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Food for thought. Contact with ducks—which can carry H5N1 without symptoms—is a risk factor for human infection.

True Numbers Remain Elusive in Bird Flu Outbreak

Confounding reports about human cases of bird flu have fueled concerns about a pandemic. But the true spread of H5N1 remains unknown

When 5-year-old Hoang Trong Duong from Vietnam's Quang Binh province was diagnosed with avian influenza last week—about 10 days after his 13-year-old sister died, presumably from the same disease—he became the 70th victim since the H5N1 bird flu strain started its march across Asia.

That's the official number. But most flu experts believe that H5N1 has infected many more people, and some are increasingly worried that, 17 months into the current outbreak, there still hasn't been a concerted effort to establish the true extent of the spread of the virus—which could spawn a pandemic—among humans. "I'm very worried that information has been slow to emerge," says flu scientist Nancy Cox of the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

There are many reasons for the information gap—from quirky test results to a lack of lab capacity in the affected countries to political sensitivities. A broad testing program, combined with carefully collected epidemiological information, is "absolutely crucial" to answer some basic questions, says virologist Albert Osterhaus of the University of Rotterdam, the Netherlands. Among them: How many people have become infected? What are the ways in which the virus spreads? And is the virus getting better at human-to-human transmission—the first step on the road to a pandemic?

There's good reason to assume that there are more cases than those found so far, researchers say. Mostly seriously ill patients get tested for H5N1, says Cox; milder cases are likely to slip through the cracks. (That may also be why the official death rate stands at a staggering 67%.) Moreover, during H5N1's first outbreak, in 1997 in Hong Kong, several infected children had mild or no illnesses. Two weeks ago, Vietnam also reported two asymptomatic infections.

As an example of what needs to be done, Osterhaus points to a study done after the 1997 outbreak by a team from the Hong Kong Department of Health and CDC, which included Cox. They screened 51 household contacts of H5N1 patients, as well as 26 people who went on a 4-day plane and bus trip with one of the patients and 47 co-workers of a bank employee who became ill; they also collected detailed information about each subject's contacts with the patients. (The results were somewhat reassuring: Only one member of the tour group and six household contacts had antibodies to H5N1.)

Cox says several recent developments reinforce the need for broader testing. A paper published online by the *New England Journal of Medicine* on 17 February reports that H5N1 can cause diarrhea and brain inflammation, suggesting that cases may be missed because doctors simply don't think of bird flu. The increasing number of reported family clusters of H5N1 in Vietnam might also signal human-to-human transmission, she says.

But broad efforts have been stymied. One problem is the technical difficulty of testing for antibodies. Flu researchers traditionally rely on hemagglutinin inhibition tests to detect antibodies in serum samples. But those have proven "simply not sensitive enough" in the case of avian influenza, says Klaus Stöhr, who coordinates WHO's global influenza program. The alternative—a so-called microneutralization assay—is more reliable but also more time-consuming and expensive. And because it uses live H5N1 virus that infects cells, it should only be carried out in a biosafety level 3 laboratory, of which the region has very few.

Amassing samples and epidemiological questionnaires is labor-intensive. "The Vietnamese are too busy just trying to keep track of the cases of serious illness," says Peter Cordingly, spokesperson for WHO in Manila. Nonetheless, the Hospital for Tropical Diseases in Ho Chi Minh City now has several hundred samples—from cullers, contacts of patients, health care workers, and controls—that may be shipped to the WHO collaborating center in Hong Kong, says Peter Horby, a WHO official in Hanoi.

In Thailand, meanwhile, two groups have tested hundreds of samples collected during the outbreak last year. Unfortunately, some of the corresponding epidemiological data weren't properly recorded. The results are still being reviewed, but Scott Dowell of the International Emerging Infections Program in Bangkok, a collaboration of the Thai Ministry of Health and CDC, says that so far, the data don't suggest large numbers of subclinical cases—a result virologist Malik Peiris of the University of Hong Kong characterizes as "surprising."

The lack of information has been frustrating for labs with the expertise but no samples to test. CDC, for instance, has trained Vietnamese researchers and has tested some samples from Thai health care workers, but would like to do more, says Cox. Getting renowned international labs involved should also help avoid mistrust and confusion about the results, says Osterhaus. But such collaborations require diplomacy, says Stöhr: "You can't just march into Vietnam with an army of researchers."

Meanwhile, fresh bird outbreaks of H5N1 were reported in Indonesia last week, and South Korean newspapers reported that North Korea culled thousands of chickens last month to curb an outbreak near Pyongyang. As a member of the World Organization for Animal Health, North Korea must report outbreaks of avian influenza, which so far it hasn't done. Stöhr notes that an outbreak in the secretive nation would be hard to investigate or bring under control.

–MARTIN ENSERINK AND DENNIS NORMILE

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