



FEATHERED THREAT *In Thailand ducks wait for a clean bill of health from veterinary workers, far left, gowned and masked against a flu virus that can lurk in ducks but kills chickens and sometimes people. Thai duck herders traditionally drive flocks from field to field to eat leftover rice—a practice that can spread the virus.*

**SOONER OR LATER A DEADLY VIRUS
THAT CAN JUMP FROM BIRDS TO PEOPLE
WILL SWEEP THE GLOBE.**

TRACKING THE NEXT KILLER



FLU



ONCE AND FUTURE PLAGUE *Nguyen Si Tuan, 21, fights for his life in Hanoi's Bach Mai Hospital (far left), lungs devastated by a virulent flu he caught from an infected chicken. John Oxford of Queen Mary's School of Medicine in London, who studies the 1918 flu, visits the grave of a victim, a World War I nurse named Phyllis Burn.*

BY TIM APPENZELLER

NATIONAL GEOGRAPHIC SENIOR EDITOR

PHOTOGRAPHS BY LYNN JOHNSON

LITTLE NGOAN WAS BURIED behind her parents' hut three weeks ago. Her grave, a bulky concrete tomb like others dotting the Vietnamese countryside, rests on high ground between a fishpond and yellow-green rice fields. At one end her family laid out her cherished possessions: a doll's chair, a collection of shells, plastic sandals. They painted her tomb powder blue.

While Ngoan's parents are off helping with the rice harvest, other relatives share their memories. "She was so small, just ten years old," says her grandmother, sitting on a hammock. "She was very gentle



and a good student. If you look at her older sister"—the 17-year-old hangs back shyly—"you can imagine what she was like." Ngoan's grandfather, silent with grief, lights a stick of incense at her grave.

The loss of a beloved child has hit this family hard. But ordinarily, the wider world would pay little attention to a child's death

from infectious disease in this remote corner of Vietnam's Mekong Delta. Old scourges like dengue fever and typhoid still take a toll here, and HIV/AIDS is on the rise.

Yet Ngoan's death and more than 50 others in Southeast Asia over the past two years have raised alarms worldwide. Affected countries are struggling to take action; other nations are sending aid and advisers while stockpiling drugs and developing vaccines at home. And scientists have stepped up their research into the fateful traffic of disease between animals and people.

Why? Because Ngoan died of the flu.

WARNINGS John Oxford holds paraffin-embedded samples of tissue from people who died of the flu in 1918 and earlier years (opposite). He hopes the samples will yield traces of the virus, which might show how it honed its deadliness before the global pandemic erupted in 1918. Yi Guan, at the University of Hong Kong, is tracking the evolution of the H5N1 bird-flu virus (shown in the model on his desk, below). "This virus is bad news for us," Guan says. He fears it could spark a new pandemic.

To most of us, flu is a nuisance disease, an annual hassle endured along with taxes and dentists. Some people think a flu shot isn't worth the bother. But flu is easy to underestimate. The virus spreads so easily via tiny droplets that 30 million to 60 million Americans catch it each year. Some 36,000 die, mostly the elderly. It mutates so fast that no one ever becomes fully immune, and a new vaccine has to be made each year.

That's ordinary flu. But the disease that is taking lives in Southeast Asia is no ordinary flu. Its primary victims have been chickens, more than a hundred million of them, killed either by the virus or in often futile control efforts. It's not unusual for chickens to get flu; in fact, avian-flu viruses far outnumber human ones. But Robert Webster of St. Jude Children's Research Hospital in Memphis has studied flu viruses for 40 years and has never seen the likes of the one that killed Ngoan.

"This virus right from scratch is probably the worst influenza virus, in terms of being highly pathogenic, that I've ever seen or worked with," Webster says. Not only is it frighteningly lethal to chickens, which can die within hours of exposure, swollen and hemorrhaging, but it kills mammals from lab mice to tigers with similar efficiency. Here and there people have come down with it too, catching it from infected poultry like the chickens that died on Ngoan's farm a few days before she fell ill. Half the known cases have died.

