Scientists have uncovered the structure of 1918 flu virus

Debashis Singh *London*

Scientists at the Medical Research Council have discovered the crucial structural changes the avian influenza virus underwent that resulted in its killing 20 million people worldwide in 1918—more people than were killed in the first world war and making it the largest pandemic in history.

The study, published last week in the online version of *Science* (5 February; www.sciencemag.org/scienceexpress/recent.shtml), found that subtle alterations to the shape of a protein molecule, called haemagglutinin (HA), on the virus allowed transmission from birds to humans, among whom it spread rapidly to infect an estimated billion people—half the world's population at the time.

The haemagglutinin molecule protrudes from the surface of the virus as a series of spikes and

enables it to lock on to receptors on the surface of cells in the body. It then gains entry into the cell to infect it.

Human and bird virus haemagglutinins interact with different receptors, which means that bird viruses are normally unable to be transmitted to humans. But in the 1918 virus the shape of the haemagglutinin changed subtly, giving it the capability to attach to receptors in human cells as well as bird cells. This structural change first allowed bird to human and then human to human transmission, resulting in the pandemic.

The team, from the council's National Institute for Medical Research, pieced together the haemagglutinin gene of the 1918 virus from samples from the body of an Inuit woman buried in the Alaskan tundra and from preserved samples from US soldiers who fought in the first world war. They then used x ray crystallography to determine the three dimensional structure of the haemagglutinin.

All the devastating flu pandemics of the last century were caused by viruses that came from birds, such as Spanish flu in 1918, Asian flu in 1957, and Hong

Nurses care for victims of the 1918 influenza epidemic in canvas tents in Lawrence, Massachusetts

Kong flu in 1968. Unfortunately this research will not have any immediate impact on the outbreak of chicken flu currently unfolding in east Asia. In this outbreak the virus has been transmitted from birds to humans but has not yet adapted for human to human transmission.

The study's lead researcher, John Skehel, said, "This paper is important because of the knowledge it brings about how these viruses, which originate in birds, can jump to humans. This allows us to track and monitor the changes in the virus for public health purposes." □

Mortality from avian flu is higher than in previous outbreak

Jane Parry *Hong Kong*

The number of infections in humans from avian influenza continues to rise in Vietnam, and outbreaks among poultry have now been reported in virtually every province and city in the country.

By 9 February the death toll in Vietnam stood at 14 out of 19 confirmed cases. In Thailand the Ministry of Health reported five deaths and another 23 suspected cases, of which nine were fatal. Each case in humans presents another opportunity for the virus to combine with an existing human flu strain, reassort, and potentially spark a new flu pandemic.

The mortality in Vietnam of between 60% and 70% is much higher than the 30% mortality of the 1997 outbreak in Hong Kong, said Professor David Hui, a respiratory medicine specialist at the Chinese University of

Hong Kong. Professor Hui is in Vietnam as part of a team of specialists who are training medical staff in infection control and treatment of H5N1 avian flu.

"This is a puzzle... we are trying to find out: is the virus changing in structure? Is it becoming more virulent? Is the clinical spectrum different from 1997?" Professor Hui told Reuters Television.

Peter Cordingley, WHO's spokesman in Manila, noted that there may have been milder cases that had gone unreported because they had not been picked up by the major hospitals in Vietnam. "We think there's lots more people in Vietnam sick with this. If or when reports of those cases come in, that would make the mortality rates come down," he said.

While the spread of H5N1

avian flu among poultry continues unabated across China, the Chinese government has not yet reported any cases of infection in humans. WHO is not convinced that the government's figures reflect the true situation.

"Given the dimension of the outbreak in China it seems highly unlikely that there are no human cases in China. The task is to find them as soon as possible. When the Chinese government tells us that it has no reports of human cases, our response is we would like to know just how good their surveillance system is," said Mr Cordingley.

H5N1 avian flu outbreaks have now been detected among poultry in China, Vietnam, Thailand, Cambodia, Indonesia, Laos, Japan, and South Korea. Outbreaks of milder strains of avian flu have been reported in Taiwan, Pakistan, and most recently in Delaware, none of which pose a known threat to human health.

A joint meeting between the Food and Agriculture Organization, WHO, and the Office Inter-

national des Epizooties (OIE) on 4 and 5 February concluded that culling is still the preferred option for controlling outbreaks but that targeted vaccination of healthy poultry can be used as a complementary measure.

Culling of poultry continues in Thailand and Vietnam, as well as in China and Indonesia, although the last two countries have decided also to use vaccination. But WHO is worried about the use in Indonesia of vaccines made in China and the reported use of vaccines from unapproved sources in Guangdong province, China. "We've always wondered about the role of inferior vaccines in the outbreak," said Mr Cordingley. WHO has urged the Chinese Ministry of Agriculture to provide more information about the quality and types of vaccines being used.

Meanwhile, researchers at the UK National Institute for Biological Standards and Control are trying to develop a human vaccine by combining avian flu and human flu genes. They expect to have the basis for a vaccine in about two months. □