

Vietnam's war on flu

Having suffered heavily from avian influenza in 2004, Vietnam might now be brewing the next human flu pandemic. Yet, as Peter Aldhous discovers, local researchers don't have the resources to investigate the risk properly.

Each year around the end of January, the swarm of motor scooters on the streets of Ho Chi Minh City thins out as offices and shops shut down. Tet, the lunar New Year festival, is a time for rest and family gatherings.

But things were far from restful this time last year, as disease stalked the city. At the Hospital for Tropical Diseases and the nearby Pasteur Institute, Tet celebrations were forgotten as virologists raced to analyse nose and throat swabs taken from patients with respiratory problems, looking for the deadly H5N1 avian influenza virus. "I worked ten hours a day, seven days a week," recalls Tran Tan Thanh, a virologist at the hospital.

Now there are fears of a repeat performance for this year's Tet. Two Vietnamese boys have died of avian flu since 30 December and, as *Nature* went to press, a 16-year-old girl remained critically ill.

H5N1 avian flu swept through Asian poultry flocks in 2004. And the latest human cases bring the death toll to at least 22 people in Vietnam and a further 12 in Thailand. If the virus evolves to become easily transmissible from person to person, H5N1 has the potential to trigger a pandemic that could claim millions of lives worldwide. This is why public-health experts worry that more isn't being done to understand the outbreak, and to monitor for the virus.

Vietnam is a particular concern. Not only has the virus hit this country especially hard, but the population still lives day-to-day in close quarters with chickens and ducks. The good news is that Vietnam has just enough scientific infrastructure from which to build a proper monitoring effort. But experts on the ground complain that the international community hasn't prioritized such efforts — leaving them frustrated by a lack of funding,



and alarmed by what might happen next.

"There has been a large amount of activity, but it could do with more energy, more money and more communication," says Peter Horby, who is responsible for communicable disease surveillance at the office of the World Health Organization (WHO) in the Vietnamese capital, Hanoi.

Initial outbreak

Before the first human cases emerged last year, H5N1 flu had been working its way through Asian poultry flocks for several months, triggering widespread culls of chickens throughout the region. Researchers knew that transmission of the virus to humans was a possibility. And on 8 January 2004, virologist Le Thi Quynh Mai and her team at the National Institute of Hygiene and Epidemiology (NIHE) in Hanoi confirmed these fears, showing that a Vietnamese patient was suffering from H5N1.

More cases were soon identified. And in



As bird flu swept across Asia last year, millions of birds were culled in Vietnam (above). But exposure to poultry (left) still led to the deaths of at least 20 children and young adults infected with the H5N1 virus. Rapid diagnosis, including chest X-rays, helped the Vietnamese to identify cases of H5N1 among the population.



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the initial stages, those at the sharp end knew that there was no time for delay, nor any room for error. “This really was crisis diagnostics,” says Menno de Jong, who had moved from Amsterdam only months before to help establish the virology lab at Ho Chi Minh City’s Hospital for Tropical Diseases.

In the weeks following Mai’s identification of the initial human case, her lab and the two main diagnostic labs in Ho Chi Minh City worked closely with a team of 28 international experts sent in by the WHO and the US Centers for Disease Control and Prevention — who brought with them badly needed reagents, and considerable expertise. A paper describing the first ten Vietnamese patients with H5N1 influenza was soon on its way to *The New England Journal of Medicine*, and appeared online on 25 February¹.

All in all, Vietnam’s response to the health emergency has won cautious praise. “They are doing a good job, given the circumstances and the amount of funds,” says Horby. From the start, Vietnamese officials seemed determined to avoid the mistakes made in China a year previously, when secrecy hampered the international response to the emergence of severe acute respiratory syndrome, or SARS. Phan Van Tu, who heads the Ho Chi Minh City Pasteur Institute’s microbiology and immunology department, makes a point of showing me an official data sheet recording all human cases of H5N1 flu in each of the 20 provinces in southern Vietnam. “We don’t hide anything,” he says.

But the initial momentum has not been maintained. Today, the crisis teams that helped with the initial diagnosis and epidemiology have long since departed. Yet the need for surveillance of H5N1 and other flu viruses has scarcely diminished — all of the ingredients to brew a pandemic strain of influenza are still in place, and people continue to get infected. In addition to the latest crop of cases, four deaths were confirmed between August and September 2004.

