

Novel bird flu kills two in China

Scientists are racing to assess the pandemic potential of H7N9 flu virus.

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02 April 2013

Scientists and public-health officials worldwide are on alert after China announced on 31 March that two people had died and a third was seriously ill from being infected with a new avian influenza virus, H7N9, that has never been seen before in humans.

Emerging preliminary analyses of the genome of the virus point to the possible spectre of a pathogen that might spread silently in poultry without causing serious disease. That would make the virus difficult to monitor, with animal reservoirs of the virus likely going undetected. Should the virus become established in birds or other animals, regular human infections might then occur — providing opportunities for the virus to adapt better to humans, and ultimately to spread between them, potentially sparking a pandemic.

Scientists stress that it is much too early to do a full risk assessment of the potential pandemic threat. But the initial analysis of viral sequences is “worrisome” because they show several features that are suggestive of adaptation to humans, says

Masato Tashiro, a virologist at the Influenza Virus Research Center in Tokyo, the World Health Organization (WHO) influenza reference and research centre in Japan.

The epidemiological picture is troubling too, says Malik Peiris, a flu virologist at the University of Hong Kong. “Any time an animal influenza virus crosses to humans it is a cause for concern, and with three severe cases [of disease] over a short period of time, we certainly have to take it seriously,” he says. “There’s no obvious indication of human-to-human spread, so we should not overreact, but neither should we be complacent.”

The first case infected by the novel H7N9 virus was an 87-year-old man in Shanghai who became ill on 19 February and died on 4 March. A 27-year-old man in the same city fell ill on 27 February and died on 10 March. A 35-year-old woman in Chuzhou City in Anhui province, some 350 kilometres west of Shanghai, fell ill on 9 March and remains seriously ill. All three developed flu-like symptoms before developing severe pneumonia. The cases were announced on 31 March by China’s health ministry, the National Health and Family Planning Commission, which informed the WHO on the same day.

So far, there seems to be no sustained spread of the virus between people. Chinese authorities tracked dozens of contacts of the three cases and reported that none showed relevant symptoms or tested positive for the virus. Some uncertainty hangs over whether family members related to the first patient — who were hospitalized with severe pneumonia just before their elderly father — might have passed on the virus to the housebound man. Although the family members reportedly tested negative for the virus, the results might have been false negatives. Still, for the moment, experts say, if any human spread is occurring, it is not happening easily.

Sequence yields first clues

Chinese researchers have moved swiftly to decipher the new virus. The WHO Chinese National Influenza Center in Beijing has sequenced isolates from each of the three cases, and published them on the [GISAID flu sequence database](#) on 31 March.

Researchers around the world have since been racing to discover what clues the genome might hold — including the source of the virus, its pathogenicity and its potential to infect, and spread between, humans.

Analyses suggest that the virus is a novel virus that has been generated by reassortment — which occurs when different virus strains infect a host at the same time and swap genes with each other.

Flu viruses have eight genes: two that encode the haemagglutinin (H) and neuraminidase (N) proteins that stud the surface of the virus, and six that code for internal proteins. In the three human cases, the genes coding for the internal proteins seem to come from



Li Wen/Xinhua Press/Corbis

A technician holds test reagents for H7N9 bird flu virus at the Center for Disease Control and Prevention in Beijing.

H9N2 viruses — a class that is endemic in birds, including poultry, in Asia and elsewhere. More specifically, the sequences appear similar to recent H9N2 viruses found in China and South Korea.

The gene for the N protein, says Tashiro, seems to be similar to avian H11N9 viruses that were found in South Korea in 2011; in Hongze, Jiangsu, in 2010; and in the Czech Republic in 2005. The gene for the H protein — especially critical, because this protein allows the virus to bind to host cells — seems to belong to a Eurasian group of H7 avian flu viruses.

In other words, the new virus seems to stem from a reassortment of three virus strains that infect only birds. This is in contrast to the 2009 H1N1 pandemic virus, which was a mix of viruses that infect birds, pigs and humans. Most of the genetic analyses are still being carried out confidentially within the WHO's global flu-research networks. But some researchers, such as a team at the University of Edinburgh, UK, have also started [posting their preliminary analyses online](#).

A striking feature of the novel virus is that its H protein is structurally similar to that of viruses that don't cause severe sickness in birds, and different from those that do, such as the H5N1 virus that has been ravaging poultry flocks in Asia since late 2002. Flu viruses that don't sicken birds can, however, cause severe disease in humans simply because we lack any immunity to them. They also may be more lethal in people depending on how the viruses bind to receptors in the human airway.

Although it is early days, scientists say that it seems clear from the sequence that the novel virus has acquired key mutations that permit the H protein to latch onto receptors on mammalian cells in the airways instead of onto avian receptors. The virus also contains several other genetic variations that are known from past studies in mice and other animals to cause severe disease.

Initial data also suggest that the virus is affecting cells deep in the lung, which would fit with a picture of a virus — much like that of the novel coronavirus that [emerged in the Middle East last year](#) — that can cause severe disease. But it could also indicate that the virus doesn't spread as easily as one that affects the nose and throat, which can be coughed and sneezed out more readily. The full pattern of receptor binding has yet to be worked out, cautions Peiris.

Silent spreader?

The fact that the virus does not seem to cause serious disease in birds has potential epidemiological and public-health implications, Peiris adds. It could be spreading in poultry undetected — and thus could create a reservoir of infection that would lead to frequent sporadic human infections that crop up without warning.

A highly pathogenic virus such as H5N1 is easy to spot because it wipes out flocks, and can be controlled by extended culling. But it might be almost impossible to control a virus in birds that generates few visible symptoms, says Peiris. "That really would be quite a problem," he says. "The question is whether it's already too late to stamp out or not."

China has not reported any recent H7 flu infections in birds, perhaps because such infections would not show up as serious disease, or maybe because of shortcomings in surveillance or reporting. A key requirement now, Peiris says, is to track down which birds or animals the affected humans caught the virus from.

H7 viruses are common in wild birds but much less so in poultry. It therefore seems unlikely that three human cases in such a short space of time could result from contact with wild birds, says Peiris. Domestic fowl are the most likely alternative source of the virus. But given that H7N9 has mutations that enable it to infect mammals, pigs might be another source, says Tashiro.

Flu experts say that other urgent requirements include testing any human cases of serious pneumonia for traces of the virus and tracking down people who have come into contact with new cases. Among researchers and public-health officials, says Peiris, "It's not an atmosphere of alarm, but an atmosphere of concern."

Nature | doi:10.1038/nature.2013.12728