

Yes, but will it jump?

As the world braces itself for a potential flu pandemic, experts are wrestling with the key question: whether the H5N1 virus is likely to evolve the ability to spread between people. Several researchers are arguing that the risk has been overplayed. But others are now attacking this view, stating that there is no evidence to support such a claim.

H5N1 has led to the death or slaughter of hundreds of millions of poultry in Asia, and is spreading relentlessly among birds worldwide. It has killed about half of the 156 people so far identified as having been infected, and last week it claimed its first human victims outside Asia — at least two youngsters in a family in eastern Turkey (see 'Bird flu takes its toll on Turkey').

Despite the apparent threat, some virologists, including Peter Palese of the Mount Sinai School of Medicine in New York and Paul Offit of the University of Pennsylvania School of Medicine, believe that much of the attention focused on H5N1 is unwarranted. They argue that H5 viruses may be inherently incapable of transmitting efficiently from human to human. The viruses have had ample opportunity to mutate into a pandemic strain, they argue, and if they haven't already done so they probably never will.

Of the 16 H subtypes of flu, only H1, H2 and H3 are known to have caused human pandemics, including the most recent ones in 1918, 1957 and 1968. "There is a possibility that another subtype may jump among people," Palese says. "However, that has never been observed."

But other experts have told *Nature* that

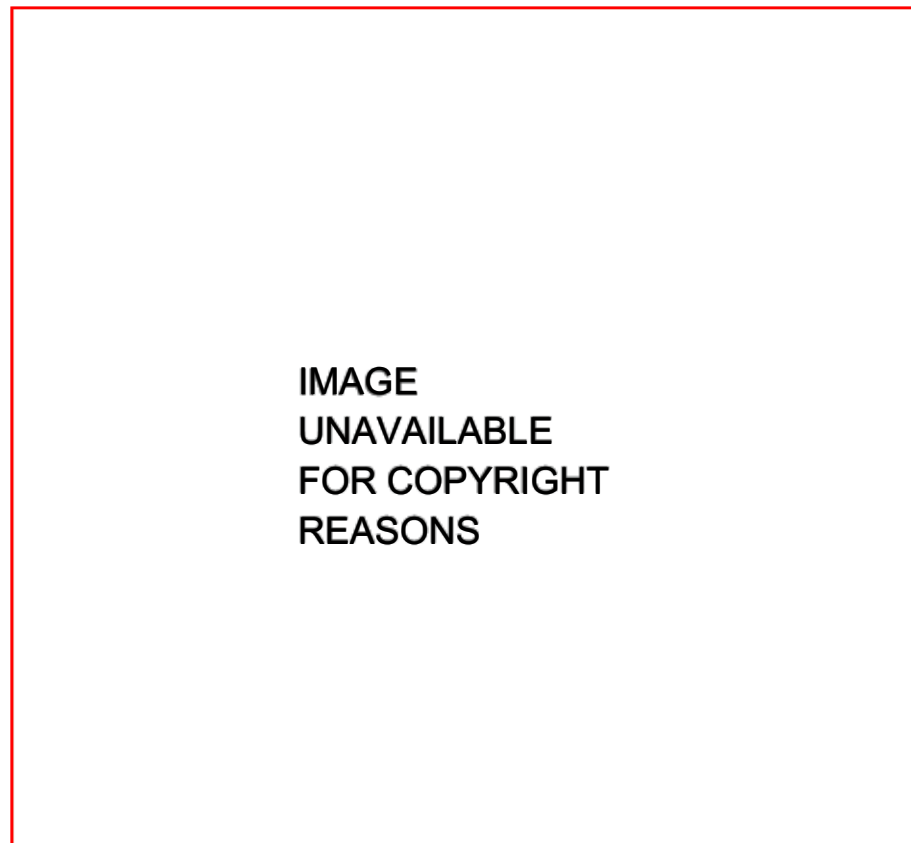


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Clusters of bird flu in Turkey have increased fears of possible human-to-human transmission.

this cannot be used to predict the chance of H5N1 or any future H5 strain triggering a pandemic, and that to state otherwise sows unnecessary confusion.

So who is right? Much of Palese and Offit's argument stems from the idea that many asymptomatic cases of H5N1 have gone undetected. The reported death rate of about 50% is "a complete exaggeration, and not scientifically justified," says Palese.

"If there were indeed many other people infected without showing symptoms then Peter might have a point," says Albert Osterhaus, a

virologist at the Erasmus Medical Center in Rotterdam, the Netherlands. But he says that is far from proved. Studies to find out how many people in the general population of affected countries have antibodies to H5N1 have only just started. Osterhaus says that the first, so far unpublished, results suggest that large numbers of poultry workers do not seem to have been infected. "The data we have suggest that the clinical cases are not the tip of the iceberg, but rather the only people who have been infected," he says.