Living with danger

Vietnam’s economy may be growing rapidly, but the vast majority of its people are still small-scale farmers who share their living space with chickens and ducks. “The hinterland of Vietnam is, for all practical purposes, one huge free-roaming farm,” says Anton Rychener, who heads the Hanoi office of the UN Food and Agriculture Organization (FAO). This, experts agree, provides the ideal breeding ground for deadly strains of flu, which are likely to emerge when viruses pass between different species of livestock and people, and exchange genetic material in the process.

Similar conditions prevail in southern China, although no human cases of H5N1 flu were reported there in 2004. That may be a true reflection of the Chinese situation, but few experts believe that H5N1 has claimed no human victims in Cambodia and Laos,

given the distribution of the disease in poultry — it’s just that these two impoverished countries have negligible disease surveillance. Thailand, meanwhile, has reported human deaths. But some experts question privately whether Thailand’s desire to protect lucrative poultry exports has prevented it from acknowledging the true extent of infection in its flocks.

So Vietnam may present the best opportunity to get a handle on the risks posed by H5N1 influenza, and to answer some nagging questions. Comparison of the current crisis with previous experiences of the virus, for example, reveals some mysteries. When H5N1 first made the jump from poultry to people in 1997 in Hong Kong — an outbreak that was thankfully contained by culling stocks — the human cases spanned a wide age range². Most of these cases were linked to exposure to chickens at live poultry markets. But in Vietnam and Thailand, the human cases have all been in children or young adults. And there is no clear link between the human cases and occupational exposure to poultry. None of the 15,000 or so Vietnamese workers who culled millions of chickens at the height of the outbreak became sick, even though most of them did not wear protective clothing.

One theory is that Vietnamese adults, particularly those who work closely with poultry, have some immunity to H5N1, perhaps through earlier exposure to a related avian flu virus. But Vietnamese children would have no such earlier exposure, and could come into contact with the virus by playing with poultry in their backyards. The first case to show up in Ho Chi Minh City, for instance, was an eight-year-old girl who had kept a pet duck that became sick and died¹.

To confirm or refute such theories, researchers will have to look at a large number of human blood samples to see who has antibodies against H5N1. Detailed epidemiological data will also be needed to work out how these people were exposed to the virus.

At the same time, researchers want to examine poultry, other livestock and migratory birds — the last of which may play a role in spreading H5N1 (ref. 3) — to see whether they carry antibodies against the virus.

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Domestic ducks are a particular concern, as they can become infected and excrete large quantities of the virus in their faeces without becoming obviously sick⁴. This silent reservoir of infection probably explains why

H5N1 began showing up in Vietnamese chickens again in late June, after being declared eradicated at the end of March.

Monitoring the genetic evolution of H5N1 will also be key to assessing the danger that it poses. Despite one report of a Thai woman being infected by her daughter, there is so far no clear evidence that H5N1 is passing from person to person. But the big fear is

that it will slowly adapt to infecting mammals, or exchange genes with a human flu virus to create a lethal and easily transmissible strain. If that occurs, we would soon have a global health emergency on our hands.

It is already clear that the viruses that caused the current outbreak are subtly different, genetically, from those that hit Hong Kong in 1997 (ref. 3). And there are ominous suggestions that H5N1 is evolving to infect a wider range of species. Robert Webster, a leading influenza virologist at St Jude Children's Research Hospital in Memphis, Tennessee, in unpublished work has found that H5N1 can infect pigs. Viruses isolated from a Vietnamese patient have already been shown to cause disease in domestic cats⁵, which are usually resistant to influenza A, the subtype to which H5N1 belongs. And in October, there was an outbreak of H5N1 flu in tigers at a zoo in eastern Thailand.

Increasing threat

Findings from Chinese veterinary scientists, working with Webster, have caused further alarm. They sampled H5N1 viruses from ducks in southern China between 1999 and 2002, and transmitted them to mice. Judging from these experiments, H5N1 has become progressively more pathogenic to mammals⁴. And in further unpublished work, Webster infected ducks with H5N1 samples collected in Vietnam in 2003 and 2004; those given the 2004 isolates excreted the virus for a longer period.

