

On a wing and a prayer

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In the past two months, a lethal new strain of avian flu has killed 14 people in Vietnam. And experts warn it is only a matter of time before the virus mutates to become a devastating pandemic. If that happens, 2 million Britons could die. Mark Honigsbaum reports from the Hanoi hot zone

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To say that the Lunar New Year, Tet Nguyen Dan, is an all-consuming holiday in Vietnam is something of an understatement. Imagine Christmas, New Year and America's Thanksgiving rolled into one and you begin to grasp the scale of the Tet festival and the centrality to it of food - especially poultry. During the run-up to Tet, millions of chickens and ducks change hands as Vietnamese families stock up for the coming festivities. The celebrations begin around 23 December with the Feast of the Kitchen Gods, or Lê Táo Quân, and continue right into February with an orgy of culinary delights, at which a duck or chicken, either roasted or live and awaiting slaughter, is never far from the table.

In Hanoi, and other parts of northern Vietnam, one of the most popular dishes of all is duck's blood pudding - a hearty soup made from simmered duck innards and raw duck blood. Traditionally eaten on the eve of Tet - which this year fell on 9 February - it is meant to mark the passage from the old to the new. On New Year's Day, and for two weeks after Tet, it is considered bad luck to eat duck. That's when the chickens make their culinary appearance. From the point of the avian flu virus, H5N1, Tet is an accident waiting to happen.

On the morning of 8 February, Nguyen Sy Tuan, a 21-year-old man from Thai Binh, a province 100 miles southeast of Hanoi, visited a neighbour who, like millions of rural Vietnamese, raises chickens and ducks in his yard, and bought some duck for the pot. With the help of his mother he slaughtered the fowl in the kitchen, then poured the duck's blood into a bowl and added vinegar to stop it congealing. He then set about preparing the broth.

Within an hour or so the pudding was ready and he, his mother, his father and his two sisters, aged 14 and 27, sat down to consume several bowls. Five days later, on 13 February, Sy Tuan began to feel unwell. He had a headache and a slight fever. Thinking he had common or garden flu, his family dosed him with aspirin and tucked him up in bed. But two days later, on 15 February, his fever shot up to 40C. On 20 February, he started coughing and complaining of chest pains. By the time Sy Tuan was transferred from the local Thai Binh hospital to Hanoi's Institute for Clinical Research into Tropical Diseases two days later, the damage had been done. According to Dr Nguyen Tuong Van, the director of the hospital's emergency ward, it was like looking at a patient 'in the advanced stages of HIV'. 'When I examined his chest X-ray there were white shadows everywhere,' she told me in her consulting office in Hanoi, on a brief respite from her rounds. 'I had no choice but to intubate and put him on a respirator.'

The shadows were a sure sign that the infection had already invaded Sy Tuan's respiratory tract and begun eating away at his lung tissue. That evening, mindful of scientists' warnings that H5N1 was on the brink of mutating into a virus that could transmit itself between humans, I donned a surgical gown and mask and went to see Sy Tuan for myself. I found him in a room off a corridor marked 'quarantine'. A plastic hose led from his mouth to a respirator beside his bed. Although the machine was the only thing keeping him alive it was doing little to ease his breathing. His knees were doubled up in pain and beneath the blanket I could see that his heart was pounding furiously.

To my surprise, Sy Tuan was not alone. In the bed next to him, watching with wide black eyes, was his 14-year-old sister. Two days after her brother had been rushed to hospital she'd also started running a high fever and had to be admitted. Like her brother she would also test positive for H5N1. 'We'd heard about the bird flu, but we never imagined it would infect our family,' their older sister, Nguyen Nhung Ngoan, told me in the corridor that evening. 'We are really scared because we know it is a very serious disease.' Then, grasping her own mask closer to her mouth for protection, she added: 'All we can do is pray they will recover.'

Since the present strain of H5N1 emerged in Vietnam in late 2003, Dr Van and her counterparts at the tropical diseases institute in Ho Chi Minh City have treated 35 people for bird flu and recorded 18 fatalities - 13 of them since December. Including Thailand, the next-worst infected country, and

Cambodia - which reported its first death last month - there have been 46 deaths in southeast Asia since the epidemic began. Those deaths represent 70 per cent of all known avian-flu infections. In contrast, Sars (Severe Acute Respiratory Syndrome), the corona virus which struck Hong Kong and Vietnam in 2002, had a mortality rate of just 10 per cent. No wonder scientists are spooked.

