Experts Unlock Clues to Spread of 1918 Flu Virus

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The 1918 influenza virus, the cause of one of history's most deadly epidemics, has been reconstructed and found to be a bird flu that jumped directly to humans, two teams of federal and university scientists announced yesterday.

It was the culmination of work that began a decade ago and involved fishing tiny fragments of the 1918 virus from snippets of lung tissue from two soldiers and an Alaskan woman who died in the 1918 pandemic. The soldiers' tissue had been saved in an Army pathology warehouse, and the woman had been buried in permanently frozen ground.

"This is huge, huge, huge," said John Oxford, a professor of virology at St. Bartholomew's and the Royal London Hospital who was not part of the research team. "It's a huge breakthrough to be able to put a searchlight on a virus that killed 50 million people. I can't think of anything bigger that's happened in virology for many years."

The scientists painstakingly traced the genetic sequence, synthesized the virus using tools of molecular biology, and infected mice and human lung cells with it in a secure laboratory at the Centers for Disease Control and Prevention in Atlanta. The research is being published in the journals Nature and Science.

The findings, the scientists say, reveal a small number of
genetic changes that may explain why this virus was so lethal. It is significantly different from flu viruses that caused the more recent pandemics of 1957 and 1968. Those viruses were not bird flu viruses but instead were human flu viruses that picked up a few genetic elements of bird flu.

The research also confirms the legitimacy of worries about the bird flu viruses, called H5N1, that are emerging in Asia. Since 1997, bird flocks in 11 countries have been decimated by flu outbreaks. So far nearly all the people infected - more than 100, including more than 60 who died - contracted the sickness directly from birds. However, there has been little transmission between people.

The 1918 virus, in contrast, was highly infectious, and in recent weeks the fear that a transformation of one of the current bird flus could make it infectious in humans has prompted politicians of both major parties to scramble to demonstrate that they are taking the threat of an avian flu outbreak seriously.

Bush administration officials have been talking about pandemic flu preparedness for years, and they say they will soon release a pandemic flu plan, in the works for more than a year. Senate Democrats say that the administration is not doing enough, and they are writing their own bills that call for more spending and coordination.

President Bush this week asked the leaders of the world's top vaccine manufacturers - Chiron, Sanofi-Aventis, Wyeth, GlaxoSmithKline and Merck - to come to the White House on Friday to discuss preparations for pandemic flu, said people with knowledge of the meeting who insisted on anonymity because the White House has not yet announced the meeting.

The research on the 1918 virus is directly applicable to current concerns, Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, and Dr. Julie L. Gerberding, director of the Centers for Disease Control and Prevention, said in a joint statement. "The new studies could have an immediate impact by helping scientists focus on detecting changes in the evolving H5N1 virus that might make widespread transmission among humans more likely," they said.

The bird flu viruses now prevalent share some of the crucial genetic changes that occurred in the 1918 flu, scientists said, but not all. The scientists suspect that with the 1918 flu, changes in just 25 to 30 out of about 4,400 amino acids in the viral proteins turned the virus into a killer. The new work also reveals that 1918 virus acts much differently from ordinary human flu viruses. It infects cells deep in the lungs of mice and infects lung cells, like the cells lining air sacs, that would normally be impervious to flu. And while other human flu viruses do not kill mice, this one, like today's bird flus, does.
Other scientists said the new work was immensely important, leading the way to identifying dangerous viruses before it is too late and to find ways to disable them.

The 1918 flu, which killed as many as 50 million people worldwide, showed how terrible that disease can be. It had been "like a dark angel hovering over us," said Dr. Oxford, the virology professor at St. Bartholomew's. The virus spread and killed with terrifying speed, preferentially striking the young and the healthy. Alfred W. Crosby, author of "American's Forgotten Pandemic: The Influenza of 1918," said that it "killed more humans than any other disease in a similar duration in the history of the world."

The research, and its publication, raised concerns about whether scientists should actually resurrect this killer that vanished from the earth nearly a century ago.

"It is something we take seriously," said Dr. Fauci, whose institute helped pay for the work. The work was extensively reviewed, he added, and the National Science Advisory Board for Biosecurity was asked to decide whether the results should be made public. The board "voted unanimously that the benefits outweighed the risk that it would be used in a nefarious manner," Dr. Fauci said.

Others are not convinced.

Richard H. Ebright, a molecular biologist at Rutgers, said he had serious concerns about the reconstruction of the virus. "There is a risk verging on inevitability, of accidental release of the virus; there is also a risk of deliberate release of the virus." And the 1918 flu virus, Dr. Ebright added, "is perhaps the most effective bioweapons agent ever known."

But Dr. D. A. Henderson, a resident scholar at the University of Pittsburgh Center for Biosecurity and a leading expert on bioterrorism, said he agreed with the decision to reconstruct the virus and publish its genetic sequence. "This work is of the greatest importance, and it is very important that it be published," he said.

The story of the resurrection of the 1918 flu began in 1995. Until then, scientists had thought the task hopeless. Viruses had not been discovered in 1918, so no one had isolated and saved the one that caused the flu.

But Dr. Jeffery Taubenberger, chief of the molecular pathology department at the Armed Forces Institute of Pathology in Washington, had an idea for finding that ancient virus. He recalled that his institute had a warehouse of autopsy tissue, established by President Lincoln.

Dr. Taubenberger investigated and found tissue from two soldiers who died of the 1918 flu, one in Massachusetts, one on Long Island. The tissue was snips of lung soaked in
formalin and encased in little blocks of wax. In that tissue was the virus, broken and degraded, but there, untouched for nearly 80 years.

Then Dr. Taubenberger received a third sample, from a woman who had died in Brevig, Alaska, when the flu swept through her village, killing 72 adults and leaving just five. The dead were buried in a mass grave in the permafrost. A retired pathologist, Johan Hultin, hearing of Dr. Taubenberger's quest, had traveled from his home in San Francisco at his own expense. He dug up the grave with the villagers' permission, extracted the woman's still frozen lung tissue and sent it to Dr. Taubenberger.

Dr. Taubenberger and his colleagues spent nearly a decade carefully extracting and piecing together the viral genes, like putting together a jigsaw puzzle. Along the way, they published findings that they and others used to try to understand the 1918 flu, but until now they had published only the sequences of five of the eight genes that make up the virus. The last three, which make up half of the virus's length, are published today in their paper in Nature.

In August, Terrence M. Tumpey of the Centers for Disease Control and his colleagues used the viral genome to reconstruct the 1918 virus, and they wondered what would happen if they infected mice and if they infected tissue from human lungs. And, they asked, would the virus remain as lethal if they switched some of its genes with genes from today's influenza viruses?

The scientists took great precautions, Dr. Gerberding said, using special labs that were designed to protect the researchers and prevent the spread of the viruses. "We have erred on the side of caution at every step of the process," she added.

And now, the scientists say, the work is starting to unmask that virus's secrets.

In gene-swapping experiments, the scientists found that small substitutions weakened the reconstructed virus so that it could no longer replicate in the lungs of mice, kill animals, or attach itself to human lung cells in the lab.

The ultimate goal, Dr. Taubenberger says, is to make a checklist of changes to look for in the bird viruses. "Now you have all these viruses going around and we don't know, is it going to adapt to humans? Is it going to cause a pandemic? We don't understand the rules," he said. "There is a lot of science to go."

Gardiner Harris contributed reporting from Washington for this article.