Palese argues that other evidence suggests

Bird flu takes its toll on Turkey

At least two people have died from avian flu in Turkey. And, as *Nature* went to press, the country's health ministry had confirmed that a further 12 people are infected with the H5N1 virus. Together, these are the first reported human cases outside Asia. Avian flu first arrived in Europe's birds last July, when outbreaks occurred in Russia. It has since appeared in birds in Kazakhstan,

Croatia, Romania and Turkey.

The death of a 14-year-old boy from Dogubayazit, a town on Turkey's border with Iran, on 1 January, was followed by that of his 15-year-old sister on 5 January. Their 12-year-old sister died the following day, although lab tests have yet to confirm H5N1 as the cause of her death. The children's six-year-old brother is currently in hospital.

H5N1 infection has since been confirmed in two other children from another family living in the region, and some 30 suspected cases in the area and in the northern Black Sea region are under surveillance. Last weekend, the Turkish health ministry announced three cases in Ankara, 1,000 km west of the first outbreak. Two brothers, aged five and three, and an unrelated 65-year-old

man are thought to be infected.

Like many of the recent outbreaks in Asia, the Turkey cases have occurred in family clusters, raising the worrying prospect of limited human-to-human transmission. This is extremely difficult to prove, as it requires working out how the first case got infected, then ruling out the possibility that other family members got ill the same way.

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H5 strains have been infecting humans from birds for decades. In particular, he cites a paper from 1992, which found H5 antibodies in 2–7% of the population in rural China (K. F. Shortridge *Semin. Respir. Infect.* 7, 11–25; 1992). There is no reason then to believe that an H5 virus should suddenly trigger a pandemic now, he says.

Edward Holmes, who studies virus evolution at Pennsylvania State University, is unconvinced by Palese's argument. "I don't think you can say that it should have happened already," he says. "The history of evolution is that rare things can happen." And in unpublished work, Yi Guan of the University of Hong Kong, who

worked on the 1992 study, says that his group has since tested 4,000 blood samples collected in southern China in 2001 and found no antibodies against H5 viruses.

Experimental evidence about whether H5N1 could spread between people is also lacking. Although scientists are beginning to understand what genes make flu viruses pathogenic, they know little about what determines their transmissibility.

Where a virus is excreted from seems to be one factor. Viruses infecting the upper respiratory tract, for example, are thought to jump more easily than those lower down. But scientists aren't sure about this with H5N1, as only a handful of autopsies have been done on human victims, largely because of religious concerns in the relevant countries.

Another way to study the question would be to study viruses such as the 1918 flu strain in mammals, replacing the genes one at a time to investigate their roles in transmissibility. This work hasn't been done either, because such dangerous viruses are strictly regulated.

More data are desperately needed, says Holmes, and in the meantime we should not assume that H5N1 won't cause a pandemic. "Trying to put numbers on how long it is going to take or how many people are going to die is a pointless exercise. We scientists should just hold up our hands and say we don't know what is going to happen." Palese himself accepts this view as reasonable. "OK; that I can agree with," he says.

Palese also strongly supports the need for better surveillance and research. Whatever he thinks about H5N1, he emphasizes that further flu pandemics are inevitable. His views have been picked up by the media as evidence that the pandemic threat is being hyped, but Palese argues that the need to prepare has not been driven home strongly enough: "People are just not willing to accept that we are not doing enough across the board — in research, surveillance or in developing vaccines." ■

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It's hard to say how significant the clusters are, says Albert Osterhaus, a virologist at the Erasmus Medical Center in Rotterdam, the Netherlands. Families are likely to be exposed to the same things, he points out, "so you wouldn't necessarily expect a random distribution of cases".

Scientists are also intrigued by the fact that in the clusters, it tends to be blood relatives

who get infected, rather than, say, husband and wife. This suggests that some people might be genetically more susceptible than others. But there are too few cases to confirm this, says Peter Palese, a virologist at the Mount Sinai School of Medicine in New York. It could just depend on who prepares the food, or kills the chickens.

He adds that research on

genetic differences among victims could be used to look for differences in, for example, the immune response — although researchers are rarely able to get hold of such data.

But the new cases in Europe do not fundamentally increase the chances of a pandemic, says Osterhaus. "With 142 cases in Asia, a couple of new ones on the doorstep of Europe doesn't change much," he says. **D.B.**