'We think it is only a matter of time before H5N1 or a related strain of the virus becomes infectious between humans,' Professor John Oxford, a virologist at the Queen Mary and Westfield School of medicine in east London, had warned me before I embarked for Vietnam. 'When that happens it will be too late to do anything about it, which is why we have to prepare now. Forget al-Qaeda, the biggest terrorist threat we face today is Mother Nature.'

Oxford isn't the only scientist who fears a viral meltdown. At a conference of international bird-flu experts in Ho Chi Minh City a few days later, I heard Dr Shigeru Omi, the WHO's Western Pacific regional director, warn that the world was 'now in the gravest possible danger of a pandemic'. At that point, Vietnam had not recorded a new H5N1 case for three weeks and the Vietnamese government was hopeful that its stringent anti-poultry measures were at last beginning to pay dividends. Since late 2003, agriculture officials have culled 44m infected chickens, a sixth of the country's poultry population. And following the most recent outbreaks this winter, the government ordered a further 800,000 chickens killed, and banned the sale of poultry at Ho Chi Minh's unhygienic wet markets. But for all that these measures had restored confidence in farmed chickens, vets and public health experts attending the conference warned that Vietnam now faced another challenge: the chickens and ducks which roam freely in people's backyards and paddy fields. In particular, said Dr Omi, the Vietnamese should beware of ducks that, according to the latest evidence, were playing a 'silent role' in the transmission of the disease, harbouring the virus and excreting it in their faeces for up to 17 days without showing any obvious signs of illness. 'The public health implications of this are very serious,' warned Omi. 'How can people avoid exposure to the virus when they don't know which ducks are infected and which are not?'

The ducks are not the only worry, of course. The even bigger unknown is the virus itself. The problem is no one knows how fast and in what direction it is mutating. Avian flu is a type A orthomyxovirus (there are also B and C

types, but though they can cause illness they are rarely fatal in humans). Like every influenza virus, H5N1 has hundreds of microscopic spikes protruding from its surface. Most consist of a viral protein called haemagglutinin, which has the unique ability to latch onto respiratory cells and invade them. The other spikes consist of enzymes, neuraminidase, which help the virus spread. It is from the initials of these two proteins - H and N - that the avian flu virus gets its name.

What makes H5N1 and other influenza viruses so dangerous is that they are shape-shifters, possessing the rare ability to swap proteins with other influenza viruses to create new influenza viruses. The reason is that, unlike animal cells, which are coded by DNA, the influenza virus consists of RNA and does not possess an accurate proofreading mechanism to correct its genetic mistakes.

Professor Oxford, who keeps an orange, football-sized scale model of the virus on his desk, likens the RNA to coiled springs and the haemagglutinin to blue prongs. During replication, when the virus invades and colonises human cells, the RNA makes errors, resulting in genetic mutations to the prongs. Such mutations are known as 'antigenic drift'. The reason they are dangerous is that they trigger small changes to the haemagglutinin, enabling the prongs to stick better to human cells and evade the antibodies produced by the immune system. In addition, type A viruses such as H5N1 can also 'swap' or re-assort genetic material with other viruses. This process, known as 'antigenic shift', occurs when animal strains mix with human strains, producing viruses to which no animal or human has immunity.

'The problem is, one chicken can contain hundreds of thousands of strains of H5N1,' explains Oxford. 'Let's say there are a billion chickens in Asia and 10 per cent are infected - that's a vast population of viruses, more than the entire human population of the planet. Now let's further suppose some of these strains have mutated so they can latch not only on to a chicken but on to you or me, but they cannot do it very efficiently. That's the position we appear to be in. If a child catches the virus from a chicken they may transmit it to their mother, but the mother won't be able to go out and infect the grocer.'

Armageddon only comes at the next stage, when the virus learns to pass efficiently between humans. By the time that happens, says Oxford, 'it's already too late'. He examines his orange ball, pausing to consider the simplicity of the virus and its awesome destructive power. 'At the moment

it's a slow greyhound of a virus. It's when it develops into a normal greyhound that we're in for it,' he says.

One man who may be able to offer us clues to the virus's mutability is Nguyen Thanh Hung. A 42-year-old cement salesman, with a boyish face and thick black hair, Hung lives on his own in a small apartment approached through a metal grille off a maze-like backstreet in Hanoi. Slight of build, Hung likes nothing better than to tend to his bonsai trees, play his guitar and jog 10km every day. 'It's hard going, but I'm trying to train my lungs,' he explained, when I visited him at his apartment on a winter's evening in late February.

Hung has good reason to persevere with his punishing regime. In December his elder brother contracted bird flu and died. Then, four weeks before Tet, Hung also fell ill with H5N1. If it wasn't for his extraordinary physical fitness he might not be here to speak about it today.

