
1933	Wilson Smith, Christopher H. Andrewes and P.P. Laidlaw identify human influenza virus and successfully transmit to ferrets <sup>13</sup>
1956–1957 Pandemic	H2N2 pandemic, “Asian flu” (antigenic shift); H1N1 disappears <sup>5,7,14</sup>
1968–1969 Pandemic	H3N2 pandemic “Hong Kong flu” (antigenic shift); H2N2 disappears <sup>5,7,14</sup>
1976	H1N1 swine-origin influenza outbreak Fort Dix, NJ: 13 soldiers, 1 death; extrapolation of serology suggests ~230 cases; >40 million U.S. citizens immunized with swine flu vaccine; no evidence of swine H1N1 transmission beyond Fort Dix; vaccine campaign halted due to concerns about excess incidence of Guillain-Barré Syndrome associated with vaccine <sup>15</sup>
1977	H1N1 reemerges (pre-1957 era virus, possible laboratory release) cocirculates with H3N2 to present time <sup>16</sup>
March 1997	Taubenberger et al <sup>17</sup> PCR amplify segments of the 1918 influenza viral genome preserved in autopsy material from soldier who died of the “Spanish flu” in 1918
1997	Report of fatal human case of H5N1 avian influenza in 3-yr-old child in Hong Kong; total 18 people hospitalized, 6 deaths; culling of 1.2 million chickens in Hong Kong <sup>1</sup>
1998	Rare sporadic triple reassortant H1N1 (avian, human and swine gene segments) disease in humans, most with exposure to pigs; limited human-to-human transmission <sup>18–20</sup>
October 2005	Full sequence of 1918 influenza virus available <sup>21,22</sup>
November 2005	National strategy for pandemic influenza published <sup>23</sup> ; key strategies: (1) preparedness and communication, (2) surveillance and detection and (3) response and containment
2009–2010 Pandemic	H1N1 swine-origin triple-reassortant virus (containing 2 avian, 1 human, 3 classical swine and 2 Eurasian swine gene segments) emerges in Mexico and quickly spreads worldwide <sup>3,20,24</sup>

CDC promptly modified existing real-time RT-PCR assays for detection of the newly identified virus and disseminated details of the methodology on the World Health Organization (WHO) Web site.<sup>3,41</sup> Faix et al<sup>40</sup> compared results of rapid influenza testing with those of the gold standard RT-PCR and found only 51% sensitivity with 99% specificity of the rapid test in detecting the 2009 H1N1 virus. The sensitivity of rapid test performance was equally poor for seasonal H1N1 and H3N2 (63%

and 31%, respectively) compared with the PCR-based assay.<sup>40</sup> In a small sample from Australia, lower respiratory tract samples were more likely than upper respiratory samples to be positive for 2009 H1N1 by RT-PCR in patients requiring mechanical ventilation; rapid antigen testing was positive in only 25% of such patients.<sup>42</sup> Chan et al<sup>43</sup> reported that the limits of detection of 5 antigen-based rapid tests were comparable for 2009 H1N1 and seasonal H1N1, suggesting there are similar limitations to the use of rapid tests in both seasonal and pandemic disease. RT-PCR tests remained positive for a median of 6 days in a study from China, but detection persisted for up to 17 days in some cases, most often in children younger than 14 years and those with a delay in antiviral therapy.<sup>28</sup> Because the RT-PCR test was not commercially available for routine clinical laboratory use, many U.S. public health laboratories became overwhelmed with requests for the CDC-developed PCR diagnostics during the summer and fall of 2009, prompting CDC to later recommend reserving the molecular diagnostics for hospitalized influenza cases.

**Treatment**

All 2009 H1N1 viruses are resistant to the adamantane (amantadine and rimantadine) class of antiviral agents. The virus is uniformly sensitive to the NA inhibitor zanamivir. Rare occurrences of oseltamivir resistance have been reported, generally in individuals with prior exposure to the drug.<sup>44,45</sup> All oseltamivir-resistant strains have been susceptible to zanamivir. Emergency use authorization was granted for peramivir, a non-Federal Drug Administration (FDA) approved NA inhibitor currently in clinical trials, to address the need for an intravenous formulation in some critically ill patients.<sup>46</sup> More-