Yet despite these troubling results and the yawning gaps in our knowledge of the dangers posed by H5N1, it is proving tough to find funding for surveillance in Vietnam. Such work falls between the cracks, says Horby: it isn't covered by the initial crisis response to a disease outbreak, and conventional channels of scientific grant funding are too sluggish. So Horby has, until now, had to scramble around for small amounts of aid money to launch studies to survey people for H5N1 antibodies. Unfortunately, this doesn't provide much scope for building up the scientific infrastructure required if such studies are to be conducted routinely in Vietnam.

Vietnamese officials are reluctant to criticize the international response to the H5N1 outbreak. But foreign scientists working in Vietnam are less polite. "When there's a problem, everyone flies in, creates a certain amount of havoc, flies out, and leaves nothing behind to change the situation," complains Jeremy Farrar, who heads the Oxford University Clinical Research Unit at the Hospital for Tropical Diseases in Ho Chi Minh City.

Kenjiro Inui, a virologist seconded to the National Institute of Veterinary Research in Hanoi by the Japan International Cooperation Agency, echoes Farrar's view. After the



Silent source: ducks can harbour and readily excrete the deadly H5N1 virus without getting sick.

initial outbreak, he says, the institute was deluged with requests from foreign scientists who wanted to come and collect samples for their projects. But it was unclear how this would benefit the Vietnamese partners. And offers to help Vietnamese scientists build their monitoring infrastructure were thin on the ground. "Everyone is welcome," says Inui, "but you can't come here just to get samples..." Inui's colleague Nguyen Tien Dung glances at him wryly and finishes his sentence for him: "...and then run away."

But Dung is pleased with his ongoing collaborations with Webster and another leading authority on flu viruses, Malik Peiris of the University of Hong Kong, to investigate the evolution of H5N1 in Vietnamese livestock. Researchers from the Hanoi veterinary institute have also visited Hong Kong for training.

Emergency team

De Jong and Thanh's diagnostic lab further illustrates what's possible through a genuine collaboration. It is part of Farrar's unit in Ho Chi Minh City, which is financed jointly by the Vietnamese government and the Wellcome Trust, Britain's largest medical research charity. If the virology lab hadn't been in place, says Tran Tinh Hien, deputy director of the Hospital for Tropical Diseases, the situation last January would have been chaotic. "Patients were in panic," Hien recalls. "As soon as people got respiratory symptoms, they came to us."

The viral lab's rapid diagnostic work allowed doctors quickly to determine the combination of symptoms likely to represent a case of H5N1 flu — including severe lesions on chest X-rays, a high fever, and a reduced count of white blood cells¹. So most patients could be reassured that they weren't infected with the killer virus, and were sent home. "It was very important that we had

this diagnostic capacity," says Hien.

But hospitals in the less-developed central regions of the country can't call on state-of-the-art diagnostic labs. This is a source of concern for Mai, who fears that human H5N1 cases may have been missed. Her lab at the NIHE was sent some samples from suspected cases in central Vietnam last year. But by the time the samples had reached Hanoi, they had degraded and couldn't be analysed.

Even if surveillance for human cases is improved, that still leaves the mammoth task of looking for the virus in poultry and other livestock. Here, there is a huge amount of work to be done, if Vietnam's capacity is to be brought up to the desired standard. At present, some local veterinary offices lack even basics such as reliable phone and fax connections. "We must strengthen the capacity of staff, and improve working conditions, equipment and infrastructure at the lower levels," says Hoang Van Nam, chief of epidemiology in the agriculture ministry's Department of Animal Health.

The FAO has recognized the problem, and with the World Bank has put together a two-year Avian Influenza Emergency Recovery Project for Vietnam, which includes US\$2.8 million for lab diagnostics, surveillance in the field, and other research into avian flu. But Rychener argues that much larger sums are needed, given that H5N1 is now believed to be endemic in southeast Asia. "The international community is not reacting properly," he says. "It underestimates the gravity of the situation."

Just imagine, Rychener adds, the huge sums of money that would be mobilized if a similar situation were to emerge in Europe or North America. "But here, we are talking about chicken feed." ■

Peter Aldhous is Nature's chief news & features editor.

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