Hung's ordeal began on 24 December last year, when he boarded a bus to Thai Binh to attend the funeral of his elder brother's infant son, who had tragically drowned in a fishpond near his home. To mark the occasion, Hung's brother had bought a live duck in the village market and, with the help of his younger brother, slaughtered and cleaned it before Hung arrived. He then prepared the local delicacy - duck's blood pudding.

On the day of the funeral - 25 December - all three men sat down to eat the broth, but Hung and his younger brother found it too salty and hardly touched it. After lunch, Hung took the bus back to Hanoi. Two days later, complaining of a headache, his brother took to bed. At first, the family put his illness down to grief over the loss of his son, but by 31 December he was running a high fever and coughing. The family took him to the local Thai Binh hospital, from where he was transferred to Hanoi's Tropical Diseases Institute. There he was seen by Dr Van, the same physician who has been treating the latest Thai Binh cases. According to Dr Van, she and her colleagues did not initially suspect the elder brother had bird flu, so she gave him a range of drugs to relieve his symptoms. But a few days later his breathing became laboured and she had to intubate and put him on a respirator.

For five days, Hung and other members of the family sat vigil at his bedside. 'He kept struggling to remove the monitor and I had to keep leaning forward

to put the mask back on him. I was about 30cm from his face,' Hung told me. Was he wearing a mask himself? 'Sometimes, but I found it uncomfortable, so I kept taking it off.'

On 9 January, Hung's brother died, the disease having spread from his lungs to his kidneys and liver. The following day, back in Thai Binh for his brother's funeral, Hung also began to feel unwell. On his return to Hanoi, now running a high fever, he made an appointment at another hospital, where his wife worked as a nurse. There an X-ray showed a small white shadow on his lung, which was misdiagnosed as tuberculosis. His fever soaring, Hung decided to check himself into the Tropical Diseases Institute. There he was given five different medications, although not Tamiflu, a costly anti-viral drug used to treat known cases of H5N1 (as yet, there is no vaccine).

By now Hung was delirious. 'My whole skull was throbbing,' he told me. 'I felt like I was going colour blind and the walls were pressing in on me.' Hung was still in the hospital when, on 19 January, a chronically backlogged lab finally sent back word that his brother had died of bird flu. Soon after, it was confirmed Hung had it, too. 'I was quite scared at first, but by then I was starting to feel better. The fever and pain were over and I thought to myself, I'm through the worst.' Nonetheless, it was a further 10 days before Hung was well enough to be discharged.

The story of Hung's survival is a riddle - one that should alarm us but also provides room for comfort and hope. The first mystery is how he contracted the virus. Dr Van and the Vietnamese government have taken the position that he got it from ingesting the raw duck's blood pudding. But, aside from his brother who had also slaughtered the duck, thus presumably exposing himself to a massive dose of the virus, no other members of his family who ate the pudding fell ill. Hung's symptoms also did not appear until 14 days after the meal - far longer, say experts, than the typical three- to seven-day incubation period seen in other cases.

On hearing of Hung's case, the WHO asked the Vietnamese government for nasal swabs and sent the specimens to a laboratory in Tokyo for analysis. But though tests confirmed Hung had H5N1, the specimens were not good enough to allow the WHO to culture the virus and conduct more precise molecular studies which would show whether or not it was identical to the avian strain or had mutated. The WHO is now conducting virulence studies

in animals which may answer that. For the moment,' says Peter Horby, the WHO's representative in Hanoi, 'we cannot rule out the possibility that this was a case of human-to-human transmission.'

The other question is, given that Hung had H5N1 and didn't receive Tamiflu, how did he manage to recover? One answer may be the speed with which he got himself to hospital. In other cases, says Dr Van, where patients have arrived too late and she has had to intubate, only one in 10 have survived. The other key factor may have been Hung's physical fitness. 'Most people who die of bird flu are poor and not in the best physical condition in the first place,' says Dr Van.

Influenza, which was first recorded in Italy more than 100 years ago, takes its name from the Latin word 'influentia', reflecting the then widespread belief that the illness was due to the influence of the stars. But respiratory diseases accompanied by fevers that read very much like influenza are also mentioned by ancient Greek and Roman physicians and it is likely flu has plagued mankind for as long as people have been living in close quarters with chickens and pigs. The virus almost certainly began as an infection of birds and in all probability has been harboured by avian populations for millennia. But for reasons still poorly understood, since the advent of the industrial revolution these avian viruses have shown an increasing propensity to spread to mammals and infect humans. Now and again, these viral 'leaps' spark pandemics.