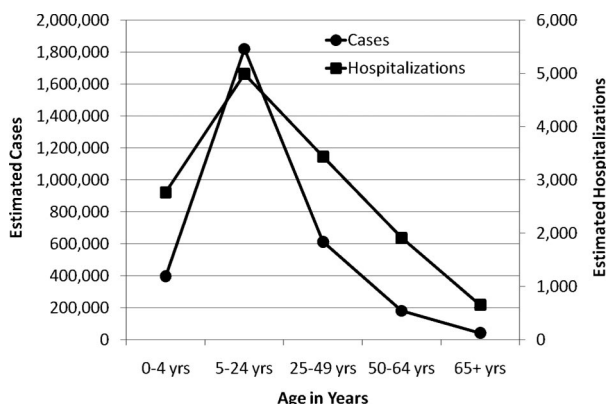


FIGURE 2. Prevalence of pandemic 2009 H1N1 by age group. Estimates of the prevalence of pandemic 2009 H1N1 in the United States, April 2009 to July 2009, by age group (with permission, based upon median case estimates in Reed et al).<sup>71</sup> Estimated 2009 H1N1 cases are shown in the closed circles and the estimated hospitalizations are shown in the closed squares.



over, authorization was also granted for the emergency use of oseltamivir in infants younger than 1 year, as this is not a current FDA-approved indication.<sup>47</sup> Among more severe, hospitalized 2009 H1N1 cases, initiation of antiviral therapy within 48 hours of onset of symptoms seemed to be associated with a better outcome. In 1 report, the median time from onset of symptoms to initiation of antiviral therapy was 3 days (range, 0–29 days) in hospitalized patients who survived compared with 8 days (range, 3–20 days) in hospitalized patients who died.<sup>29</sup> Nearly 80% of individuals hospitalized with 2009 pandemic influenza received antibiotic therapy, presumably for suspected bacterial coinfection.<sup>29</sup>

Antiviral treatment with a NA inhibitor is recommended for patients with confirmed or suspected 2009 H1N1 influenza who have severe illness or who require hospitalization.<sup>48</sup> The recommended duration of treatment is 5 days, but treatment may be extended in hospitalized patients with a complicated course. Although treatment is most effective when started in the first 48 hours of illness, mortality and/or duration of hospitalization may still be reduced in some hospitalized patients with severe illness even when antiviral treatment is started more than 48 hours after onset of illness.

## Vaccine

Influenza vaccines were first developed and tested in large scale trials in 1943, and by 1947, sufficient antigenic drift had occurred to result in loss of protection by the original vaccine.<sup>14</sup> First generation influenza vaccines were composed of formaldehyde-treated, partially purified, killed influenza viruses grown in embryonated eggs.<sup>49</sup> These formulations had significant pyrogenic toxicity and were not highly effective. An innovative zonal ultracentrifugation process was added (still requiring growth in embryonated eggs) in the 1960s to reduce egg-derived pyrogenic contaminants, and this inactivated influenza vaccine process remains the mainstay of influenza vaccine manufacturing in 2010.<sup>49</sup> In the United States, classical reassortment is used to prepare the seed viruses for egg inoculation, a process that combines the *HA* and *NA* gene segments from the selected circulating influenza A strains with 6 other gene segments from a high-growth laboratory strain. The process can be protracted and unpredictable and may limit the options available for yearly strain selection and delay vaccine production and release. A cold-adapted, attenuated live influenza vaccine approved for use in the United States in individuals aged 2 to 50 years also uses reassortment of the *HA* and *NA* gene segments from yearly selected strains but, in this case, combined with 6 gene segments from a cold-adapted laboratory strain. Current seasonal influenza vaccines contain 2 influenza A strains (a seasonal H1N1 and H3N2 in recent years) and 1 influenza B strain. Vaccines remain our best defense against both seasonal and pandemic influenza.

At the first recognition of the pandemic potential for the 2009 H1N1 influenza virus, U.S. federal agencies mobilized to address critical vaccine issues. The regulatory pathway selected for licensure of 2009 H1N1 vaccines was for manufacturers to request supplements to their seasonal influenza biologics license, similar to requesting a seasonal strain change. Use of this pathway required an identical manufacturing and quality testing process as that used for seasonal influenza vaccine production and did not require large scale clinical trials for immunogenicity. In contrast to the experience with previous major antigenic shift pandemics, the majority of adults and children aged 10 years and older responded to a single dose of unadjuvanted 2009 H1N1 vaccines in immunogenicity studies.<sup>50</sup> Monovalent, unadjuvanted 2009 H1N1 vaccines from 4

manufacturers (3 inactivated and 1 live attenuated) were licensed on September 15, 2009. Given uncertainties about the initial supply and demand for the 2009 H1N1 vaccine, the Advisory Committee on Immunizations Practices issued recommendations that the following 5 targeted groups be given priority until vaccine availability increased: pregnant women, caretakers of infants less than 6 months, healthcare and emergency medical services personnel, persons aged 6 months to 24 years, and persons aged 25 to 64 years with high-risk medical conditions.<sup>51</sup> Glaringly absent were the elderly, who despite bearing the major burden of seasonal influenza, had been relatively spared by the 2009 H1N1 pandemic.

