

## EDITORIAL



## Preparing for 2009 H1N1 Influenza

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In 1743, when disease was presumed to be astral in origin, European newspapers reported on a contagious influence (*influenza* in Italian) that was being visited on the citizens of Rome. Two hundred years later, Wilson Smith and colleagues would isolate an influenza A virus, one of the members of the orthomyxovirus family.<sup>1</sup> The key reservoirs of all influenza A viruses are migrating waterfowl, and intermittently, other hosts, such as pigs and people, are infected. Further classification of influenza A viruses is based on the specific hemagglutinin viral attachment spike and neuraminidase disengagement spike; the latter is cleaved when newly minted viruses emerge from infected cells. Smith's isolate was a variant of the H1N1 agent that caused the pandemic of 1918–1919, and H1N1 progeny persisted until the emergence of the Asian influenza pandemic strain (H2N2) in 1957. However, a new H1N1 strain of swine influenza emerged in 1976, and variants of this virus continue to circulate as one of the seasonal strains.

In April 2009, Mexican health authorities announced an outbreak of a novel H1N1 swine influenza virus,<sup>2</sup> which has subsequently caused a global pandemic. What was new was not just the virus but also the continent of origin (North America, not Asia), the season of origin (spring, not late fall), and the cohort at risk for infection and death (children and young adults, not infants and the elderly). It is now known that the eight RNA segments and their gene products are a mixture of components from avian, pig, and human influenza viruses, the result of a series of viral coinfections and gene reassortments.<sup>3</sup>

The 2009 H1N1 virus is now reported to have infected people in more than 190 countries and caused more than 4500 deaths, prompting the promotion of major vaccine programs in the

United States and other countries. Infectious-disease specialists in several Latin American countries in which outbreaks have occurred have reported that obesity and pregnancy have emerged as risk factors for admission to an intensive care unit (ICU) and that diarrhea occurred in 10 to 20% of inpatients. Among patients with documented 2009 H1N1 influenza, fever was absent in 50% of outpatients and in 15 to 30% of patients who were hospitalized but not admitted to an ICU. Globally, questions have been raised about how severe the pandemic would be and whether hospitals would have sufficient surge capacity.

In this issue of the *Journal*, two studies shed light on the clinical characteristics of patients who have been hospitalized with 2009 H1N1 influenza and on the resources that have been needed in ICUs to manage the pandemic. In the U.S. study, Jain and colleagues<sup>4</sup> studied 272 patients who were hospitalized with 2009 H1N1 influenza; of these patients, 25% required ICU care, and 19 of the 67 patients who were admitted to an ICU (28%) died. The number of patients in the study is small, but the hospitalized patients included a disproportionate number of Hispanic patients (30%) and black patients (19%). Seven percent of the patients were pregnant, and 45% were obese or morbidly obese; 16% of deaths were in pregnant patients. The proportion of deaths in obese or morbidly obese patients was not reported.

In the Australian and New Zealand Intensive Care (ANZIC) study,<sup>5</sup> investigators evaluated the situation in 187 ICUs, in which 722 critically ill patients were confirmed to have pandemic H1N1 influenza. Indigenous groups were overrepresented among patients who were admitted to ICUs: 10% in Australia and 25% in New Zealand.

Of the patients who were admitted to an ICU, 9% were pregnant, 29% had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 35 or more, and 14% died. As in the study by Jain et al., obesity emerged as a likely risk factor for increased severity of illness.

Most influenza epidemics peak after approximately 4 weeks and fall to a much lower incidence after an additional 4 weeks. So it is not surprising that the stress on resources in ICUs in Australia and New Zealand occurred 4 to 6 weeks after the first ICU admission for a confirmed case of 2009 H1N1 influenza. Data from the ANZIC study are useful in anticipating the surge capacity that is likely to be needed: 65% of ICU patients required intubation and mechanical ventilation for a median of 8 days. Twelve percent of intubated patients also underwent extracorporeal membrane oxygenation (ECMO), an expensive and technically demanding procedure with potentially life-threatening complications.<sup>6</sup>

Early treatment with neuraminidase inhibitors (oseltamivir or zanamivir) is ideal and may help patients with severe illness. Future studies will define the value of these drugs alone and in combination. Furthermore, the value of ECMO needs critical evaluation as a therapeutic rescue among ICU patients.

