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CHINA FOTOPRESS VIA GETTY



Chinese health workers swab a chicken to test for the novel H7N9 bird flu virus at a poultry market in Changsha, Hunan province.

INFECTIOUS DISEASE

Urgent search for flu source

Researchers suspect H7N9 virus is in bird markets as human cases rise rapidly.

BY DECLAN BUTLER

Virologists know its name: H7N9. What they don't yet know is whether this novel avian influenza virus — first reported in humans in China less than two weeks ago — will rapidly fizzle out, become established in animal hosts to fuel future human outbreaks, or morph into a virus that can spread easily between people and spark a deadly pandemic.

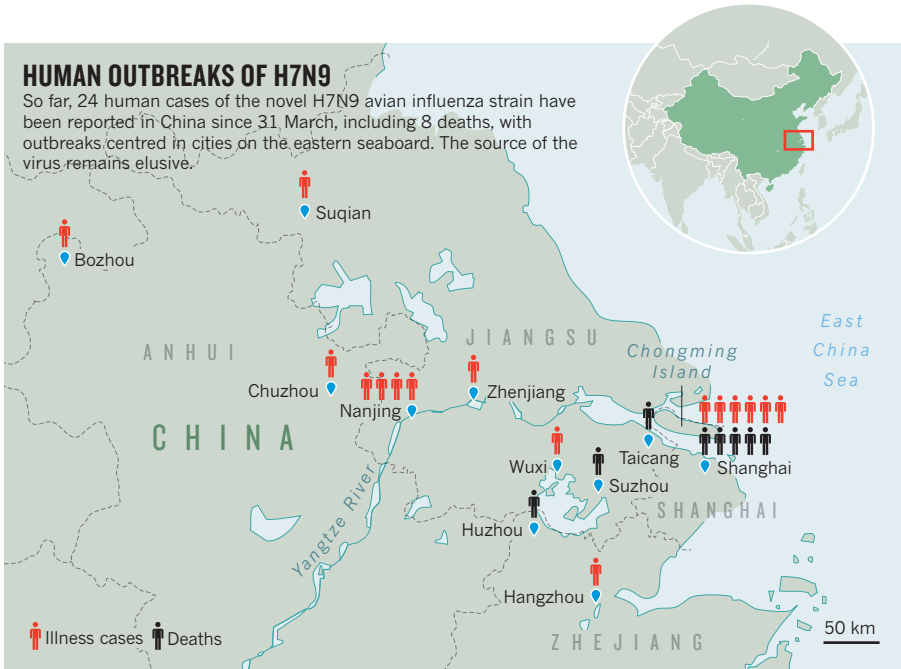
In a frantic effort to find answers, scientists are bearing down on H7N9 on multiple fronts. They are testing wild birds and thousands of domestic fowl; analysing the viruses they find;

and trying to trace people who have been exposed to infected patients. Chinese health authorities say that they have 400 laboratories looking for genetic changes in the virus.

“We are going to be sitting with bated breath over the next month to find out what happens,” says Michael Osterholm, who heads the University of Minnesota's Center for Infectious Disease Research and Policy in Minneapolis. As *Nature* went to press, 24 human cases, including 8 deaths, had been reported in 11 cities, some a few hundred kilometres apart, in eastern China (see map). So many cases in such a short time over such a wide area — up from three cases in two cities a week ago — is “a very

concerning situation”, says Osterholm.

Scientists urgently want to find out which sources are stoking the human infections that result in flu-like symptoms and, in most reported cases, severe pneumonia. So far, investigations of the cases remain largely inconclusive: some patients had contact with poultry or other animals just before falling ill, whereas others had not. Late last week, the H7N9 virus was found in chickens, pigeons and ducks in live bird markets in Shanghai and Hangzhou — making markets the leading suspected source. Authorities have since culled tens of thousands of birds and closed down markets in Shanghai, Nanjing and Hangzhou. ▶



impossible to detect H7N9 through routine surveillance for sick poultry among China's 6 billion domestic birds. "This means stopping animal-to-human transmission is impossible," says Masato Tashiro, a virologist at the Influenza Virus Research Center in Tokyo, the World Health Organization's influenza reference and research centre in Japan.