Delays in the manufacturing process resulted in a lower-than-anticipated initial vaccine supply, and pockets of significant supply and demand mismatches were noted in the fall of 2009. By February 13, 2010, approximately 126 million doses of monovalent 2009 H1N1 vaccine had been made available in the United States and 96 million doses had been administered to 86 million individuals (28.8% of the total population aged 6 months and older, 30% of those aged 6 months to 24 years and 39% of healthcare workers).<sup>52</sup> Both the WHO and FDA have recommended that a 2009 H1N1 (A/California/7/2009 H1N1-like) strain be included in the 2010 seasonal influenza vaccine formulation along with a seasonal H3N2 (A/Perth/16/2009-like) strain and an influenza B (B/Brisbane/60/2008-like) strain.<sup>53,54</sup>

Had the virulence of the 2009 H1N1 influenza virus been greater in the early phase of the pandemic or had a 2-dose vaccine regimen been required to achieve sufficient immune response in all ages, delays in vaccine availability could have had grave consequences. The potential for shortages in the egg supply during a pandemic, particularly in the setting of a highly lethal avian influenza pandemic (eg, H5N1), adds further uncertainty to vaccine production. Given the continuous antigenic drift in interpandemic periods and the ever present threat of major pandemic antigenic shifts, modernization of the influenza vaccine process is of critical importance. Intensive research and regulatory commitment will be necessary to move forward with advances such as the utilization of reverse genetic techniques to produce seed viruses, evaluation of safe and effective adjuvants that reduce antigen requirements and development of alternatives to the current reliance on tens of millions of embryonated eggs for vaccine production.<sup>49</sup>

## Modeling/Mitigation

Modeling techniques were incorporated actively in pandemic planning to evaluate the relative impact of both pharmaceutical (eg, antivirals and vaccines) and nonpharmaceutical (eg, quarantine, school closures and social distancing) interventions on influenza infection rates within a community.<sup>55–57</sup> An essential element in modeling the dynamics of an epidemic is the determination of the basic reproductive number, the  $R_0$ , which predicts the number of new infections produced by 1 infected individual when the population is completely susceptible to infection (ie, no preexisting immunity and unvaccinated). Calculation of the  $R_0$  takes into account the average duration of infectiousness, the rate of contact of the primary case with susceptible individuals per unit time and the probability of transmission per contact.<sup>55,57</sup> An  $R_0$  of 3 indicates that a primary case of disease generates an average of 3 secondary cases in a susceptible population. Sustained transmission of a disease will not occur if  $R_0$  is 1 or less. Also, of importance in predicting the potential for spread of an epidemic is the time it takes for the index case to cause secondary infections (the generation time), which is relatively short for influenza, in the range of 2 to 3 days.<sup>57</sup> The estimated  $R_0$  for previous influenza

pandemics ranged from approximately 2.0 for the 1918 pandemic,<sup>56</sup> 1.89 for the 1968 “Hong Kong” influenza and 1.5 to 1.7 for the 1957 “Asian” influenza pandemic.<sup>55</sup> The 2009 H1N1 influenza had a  $R_0$  of approximately 1.5 in the first wave of disease.<sup>57</sup>

The goal of mitigation efforts is to reduce the transmission of influenza to a level that falls below that which is necessary to sustain the epidemic (reduce the  $R_0$  to  $\leq 1$ ). The 1918 influenza pandemic produced some of the earliest evidence that social distancing measures could significantly impact disease burden in a community. City officials were not particularly alarmed when on September 17, 1918, the first civilian cases of H1N1 “Spanish flu” were identified in Philadelphia, a city with a population of approximately 1.75 million at the time. A Liberty Loan parade, designed to raise money for the war effort, was allowed to proceed on September 28, 1918, and attracted several hundred thousand spectators lining the streets over a 2-mile parade route.<sup>58,59</sup> Within days, influenza cases and deaths dramatically increased and followed an explosive course reaching a peak rate of weekly excess pneumonia and influenza (P&I) deaths of 257 per 100,000 by October 19, 1918.<sup>60</sup> School closures and restrictions on public gatherings were not implemented until 16 days after recognition of the first influenza cases.<sup>58–60</sup> In contrast, authorities in St. Louis, a city with a population of approximately 775,000 in 1918, moved quickly to institute social distancing 2 days after its first civilian influenza cases were recognized, and this Midwestern city experienced a peak weekly excess P&I death rate that was 88% lower and a cumulative excess P&I death rate that was approximately 50% lower than in Philadelphia.<sup>60</sup> In an epidemic model of weekly mortality in 16 cities during the 1918 pandemic, nonpharmaceutical mitigation efforts reduced the mortality by an average range of 10% to 30%, but this impact was diminished when interventions were introduced too late or released too soon.<sup>61</sup>