In those deaths many public health experts

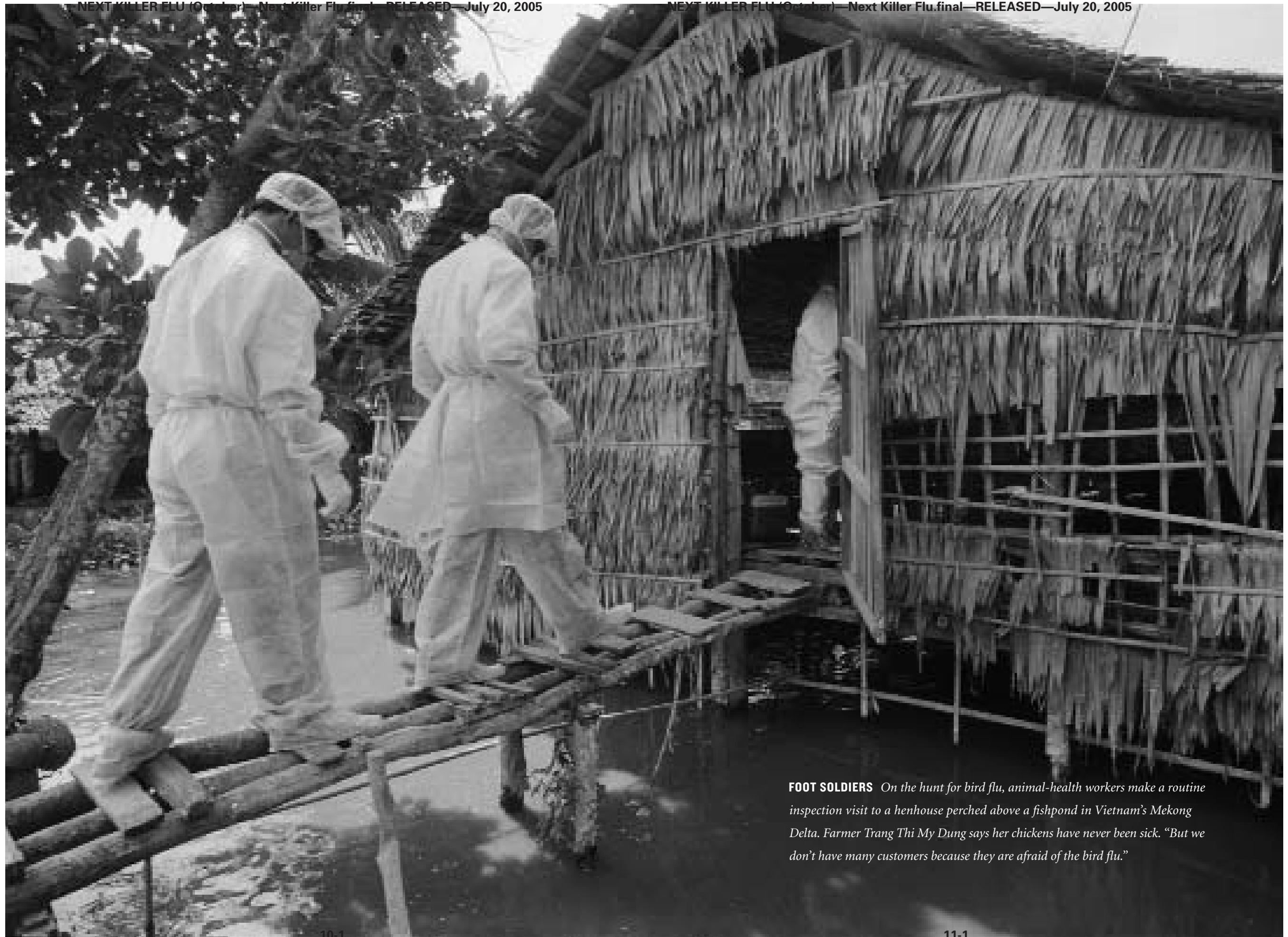
hear the distant rumblings of a catastrophe. So far this virus—classified as H5N1 for two proteins that stud its surface like spikes on a mace—isn't good at passing from birds to people, let alone from one person to the next. "It can make that first step across, but then it doesn't spread



easily from human to human," says Webster. "Thank God. Or else we'd be in big trouble."

Maybe H5N1 will never learn the trick of racing from person to person like the milder flus that empty offices and classrooms each year. Maybe it simply can't. Or maybe efforts to eradicate the virus—largely fitful and underfunded so far—will succeed. But experts are urging the world to prepare for the worst.

