Research Proceeding Rapidly on Novel H1N1 Flu

Influenza A(H1N1) is a direct descendant of the 1918 flu virus.

BY ROBERT FINN

Investigators have made rapid progress on several fronts in understanding the novel influenza A(H1N1) virus responsible for the current pandemic, according to a series of reports.

Investigators tracing the virus's evolutionary history have learned that the novel H1N1 flu virus is a direct, fourth-generation descendant of the virus that caused the disastrous 1918 flu pandemic. They've learned that the most common rapid influenza test is highly specific but not very sensitive for detecting the influenza A(H1N1) virus.

The most commonly used rapid influenza test, widely available in doctors' offices, is highly specific but not very sensitive for detecting the novel H1N1 flu virus.

In addition, the virus's worldwide spread closely matched historic patterns of airline travel from Mexico. Furthermore, the unusual age distribution of severe illness and death associated with the virus, affecting mostly children and young adults, may have resulted from relative protection among older individuals who had been exposed to H1N1 during childhood before the 1957 pandemic.

All of the reports are available online at the New England Journal of Medicine's online H1N1 influenza center (http://h1n1.nejm.org).

A review article, by Dr. Shanta M. Zimmer and Dr. Donald S. Burke of the University of Pittsburgh, traced the emergence of the influenza A(H1N1) virus to an avian virus that simultaneously appeared in humans and swine in 1918. That virus killed 40 million to 50 million people.

The influenza A(H1N1) virus consists of eight genes that have mutated steadily between 1918 and the present, but the virus has acquired no new gene segments from avian or other sources.

The virus disappeared entirely from humans in 1957 and was replaced by a new strain called H2N2. H1N1 was not detected again until 1976, when the virus was transmitted from a swine to humans, causing an outbreak of respiratory disease among soldiers at Fort Dix, N.J.

Beginning in 1977, the H1N1 virus, accompanied by H3N2, began to co-circulate seasonally in humans. Since then, new H1N1 strains have emerged in swine, with occasional cross-species transmission to humans. In 2008, two distinct H1 swine viruses combined to produce the virus causing the current pandemic.

In an editorial, Dr. David M. Morens, Dr. Jeffrey K. Taubenberger, and Dr. Anthony S. Fauci of the National Institute of Allergy and Infectious Diseases likened the interaction between the various descendants of the 1918 virus and the human community as an "elaborate dance." They wrote that the "partners have remained linked and in step, even as each strives to take the lead," and that there's little evidence that this era is about to come to an end.

In a letter to the editor, Dr. Dennis J. Faix of the Naval Health Research Center in San Diego and his colleagues determined that the most commonly used rapid influenza test, called QuickVue Influenza A+B, widely available in doctors' offices in the United States, has a 99% specificity for the novel H1N1 flu virus, compared with definitive polymerase chain reaction–based tests. This means that if the test indicates that the patient's virus is H1N1, it almost certainly is. On the other hand, the sensitivity of the test ranged from 31% to 63% in various populations, meaning that the test may well miss genuine cases of novel H1N1 flu.

In another letter to the editor, Dr. Kamran Khan of St. Michael's Hospital in Toronto and colleagues found that the March through April 2009 worldwide spread of the virus closely matched patterns of global airline transportation originating from Mexico during the same period in 2008. Of 20 countries with the highest volumes of international passengers arriving from Mexico, 16 had confirmed importations of H1N1. (The exceptions were Japan, Chile, Venezuela, and Peru.)

They calculated that countries receiving more than 1,400 passengers from Mexico were at significantly higher risk of importation, and that international air traffic volume alone was 92% sensitive and more than 92% specific in predicting importation.

In an original research study, Dr. Rogelio Pérez-Padilla of the National Institute of Respiratory Diseases of Mexico in Mexico City and colleagues investigated 18 patients who were hospitalized with pneumonia between March 24 and April 24, 2009, and confirmed novel H1N1 flu.

More than half of those patients were between ages 13 and 47 years, and only eight had preexisting medical conditions. Twelve patients required mechanical ventilation, and 7 died. Within 7 days after contact with these initial cases, 22 health care workers developed mild or moderate flulike illness, but none required hospitalization.

