

## EDITORIAL



## Implications of the Emergence of a Novel H1 Influenza Virus

Robert B. Belshe, M.D.

In this issue of the *Journal*, there are two reports of recent transmissions of swine influenza viruses in humans. One group of viruses, described by Shinde et al.,<sup>1</sup> are triple reassortants of viruses from pigs, humans, and birds, called triple-reassortant swine influenza A (H1) viruses, which have circulated in pigs for more than a decade. The other group, described by the Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team,<sup>2</sup> is a recent reassortant of the triple-reassortant swine influenza A (H1) viruses and a Eurasian swine influenza virus, resulting in the swine-origin influenza A (H1N1) virus (S-OIV), currently being transmitted among humans.

The two groups of viruses behave very differently. Triple-reassortant swine influenza A (H1) viruses are found in pigs and may occasionally be transmitted to humans but have not spread efficiently from human to human. S-OIV, in contrast, is not currently known to be epidemic in pigs (although pigs may be infected by exposure to humans), but it is exhibiting human-to-human transmission and has spread to several countries. Both viruses are H1 hemagglutinin viruses, which appeared in humans and swine in 1918 and have subsequently evolved, in both species, into divergent H1 viruses. The current situation is not “1918 again,” it is “1918 continued,” in that we are still being infected with remnants of the 1918 pandemic influenza virus.

Most adults have substantial immunity to H1 variants that have circulated among humans from 1918 through 1957 and then again from 1977 through the present. Whether cross-reacting antibodies from previous H1 infections will provide protection against S-OIV is not known, but the epidemiologic features of the current S-OIV infections suggest that there may be partial protection from multiple previous influenza infec-

tions. The age range of the 642 patients with confirmed cases of S-OIV infection was 3 months to 81 years, but 60% were 18 years of age or younger. This age distribution is typical for seasonal influenza; schoolchildren are the group with the highest rates of influenza, and they spread the virus to household contacts.<sup>3</sup> The clinical manifestations of S-OIV also were typical of seasonal influenza, with fever in 94% of patients, cough in 92%, and sore throat in 66%; in addition, however, vomiting (found in 25%) or diarrhea (found in 25%) was common. A total of 36 patients were hospitalized; of the 22 hospitalized patients for whom data were available, several had risk factors: young age (4 patients) or chronic medical conditions (9 patients) or both, or pregnancy (1 patient). The two deaths occurred in a 22-month-old child with chronic medical conditions and a 33-year-old woman who was pregnant. Several hospitalized patients had evidence of pneumonia on radiography, and some had secondary complications. The spectrum of illnesses seems very much like those of seasonal influenza.

Many questions remain. Will S-OIV virus replace the human H1 virus as the seasonal influenza virus and evolve antigenic variants every year? Will the virus reassort with H3 influenza virus to make yet another variant? Will S-OIV further adapt to humans and become more severe, causing a wave of influenza in the fall season with higher mortality? When will a vaccine be available?

The U.S. government contributed financial assistance to influenza-vaccine manufacturers to expand domestic capacity to produce vaccine<sup>4</sup>; although expansion plans are still ongoing, now is the time for those manufacturers to deliver. Completing seasonal-vaccine production and adding a monovalent S-OIV vaccine to production will be challenging both technically and in terms of pol-

icity, but it can be done. The development of high-growth seed viruses for the production of inactivated vaccine is needed, as is the creation of reassortants of S-OIV with a live-attenuated “backbone” virus for the manufacture of intranasal vaccine. Pilot lots of vaccine need to be produced quickly for testing through clinical trials to determine the safety, the dose, and the number of doses needed.

Dose–response and small safety studies should be carried out over the summer months. Many will recall 1976, when an H1 influenza virus of swine origin infected soldiers at Fort Dix, New Jersey, and one soldier died.<sup>5</sup> The concern then was that a new pandemic was brewing; a vaccine was developed over the summer months, with clinical trials used to determine the amount and number of doses. Two doses of the vaccine were necessary for persons under the age of 25 years, but older persons had been primed, through natural infection with viruses circulating in the previous H1 era (1918 through 1957) and needed only a single dose to stimulate antibodies against the virus.<sup>5</sup> The government recommended nationwide vaccination, which was performed in more than 40 million people; unexpectedly, Guillain-Barré syndrome developed in approximately 1 in 100,000 vaccinated persons — a rate 5 to 10 times the background rate.<sup>6,7</sup> The cause is believed to have been cross-reacting antibodies against peripheral-nerve antigen that may develop after vaccination with the H1 influenza virus of swine origin.<sup>8</sup> The virus did not reappear, and vaccinations were halted. Whether the S-OIV antigen will cause adverse events if used in a vaccine is not known. Difficult policy decisions loom, but the pathway to a vaccine is clear, and production needs to proceed apace. The spread of the current S-OIV is far beyond that of the 1976 event.

The emergence and spread of S-OIV brings out the best and worst of contemporary society. Within days after the first case identification of S-OIV infection in the United States, the scientific community had the complete genetic sequence of the hemagglutinin, and Internet dissemination

of the information made it available to everyone for further analysis. Public health and surveillance activities were heightened. Drug susceptibility was determined: S-OIV is susceptible to oseltamivir and zanamivir but resistant to amantadine and rimantadine.

In contrast, inflammatory political posturing has occurred that illustrates the need for effective communication by physicians and scientists to the public. Some have asked, Why didn't you close the borders? (Answer: It doesn't work.) Misguided culling of pigs has also been carried out in one country, but S-OIV is not epidemic in pigs; people are spreading the virus.

Finally, funding for surveillance, public health efforts, and vaccine development needs to be enhanced. The current S-OIV epidemic is only the latest influenza virus, not the last.

Dr. Belshe reports serving as a consultant or speaker for MedImmune and Novartis. No other potential conflict of interest relevant to this article was reported.

From the Division of Infectious Diseases and Immunology, Saint Louis University, St. Louis.

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