Recent reports from Canada show that aboriginal Canadians comprised 26% of patients who were admitted to an ICU with 2009 H1N1 influenza,<sup>7</sup> a finding that adds to concern that ethnic and racial minorities are overrepresented among patients with severe infection.<sup>4,5</sup> It will be important to know whether such findings re-

late to the presence of confounding coexisting medical conditions, such as obesity and lung disease. However, another possibility is that minorities are less likely to receive seasonal influenza vaccination than nonminority populations. A recent case-control study in Mexico showed a rate of 73% protection against 2009 H1N1 influenza among patients who had received a trivalent seasonal vaccine; none of the eight patients who had been vaccinated against seasonal influenza died.<sup>8</sup> In a Canadian study, only 6% of patients who were admitted to an ICU for 2009 H1N1 influenza had received a seasonal influenza vaccination.<sup>7</sup> Of interest, a study by the Centers for Disease Control and Prevention showed that among adults between the ages of 18 and 64 years, only 9% of subjects who had not received a trivalent vaccine had a microneutralization antibody titer of 160 or more against the 2009 H1N1 virus, as compared with 25% of subjects who had received the seasonal vaccine, a finding that suggests cross-reaction.<sup>9</sup> These are provocative studies. Whatever the risk factors, the overrepresentation of minorities in multiple countries is a serious social issue requiring a thoughtful public health response.

In the United States, there are approximately 6000 ICUs with 66,000 beds for adults and 20,000 for children. An estimated 90,000 respirators for mechanical ventilation are available. Recently, Zilberberg and colleagues<sup>10</sup> analyzed data from Mexico and the United States to explore the potential effect of 2009 H1N1 influenza on ICUs by using Monte Carlo simulations. They estimated that ICUs in the United States would need to handle more than 330,000 epi-

**Table 1. Estimated Surge Capacity Needed for the Treatment of Patients with 2009 H1N1 Influenza in Intensive Care Units (ICUs) in the United States for 3 Months, According to Event Rates in Australia and New Zealand.\***

Event	ICUs in Australia and New Zealand		Extrapolation of Rates to U.S. ICUs	
	3 Mo		3 Mo	Per Day
	no.	rate (no./million)	no.	
Admissions to ICUs	722	28.7	8,610	96
Bed-days in ICUs	8815	350.0	105,000	1167
Mechanical-ventilation days in ICUs	5249	208.0	62,400	693
Episodes of extracorporeal membrane oxygenation in ICUs†	53	2.1	630	7

\* Data have been extrapolated from the Australian and New Zealand Intensive Care (ANZIC) study<sup>5</sup> on the basis of an estimated U.S. population of 300 million. Estimates for the number of extrapolated events per day were calculated by dividing the 3-month value by 90.

† The median duration of extracorporeal membrane oxygenation per patient is 10 days.<sup>6</sup>

sodes of mechanical ventilation, an increase in volume of 23 to 45% over current use.<sup>10</sup> However, the preliminary data from the ANZIC study show a small fraction of that estimate: if the findings from Australia and New Zealand are extrapolated to the United States, they would indicate a need for only 5433 episodes of mechanical ventilation and 62,400 ventilation-days over a 3-month period (Table 1).

So far, the 4500 deaths from 2009 H1N1 influenza are approximately 2% of the 250,000 or more deaths seen worldwide from seasonal influenza each year. Nevertheless, no one should be complacent about an unpredictable virus capable of killing children and young adults in their prime.

Dr. Wenzel reports receiving consulting fees from BioMérieux, and Dr. Edmond receiving consulting fees from Merck and grant support from BioVigil and Cardinal Healthcare. No other potential conflict of interest relevant to this article was reported.

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