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pH1N1 influenza A: Timing is everything*

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On June 11, 2009, the World Health Organization declared the outbreak of a novel influenza A virus that began in the small village of La Gloria, Mexico, a pandemic, the first of the 21st century. Just like in 1918, a novel H1N1 virus caused this pandemic. The 2009 pH1N1 virus emerged as a reassortment between two swine influenza lineages and contains a hemagglutinin surface protein that is ultimately derived from the 1918 virus (1). Early reports from Mexico suggested an atypically high rate of severe disease and complications, especially in previously healthy young individuals (2), but as the pandemic spread worldwide, subsequent data demonstrated that the overall disease severity and rate of complications resulting from pH1N1 influenza infection was similar to that of seasonal influenza (3, 4).

In this issue of *Critical Care Medicine*, Satterwhite et al (5) carefully describe the epidemiology, clinical findings, and outcomes of hospitalized adult patients in Georgia with pH1N1 during the late summer and early Fall 2009. They describe this as the “second wave” of pH1N1. Whether or not the period of August 1 to October 31 described truly represents a “wave” similar to the three waves described in 1918 (6) is debatable, but the timing of this study does play an important role in what was observed and demonstrates that host factors are important in determining the outcome of any influenza A outbreak.

In this report, the authors observed a mortality rate (5.5%) and percentage of patients requiring intensive care unit care (21%) similar to that reported early in the pandemic (4–7% and 24–31%, respectively) (7–9). The differences observed by the authors include a higher prevalence (93%) of chronic underlying conditions, a greater incidence of obesity (42%), and a lesser severity of disease in pregnant patients. The timing of the study and the effect that timing had on the host population is likely the underlying reason these differences were observed.

The majority of hospitalized patients with pH1N1 observed in all studies have been between the ages of 18 to 49 yrs (7–9), likely as a result of their immunologic naïveté. Those >49 yrs have had additional exposure to seasonal pH1N1 viruses and a subset were vaccinated against the 1976 swine pH1N1 influenza, both of which have been shown to offer crossprotection against the 2009 pandemic virus (10, 11). Therefore, the exclusion of children, a limitation of this study, does not solely account for the differences noted.

*See also p. 2059.

The Centers for Disease Control and Prevention reported widespread pH1N1 circulation in Georgia during June and July 2009 (12). This widespread exposure before the study, the implementation of community infection control and early diagnosis and treatment, and the initial availability of the vaccine in September made an impact on the susceptible population. It is likely that these factors reduced the morbidity of previously healthy individuals, leaving those known to be more susceptible to increased disease severity, individuals with chronic conditions and obesity, to make up an even larger majority of the patients hospitalized in the study.

The authors aptly point out that timing affected their observations of pregnant women and that early intervention and treatment of pregnant women with influenza A may have reduced the acuity of disease seen in this group. Even before the 1918 influenza pandemic, pregnancy was recognized as a risk factor for increased severity of disease resulting from influenza (13), and since 1918, both seasonal and pandemic influenza are well described as causing more complicated disease in pregnant women, especially in later trimesters (14, 15). This study may reflect that education, vaccination, and early diagnosis, treatment, and monitoring of pregnant women had a beneficial effect on outcomes.

The bronchoalveolar lavage findings from 16 intensive care unit patients are also likely related to an issue of timing and may not be as unexpected as the authors conclude. In a lower respiratory infection with influenza, necrotizing bronchitis and alveolitis with a mixed inflammatory infiltrate occurs, and as the disease progresses in severity, the epithelial layer is lost associated with hyaline membrane formation and neutrophilic exudates in the bronchiolar lumen (16). In severe pneumonia, the pathology is even more advanced with the addition of capillary and small vessel thrombosis, interstitial edema/hemorrhage, and diffuse alveolar damage. In the ferret model, massive neutrophilic infiltration of the lungs has been observed in pneumonia resulting from both the 1918 virus as well as a classic swine pH1N1 influenza virus (17). In humans, autopsies of both 1918 and 2009 pH1N1 victims demonstrated similar pathology, pathology that was likely in part the result of the bacterial secondary/coinfections discovered in the vast majority of autopsies during the pre-antibiotic era of 1918 (16) and, despite routine use of broad-spectrum antibiotics, in >50% of autopsies during the 2009 pandemic (18).

Given these data, the findings of neutrophils in bronchoalveolar lavage fluid from patients with more severe disease requiring intensive care unit care and mechanical ventilation should not be surprising. These patients developed severe influenza-induced bronchitis and bronchiolitis, and many more than detected likely have a secondary bacterial pathogen playing a role in their illness. The authors correctly point out the limitations of bacterial culture resulting from broad-spectrum antibiotic use before bronchoalveolar lavage, because bronchoalveolar lavage can have a limited diagnostic yield of <49% in intensive care unit patients even when antibiotic-naïve (19). Given the sensitivity of sputum cultures and bronchoalveolar lavage in the presence of antibiotic use, it is highly likely that the number of bacterial pathogens being identified is greatly underestimated in this and other studies. All of these data suggests that the true importance of secondary infections in seasonal and pandemic influenza A infections has not been fully elucidated.

Clearly all influenza A outbreaks are affected by timing and a milieu of other factors, including previous exposures and immunity (stratified by age), overall health of the population, access to health care and vaccination, early intervention, type of treatment, and exposure to other pathogens. Together these factors play a key role in determining the epidemiology and outcomes in a pandemic or seasonal influenza A outbreak. To be better prepared for future pandemics, to reduce the impact of influenza A, and to effectively treat each severely ill patient, we must consider how all of these issues contribute. Further study

of how the timing of infection, timing of diagnosis, timing of hospitalization, and timing of antiviral and antibiotic treatment impact patients is necessary, because for severely ill patients with influenza A, timing may be everything.

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