In a much larger study involving 2,155 cases of severe pneumonia reported to the Mexican Ministry of Health, Gerardo Chowell, Ph.D., of the National Institutes of Health, Bethesda, Md., and colleagues found that 87% of the deaths and 71% of the cases of severe pneumonia involved patients between ages 5 and 59 years.

This contrasts with 17% of deaths and 32% of cases of severe pneumonia in that age group during the peak of seasonal influenza periods from 2005 to 2008.

Morbidity and mortality among patients aged 60 years and older during the current pandemic has been significantly lower than among younger individuals. The investigators suggested that older individuals were more likely to have acquired some immunity by being exposed to H1N1 strains before those strains disappeared from the human population in 1957.

"If there is good news," wrote Dr. Morens, Dr. Taubenberger, and Dr. Fauci, "it is that successive pandemics and pandemiclike events generally appear to be decreasing in severity over time. This diminution is surely due in part to advances in medicine and public health, but it may also reflect viral evolutionary 'choices' that favor optimal transmissibility with minimal pathogenicity—a virus that kills its hosts or sends them to bed is not optimally transmissible."

One of the authors of the report on rapid influenza tests said he had received grant support from Sanofi Pasteur. All the other authors of that article and all the authors of the other articles stated that they had no relevant conflicts of interest. ■

ACIP Votes to Reduce Doses of Rabies Vaccine From 5 to 4

BY MIRIAM E. TUCKER

ATLANTA — The Centers for Disease Control and Prevention's vaccine advisory panel voted to drop the recommended number of postexposure doses of rabies vaccine from five to four, based on data suggesting that doing so would not adversely affect outcomes for exposed individuals.

The decision of the Advisory Committee on Immunization Practices stems from the "tenuous" nature of the rabies vaccine supply since 2007. The rabies vaccine made by Novartis (RabAvert) is now available for both pre-exposure and postexposure immunization without limitations. Sanofi Pasteur's rabies vaccine (Imovax) is still available only for postexposure prophylaxis, the CDC's Charles Rupprecht, V.M.D., said at ACIP's June meeting.

An interim four-dose schedule was developed to address the supply problem, and now the committee has advised the four-dose schedule for routine use, based on data from both animal and human clinical trials suggesting that recipients develop detectable rabies virus neutralizing antibodies by day 14, when a vaccine schedule of doses given at days 0, 3, 7, and 14 is used. (The fifth dose is given at 28 days.)

In addition, no significant differences were documented between the four- and five-dose rabies vaccine schedule in the relative amount of neutralizing antibodies produced. Equivalent outcomes were observed in comparison studies using four doses of vaccine given along with rabies immune globulin, said Dr. Rupprecht, chief of the CDC's rabies program.

Nonetheless, if ACIP's vote is approved by the CDC, it presents a conflict with the labeling approved by the Food and Drug Administration, which still recommends five doses of rabies vaccine. Any change to the labeling would require a request from the manufacturers and submission by them of additional data to support the change, FDA representative Dr. Norman Baylor said, adding that only in the event of a safety concern would the FDA be able to force such a change.

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Spokesmen for Novartis and Sanofi Pasteur do not support the change. "It's what the committee feels is best based on the data available to them, but we can't talk about off-label use, and our label firmly states it's a five-dose regimen," Sanofi Pasteur's Philip Hosbach said in an interview at the meeting.

Mr. Hosbach, vice president of immunization policy and government relations at Sanofi Pasteur, added that his company's supply issue stemmed from a planned shutdown of its manufacturing plant in 2007 for an upgrade. It is set to resume operation in the fourth quarter of 2009 with a full supply.

Clement Lewin, Ph.D., head of strategic immunization planning at Novartis Vaccines and Diagnostics, also reacted negatively to the ACIP vote. "It does mean a challenge for Novartis because the FDA guidance clearly states five doses and Novartis doesn't support off-label use of any of its products."

He added, "We're currently supplying [rabies vaccine] for both pre- and postexposure prophylaxis. … Anyone who needs vaccine pre- or postexposure is able to get it. Last year the supply constraints were such that use was restricted to postexposure. Currently we are meeting all the demand of the United States. There is no supply issue at the moment," Dr. Lewin said in an onsite interview. ■