What is known about flu viruses' remarkable capacity to change and jump species has led to a sense of inevitability, a conviction that even if this menacing animal flu doesn't explode into a global pandemic that kills millions, another one will. "It's going to happen, at some point, that



FOOT SOLDIERS *On the hunt for bird flu, animal-health workers make a routine inspection visit to a henhouse perched above a fishpond in Vietnam's Mekong Delta. Farmer Trang Thi My Dung says her chickens have never been sick. "But we don't have many customers because they are afraid of the bird flu."*

THE DISEASE THAT IS NOW TAKING



a virus like this changes to be able to transmit from one person to another,” says Jeremy Farrar, an Oxford University doctor who works on the front lines of avian flu at the Hospital for Tropical Diseases in Vietnam’s Ho Chi Minh City. “It’s bound to happen. And when it does, the world is going to face a truly horrible pandemic.”

After all, it has happened before.

IN 1918, THE FINAL YEAR of the savage trench fighting of World War I, something else began felling the soldiers. No one knows for sure when or where the Spanish flu emerged, though it certainly wasn’t in Spain. As a neutral country, Spain had no wartime censorship, and the flu apparently got its false pedigree from news reports about outbreaks there in May 1918. In fact the disease was already spreading on both sides of the European front, laying low entire divisions through the spring and early summer. Then it seemed to subside.

In late summer, though, the Spanish flu returned, and this time its virulence was unmistakable. The sick took to their beds with fever, piercing headache, and joint pain. Many were young adults, exactly the group that normally shrugs off the flu. About 5 percent of the victims died, some in just two or three days, their faces turning a ghastly purple as they essentially suffocated to death. Doctors who opened the chests of the dead were horrified: The lungs, normally light and elastic, were as heavy as waterlogged sponges, clogged with bloody fluid.

After flashing through crowded military camps

and troopships in Europe and the United States, the flu leaped out of uniform to ports and industrial cities. In Philadelphia, historian Alfred Crosby found, 12,000 people died of flu and pneumonia in October—759 in a single day. Schools and businesses were shut down and church services cancelled. Morgues overflowed.

By then the sickness had spread to the far corners of the planet, from the South Pacific to the Arctic. “Everybody on Earth breathed in the virus, and half of them got sick,” says Jeffery Taubenberger of the Armed Forces Institute of Pathology in Maryland, who is trying to learn what made it such a killer. More than 50 million people died—at least three times as many as in the war. The best medical minds of the day could hardly believe that this was flu.

It was flu all right, but with a crucial difference that scientists are only beginning to understand. Scattered across Taubenberger’s desk are translucent wax blocks the size of matchboxes. Borrowed from a pathology archive, they hold fingernail-size scraps of purplish tissue, sliced from the lungs of flu victims in U.S. military hospitals almost 90 years ago. In the mid-1990s Taubenberger and his colleagues realized that a sample from someone who died quickly, lungs still seething with virus, might still hold genetic traces of the killer. They were right: In 1996 lung tissue from a soldier who died in September 1918 at Fort Jackson, South Carolina, yielded pieces of the virus’s genes.

The pickings soon got better. Inspired by Taubenberger’s discovery, a retired pathologist named Johan Hultin traveled to a remote Alaska village and excavated a mass grave that had been hacked into the permafrost after the Spanish flu swept through in November 1918. One female body still contained intact lung tissue, preserved by the cold and sheer luck. Bit by bit, Taubenberger’s group teased out the entire genetic sequence of the virus. They plan to finish publishing it this year.

So far this genetic blueprint hasn’t revealed exactly what made the Spanish flu so deadly. No single gene or protein is the obvious culprit. But comparing the 1918 sequence to those of the flu viruses that wreak mild havoc each winter has confirmed what was long suspected:

LIVES IN ASIA IS NO ORDINARY FLU

The Spanish flu virus had recently crossed into people from some unknown animal, leaving victims with little immunity to this new threat.

ONE REASON you generally get over the flu after a few days’ discomfort is that your immune system has seen it before and knows how to respond. This year’s bug won’t be a carbon copy of last year’s, because the virus mutates constantly. But it will look similar enough that your body can almost always keep it in check.