Pandemic models testing a range of  $R_0$  numbers (1.0–3.0) that incorporate case-based interventions (eg, household quarantine, antiviral treatment and household prophylaxis and prophylaxis of extended contacts) and general or network-based interventions (school closures, social distancing of children and teens and social distancing of adults and seniors) have shown that combinations of case-targeted and community-wide social distancing interventions implemented in a timely fashion are the most effective and can theoretically decrease infection rates to below 10% in a pandemic with a basic reproductive number as high as 2.0.<sup>55,56</sup> Such efforts would allow containment while an effective vaccine is developed.<sup>62,63</sup>

Less is known about the acceptability to the general public of disease-control measures, the appropriate thresholds for implementation and the likelihood for sustained compliance with mitigation efforts. In addition to considering the basic reproductive number of a newly circulating pandemic influenza strain, the decision by public health authorities to implement aggressive mitigation efforts must also take into account the overall severity and lethality of the disease.<sup>55</sup> The 2009 H1N1 pandemic illustrates the challenges of assessing transmissibility and lethality immediately after recognition of a newly circulating influenza strain. Anecdotal early reports of the human 2009 H1N1 virus infections from Mexico suggested a much higher case-fatality rate than was later documented, and many argued that initial school closing recommendations in the first wave of the 2009 pandemic in the United States were overly vigorous for the relatively mild disease produced in most cases by the 2009 H1N1 pandemic influenza strain.

The 2009 influenza pandemic offered an opportunity to reinforce basic personal infection control responsibilities such as cough and hand hygiene and the importance of staying home from work or school with febrile respiratory illnesses. Pandemic infection control and prevention efforts in the healthcare setting, including guidelines for the use of personal protective equipment, produced vigorous debate regarding the quality of the scientific evidence on which the recommendations were based.<sup>64</sup> As an example, the WHO recommended surgical masks be worn by healthcare workers for care of patients with suspected 2009 H1N1 influenza, reserving N95 respirators with 0.3- $\mu$  particle filtering capacity, for high-risk aerosol-generating procedures.<sup>65</sup> In contrast, CDC recommended fit-tested N95 respirator use by all healthcare workers with close contact with suspected 2009 H1N1 cases.<sup>66</sup> The divergent recommendations were based on very limited evidence showing superior effectiveness of the N95 mask over surgical masks for protection against the severe acute respiratory syndrome (SARS).<sup>67,68</sup> A recent report found effectiveness of surgical masks and N95 respirators in seasonal influenza prevention to be similar in a study of 446 nurses working in emergency departments and hospital units in 8 tertiary care hospitals in Ontario, Canada, although healthcare worker infection rates were surprisingly high in both groups (23.6% and 22.9%, respectively).<sup>69</sup> Given the limitations of the evidence, cost and availability of the N95 masks drove infection prevention decisions in many healthcare systems. The effective bundling of interventions that include hand hygiene, masks, gowns and gloves has been shown to be highly effective in reducing respiratory virus transmission in a healthcare setting.<sup>67</sup>

## CONCLUSIONS

Since 1918, a general decline in influenza deaths has been noted, and each successive influenza pandemic has been less lethal than the previous one.<sup>70</sup> The response to the emergence in humans of the transmissible swine-origin 2009 H1N1 virus was rapid and global in nature. Human cases were detected promptly in April 2009, molecular diagnostics were developed in a matter of weeks and the methods made widely available, and the full sequence and phylogenetic analysis of the 8 gene segments was electronically published on May 7, 2009.<sup>3</sup> Seed viruses for vaccine development were quickly produced, and a mechanism for rapid vaccine licensure was agreed on. A year into the pandemic, a number of questions remain. Will 2009 H1N1 completely replace contemporary seasonal H1N1 and H3N2 viruses in future seasons? Will there be further recombination events among cocirculating viruses in humans, swine or other mammalian hosts? Is a more lethal wave of disease yet to come?

The 2009 H1N1 pandemic and those before it highlight the need for ongoing real-time global surveillance for circulating influenza not only in humans but also in avian and swine populations. The global commitment to coordinated, collaborative and rapid international influenza response with appropriately applied mitigation efforts must be sustained. Many research and development needs have been defined, including the need to increase capacity for point-of-care influenza molecular diagnostics and the modernization of influenza vaccine development, manufacture and distribution. Additional work is needed to more rigorously evaluate the effectiveness of mitigation efforts, including specific personal protective equipment and social distancing interventions. Early access to effective antiviral therapy, advanced intensive care unit care and routine use of pneumococcal and *Haemophilus* vaccines in targeted

populations are essential tools for prevention and treatment of the most severe seasonal and pandemic influenza disease and its complications. A global commitment to addressing the many challenges presented by the complex and ever changing influenza virus will assure that we never revisit the magnitude and devastation of the 1918 influenza pandemic in the 21st century.

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