

# Review of 1918 pandemic flu studies offers more questions than answers

**Scientists and public health officials, wary that the H5N1 avian influenza virus could trigger an influenza pandemic, have looked to past pandemics, including the 1918 "Spanish Flu," for insight into pandemic planning. However, in a *Journal of Infectious Diseases* review article now posted online, David M. Morens, M.D., and Anthony S. Fauci, M.D., of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, conclude that studies of the 1918 influenza pandemic, which killed some 50 to 100 million people around the globe, have so far raised more questions than they answer.**

"Today, nearly a century after the 1918 influenza pandemic, its mysteries remain largely unexplained," says Dr. Fauci, NIAID director. "Much work remains to be done, by scientists as well as by historians and other scholars, with regard to the many unanswered questions surrounding this historic pandemic. These studies must be part of our preparedness efforts as we face the prospect of a future influenza pandemic."

Dr. Morens adds, "In addition to ongoing laboratory studies, we feel that much can be learned from examining the vast scientific literature related to the 1918 influenza pandemic and previous influenza pandemics. A treasure trove of journal articles and other materials exists in many languages that can be mined for novel information with practical applications relevant to the threat of pandemic influenza we face."

In their article, Drs. Morens and Fauci review several topics, including the origins of the 1918 pandemic influenza virus, the excess mortality of the pandemic, the predilection to kill the young and healthy, the lower-than-expected mortality among the elderly, and the cyclicity of influenza pandemics over the past 100 years. Such topics are relevant today as highly pathogenic H5N1 avian influenza viruses have spread from Asia to the Middle East, Europe and Africa.

One of the great unsolved mysteries surrounding the 1918 pandemic is why it tended to kill the young and healthy. Unlike yearly influenza epidemics, in which death rates are highest among infants, the elderly and those with chronic health conditions, the 1918 influenza pandemic took its greatest toll on healthy adults between the ages of 20 and 40. One possible explanation, supported by recent studies in mice with a reconstructed version of the 1918 virus, is that an over-responsive immune system may release a "cytokine storm," or excessive amount of immune system proteins that trigger inflammation and harm the patient in the process. Of note, most deaths among humans infected with the H5N1 avian influenza virus have occurred in individuals under the age of 40. However, as the authors point out, it is not yet known whether there is a higher percentage of young people in the affected populations compared to older people, whether younger people are more susceptible to infection or whether they have more exposure to infected birds.

Highly pathogenic H5N1 influenza viruses have primarily infected wild birds and domestic poultry populations in dozens of countries, although at least 275 people have been infected and 167 have died. As Drs. Morens and Fauci point out, the H1N1 virus that caused the 1918 pandemic appears to be avian in origin, but the host source of the 1918 virus has never been identified. Furthermore, no major disease outbreaks among birds were documented immediately before the 1918 pandemic. They suggest that an avian influenza strain could have been hidden in an obscure ecological niche, and the pandemic strain arose by the genetic adaptation of that avian virus to a new human host.

"The more we learn about influenza A viruses and what they can do to maintain their deadly relationship with the human species, the more remarkable they seem," says Dr. Morens. "The challenge for us is to learn

as much about influenza viruses as they have already 'learned' about us."

Drs. Morens and Fauci also discuss the high number of deaths associated with the 1918 pandemic and the disease process, based on clinical and autopsy studies published between 1918 and 1922. Most pandemic deaths were associated with either an aggressive bronchopneumonia, in which bacteria could be cultivated from lung tissue at autopsy, or with a severe acute respiratory distress-like syndrome (ARDS) characterized by blue-grey facial discoloration and excessive fluid in the lungs. In neither case is it known whether most deaths were caused by a secondary bacterial infection or a primary viral infection. They propose that the many excess deaths that occurred during the 1918 influenza pandemic resulted from a disease process that began with a severe acute viral infection that spread down the respiratory tree causing severe tissue damage, which was often followed by secondary bacterial invasion. More definitive answers regarding the causes of deaths due to the "Spanish Flu" may require a comprehensive re-examination of the 1918 autopsy series, they note.

If a pandemic with similar characteristics were to occur in the near future, Drs. Morens and Fauci predict that the relative number of deaths would be substantially lower than that which occurred in 1918.

"Almost all 'then-versus now' comparisons in theory are encouraging," they write. "In 2007 public health is much more advanced, with better prevention knowledge, good influenza surveillance, more trained personnel at all levels, well-established prevention programs featuring annual vaccination with up-to-date influenza and pneumococcal vaccines, and a national and international prevention infrastructure." In addition, two classes of antiviral drugs are currently available, as well as antibiotics effective against bacteria that cause influenza-associated pneumonia.

The most difficult challenge in mitigating the effects of a severe pandemic today would be to ensure access to medical care and resources, they note. Hospitals, medical personnel and drug suppliers could be overwhelmed with huge demands for services, medicines and vaccines, a situation that would be exacerbated in less developed countries and impoverished regions.

Drs. Fauci and Morens conclude that the best hope for the future lies in developing and stockpiling more broadly protective influenza vaccines. In the meantime, prevention efforts should be directed towards logistical planning, increased surveillance, the development of medical countermeasures, an improved understanding of pandemic risks, and an aggressive and broad research agenda.

Source: NIH/National Institute of Allergy and Infectious Diseases

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