The first occurred in December 1889, when the Russian flu suddenly appeared in St Petersburg and in a matter of months spread across most of the world, killing at least 250,000 Europeans (the total global death toll is unknown, but may have been as high as 1m). And it happened again at the end of the First World War, when the so-called Spanish influenza sparked the Great Influenza Pandemic of 1918-19, killing more than 50m people worldwide. And it also happened in 1957 in China and in 1968 in Hong Kong - outbreaks which caused 1m deaths on each occasion.

One reason influenza experts are so concerned now is that on average these pandemics have occurred every 27 years - and it is 37 years since the Hong Kong flu pandemic. Statistically speaking, the next outbreak is 10 years overdue. A second reason is that all the signs are that the virus, which has been widespread in Asia for some time and is highly pathogenic in chickens, appears to have acquired the ability to infect new species in just the past few

months. Indications that H5N1 might be in the process of mutating came in October, when tigers at a zoo near Bangkok who had been fed on raw chicken carcasses suddenly began dying. Prior to 2004 they had never been susceptible to the avian strain. Since then, vets have shown that cats can also be infected with the virus. The third reason for concern is the increasing incidence of concurrent infections within the same family, such as Hung's and his brother's - what epidemiologists call 'family clusters'. During Tet 2003, Dr Van treated a similar multiple infection involving two sisters, also from Thai Binh, whose brother had died of a mysterious pneumonia after slaughtering chickens for a wedding banquet. The brother's body was subsequently cremated, so Dr Van was unable to confirm he'd had H5N1, but 10 days later the sisters fell ill and were admitted to her ward with raging fevers.

At that point Dr Van had yet to treat anyone with bird flu. However, she and her colleagues had treated several SARS patients the previous year. She also knew from reading about H5N1 outbreaks in Hong Kong that the disease had a rapid onset. Nonetheless, she says she was shocked by how quickly the sisters went into decline. Seven days after she admitted the sisters, Dr Van was forced to intubate. Three days later they were both dead, expiring within an hour of one another on the eve of Tet. Tests confirmed they both had H5N1.

'I was shocked at the speed of it,' Dr Van said. 'It was like SARS all over again. I wore a mask and protective glasses and insisted my staff do the same.' But the strongest evidence for human-to-human transmission so far has come from Thailand. Last September, an 11-year-old girl from a remote village, Kamphaeng Phet, fell ill with fever. A few days earlier all her pet chickens had died suddenly. Her aunt rushed her to hospital, where she was joined by the girl's mother, who lived near Bangkok. Within 16 hours the girl was dead and, in keeping with Thai custom, her body was cremated. Two weeks later her mother, who had had no exposure to the chickens, was admitted to hospital in Bangkok with the same symptoms. She also died. Then, days later, the aunt also developed a cough and fever. Tests showed that, like her sister, she had H5N1. Unlike her sister, however, she survived. The WHO concluded both had almost certainly caught the virus while nursing the sick girl. 'The worrying thing about the Thai case,' Peter Horby told me in Hanoi, 'is the girl and her mother lived several miles apart, so they could not have been exposed to a common poultry source. The hospital bedside was the most likely contact.'

For the final piece in the puzzle of the emerging virus, however, I had to travel to Ho Chi Minh City and speak to Jeremy Farrar. A mild-mannered Englishman, Farrar is director of the Oxford University Clinical Research Institute at the Hospital for Tropical Diseases - a unit funded by the Wellcome Trust. Together with Dr Tran Tinh Hien, the vice-director of the hospital, he has been tracking H5N1 since its inception and has as good a grasp as anyone of how close we are to a viral Armageddon.

In his office decorated with Vietnamese art and a huge map of the country, Farrar appears the epitome of a tropical disease specialist. The biggest causes of infant mortality in Vietnam, he tells me, are dengue fever and malaria. But for all that he worries about mosquito-borne diseases, he will never forget his first brush with bird flu. As with the latest infections, it occurred during Tet and, once again, a duck was involved. 'It was the eve of Tet, the last night in the lunar year, a hugely auspicious day in Vietnam,' he recalled. 'At around 8pm, Dr Hien called me and said that he'd just admitted an eight-year-old girl to hospital with acute pneumonia and could I check her nasal swab for type A influenza.'

Dr Hien had taken a detailed clinical history from the girl and discovered that shortly before she'd fallen ill her duck had died and she'd buried it, then dug it up and reburied it. At that point, Vietnam had only reported one death from bird flu, in Hanoi, but Dr Hien knew enough about the disease to know that ducks might be implicated.