Each time the virus encounters new human hosts, it has fresh opportunities to mutate and to acquire the ability to spread between people. That does not seem to have occurred yet. But experts say that it will be crucial to identify and track new cases of suspicious severe pneumonia and their close contacts, and to isolate people if necessary. Researchers working on the molecular biology of the virus say that it seems to derive from a reassortment of genetic material from at least three known bird-flu groups (see *Nature* <http://doi.org/k4j>; 2013). A key component — the haemagglutinin (H) protein on the surface of the virus — already contains mutations known to shift its binding preference from bird cells to those of mammals. Scientists are watching for tell-tale changes that could signal a shift towards a form that is more transmissible between humans.

Because flu viruses evolve rapidly, comparing viral sequences from each of the human cases might reveal whether person-to-person transmission is occurring, says Andrew Rambaut, an expert in the evolution of human viral pathogens at the University of Edinburgh, UK. If many patients have very similar viral sequences, then that would imply human spread; if viral sequences are more diverse, it would imply that each person had separately picked up infections from birds. Only four sequences from four human cases are so far available, but virologists are sequencing more and posting them on the GISAID flu database.

If human-to-human transmission does start to occur, "further spread may be inevitable," warns Tashiro. Humanity has never been widely exposed to H7 or N9 flu viruses, and so lacks resistance to these subtypes. If a pandemic were to occur, it would probably have a severe toll. But it is too early to predict how events will unfold; experts in emerging infectious disease are only just becoming acquainted with the latest villain in their roster. ■

Additional reporting by David Cyranoski.

► The genetic sequences of the H7N9 viruses found in the birds are highly similar to those isolated from human patients, says Chao-Tan Guo, a virologist at the Zhejiang Academy of Medical Sciences in Hangzhou. Although the virus might have come from other sources, including mammals, the pattern of many human cases over a wide area in a short time could be explained by live markets alone, because birds from one or a few sources would be transported to multiple markets, says Malik Peiris, a flu virologist at the University of Hong Kong.

But the various bird species found to be infected may not be the original source, because much cross-infection can occur in live markets. Investigators must now trace which farms and wholesalers the birds came from, Peiris says, and test birds up through the supply chain.

Researchers know that H7 flu viruses mainly infect wild birds such as ducks, geese, waders and gulls, and that they occasionally jump into poultry flocks. Kwok-Yung Yuen, an infectious-disease expert at the University of Hong Kong, notes the proximity of the reported human cases to the Yangtze river delta, home to many wild birds, and to Chongming Island near Shanghai, a renowned site for watching migratory birds. "It's likely wild ducks and

geese that are carrying it," he suggests.

But this H7N9 virus has not yet been detected in wild birds in the area. "There is very little specific information on the source of this particular virus strain, its ecology or reservoir, and it is premature to be hypothesizing on the vectors," says Taej Mundkur, who is flyways programme manager for conservation group Wetlands International in the Netherlands. He also co-convenes the Asia-Pacific Working Group on Migratory Waterbirds and Avian Influenza with the Food and Agriculture Organization of the United Nations (FAO).

HIDDEN RESERVOIR

Wherever the virus originated, a crucial question is whether it could become established in poultry, creating a reservoir that might lead to continued, sporadic human infections.

Health authorities in China are trying to learn to what extent that has happened already. Unlike its cousin H5N1 — which has killed millions of birds and several hundred people in Asia and elsewhere since 2003 — H7N9 does not cause serious bird disease, greatly complicating efforts to control it, says Vincent Martin, interim head of the FAO's Emergency Prevention System for Transboundary Animal and Plant Pests and Diseases (EMPRES) in Rome. It would be next to


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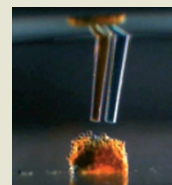


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