Farrar immediately ran a PCR (polymerase chain reaction) test. It was positive. The girl had H5N1. 'Those two weeks over Tet were a frightening time,' recalls Farrar. 'At that point we didn't know very much about the virus's clinical pathology. Was it the same as the Hong Kong strain of H5N1 or was it like Sars? Were other family members at risk? Could we catch it?' Today, Farrar and Dr Hien are in a better position to answer those questions. In the past two years, they've treated nearly 20 people for bird flu. Although Dr Hien has had nine patients die this year, he is confident that the present strain is not particularly infectious between humans.

'If H5N1 was like SARS then at least 10 of my staff ought to be dead by now. They're not,' he told me in his office, before his ward round. 'That isn't to say that the disease isn't dangerous. It is. But the main reason we are continuing to see so many deaths is the delay in referring people to hospital.'

Nonetheless, Dr Hien says we cannot afford to be sanguine. The virus could very easily mutate if Vietnam doesn't get the medicines and aid it needs to deal with its infected poultry. 'The world has to understand it's not only Vietnam's problem, it's the world's problem.'

Farrar also has a further reason for concern. Last month, he and a colleague reported on a disturbing new case of a girl and boy from Dong Thap, a province in southern Vietnam, whose deaths last year had been attributed to acute encephalitis - an inflammation of the brain. Neither the nine-year-old girl nor her brother, four, had shown any sign of respiratory illness or pneumonia prior to slipping into comas, but when Farrar received a sample of fluid from the boy's brain he got a big surprise. The fluid was heavily infected with H5N1. Post-mortem samples confirmed it was also in the boy's faeces, blood and nose. Unfortunately, no tissue samples had been taken from his sister, so Farrar could not confirm whether she had also been infected with H5N1. Nor could he establish where they might have acquired the virus. The family did not keep chickens, but did have healthy fighting cocks. A more likely possibility was a canal near their home, where the girl often swam. It was teeming with ducks and wild geese. Although further studies will need to be done to see if H5N1 is implicated in other cases of encephalitis, the implication is clear: bird flu may be much more widespread than we realise.

'The crucial question is, are we only seeing a small number of cases because we are only looking at patients who present with the most severe symptoms, or is the virus actually much more prevalent than that?' says Farrar. 'In other words, is this just a very nasty infection in a few people, or a wide-ranging infection, one that has the potential to become a global pandemic?' No one knows where or when the next mutation in the virus will occur. It could be in a duck pond in the Mekong delta tomorrow or it could be a year hence in a poultry market in Thai Binh. But one thing is certain: if the virus does become - to recall Professor Oxford's analogy - a normal greyhound, jet travel will speed it round the globe in days.

During my return flight to London via Bangkok, with passengers sneezing and coughing all around me, I had plenty of time to ponder what this might mean. In the last great pandemic in 1918, the absence of air travel and restrictions on movements during wartime meant it took two years for Spanish influenza to spread from crowded army camps in northern France - where Professor Oxford and other experts now postulate it first gained a

foothold, in troops weakened by mustard gas - to the rest of the world. Then, 50m people died. Today, given the growth in the world's population, the equivalent death toll would be 175m.

Not surprisingly, these figures, coupled with dire warnings from the WHO, have begun to command the government's attention. Two days after I returned from Hanoi, the Department of Health called a press conference to announce it was stockpiling more than 14m doses of Tamiflu as part of its Influenza pandemic contingency plan. Meanwhile, the US, France and Italy have been placing advance orders for a prototype vaccine (the British government has resisted this course, pointing out that until we know which strain of H5N1 to vaccinate against such measures are a waste of resources). In early March, I called a contact in Hanoi to check on the progress of Sy Tuan and his sister. Miraculously, both were still alive and receiving treatment. But in the meantime, a nurse who'd been with Sy Tuan had contracted the virus. That was not the end of the bad news. A 35-year-old sanitation worker whose job it was to clean the slops from slaughtered chickens at Hanoi's poultry market had also contracted the virus. In addition, officials in Thai Binh had belatedly reported that a 69-year-old man hospitalised locally had died from avian flu on 23 February - the 14th fatality in Vietnam this year. Like the other casualties he'd eaten infected poultry over Tet.

I thought of Nguyen Nhung Ngoan pacing the corridor, anxiously waiting to see if her brother and 14-year-old sister would recover. Until such time as scientists tell us otherwise the front line is Vietnam, not here. But we are no longer that far away, and like Nhung Ngoan we have little choice but to wait and pray.

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