Every so often, though, something new comes along from the animal world—a vast preserve of type A flu viruses, the ones that cause the most serious illness in humans. In far-flung studies in the late 1960s and 1970s, from Australia’s

Great Barrier Reef to lakes in northern Canada, Robert Webster and his colleagues tracked flu to its source. “Where do flu viruses come from?” he asks. “From the wild birds of the world, the wild aquatic birds—the waterfowl, the ducks, the shorebirds.”

Dozens of flu subtypes inhabit the birds’ guts, mostly harmless to their hosts or to any other creature. But occasionally one infects domestic poultry. Even more rarely, a bird virus or some of its genes slip into the much smaller pool of type A viruses that infect humans.

Normally a flu virus good at infecting birds can’t attack humans because it isn’t equipped to invade and grow in human cells. Until recently scientists thought avian viruses could gain that



TOO CLOSE FOR COMFORT Chickens are tested for flu (opposite) at a small farm in southern Vietnam, where poultry, pigs, and people live in close quarters. It’s a recipe for trouble, because pigs can catch flu viruses from both birds and people, then act as “mixing vessels,” cooking up dangerous new strains. Live-poultry markets like this one in Hanoi speed the spread of the virus from farm to farm when vendors take leftover birds back home, along with any flu viruses they’ve picked up.



EMPTY HAMMOCK *Pranom Thongchan and her daughter lost two of their family to bird flu last year. The chickens living under their house in rural Thailand infected Pranom's 11-year-old niece; while caring for the girl, Pranom and her sister also caught the disease, in a likely case of human-to-human spread. Only Pranom recovered.*

EVERY SO OFTEN A NEW FLU VIRUS



ability only by indulging in the viral equivalent of sex. Because flu viruses carry their genetic information on eight separate RNA segments, it's easy for different subtypes to swap genes if they happen to meet. The result: offspring with new abilities.

For an avian flu and a human flu to mix it up, they have to infect the same animal. Scientists have long considered the pig a likely mixing vessel, because pig cells have surface molecules that allow entry to both kinds of virus. A pig could conceivably catch a human flu from a farmer and a bird virus from, say, ducks at the same farm. The two viruses could then "reassort," creating a hybrid that—in the worst case—would now be able to infect human cells while still carrying bird-virus genes that would make it radically new to the immune system of the people who catch it, and unusually virulent.

Reassortment explains the two lesser flu pandemics of the 20th century, in 1957 and 1968. In each year a new flu subtype appeared, combining genes from the human virus that had been causing mild outbreaks in prior years with new genes from a bird virus. The new pandemic viruses raced around the world, together killing about two million people.

But in 1918, Taubenberger now believes, something different happened. "We think it's pretty likely that the virus was not derived from a previously circulating human virus," he says. All of its genes mark it as an animal virus, pure and simple, that somehow crossed to people without the help of genes from a previous human strain.

Now H5N1 is doing the same thing. So far, its steps across the species barrier are tentative, which is why it has caused tens of deaths, not millions. But as in 1918, doctors who have seen its effects close up are shaken.

THE X-RAYS TELL THE STORY as Tran Tinh Hien, a doctor at the Hospital for Tropical Diseases in Ho Chi Minh City, clips them to a light box. In the first image, made the day the 18-year-old girl was admitted with bird flu, a whitish cloud appears at the base of her rib cage. Her lungs were partly filled with fluid. In a second film, four days later, the haze has spread throughout her chest. "All the lung tissue was destroyed," Hien says. "The process still happened when we treated." A week later the girl was dead.

So it went for Hien and his staff throughout January, when the latest bird-flu outbreak reached its peak in southern Vietnam. They cleared a 50-bed ward normally reserved for malaria and dengue fever and turned it into an isolation unit. They sustained patients with oxygen masks and ventilators and treated them with oseltamivir, or Tamiflu, an expensive antiviral drug that can fight H5N1. Nurses worked 24-hour shifts, gowned, masked, and goggled for protection against the virus. As Hien says: "We were pushed to the wall."

He and his staff did everything they could for their nine bird-flu patients. "Unfortunately," he says, "we could not save any lives."

As an elite facility, the Hospital for Tropical Diseases saw the bleakest face of the disease. Only the sickest patients were sent there, and by then they may have been beyond help. In fact H5N1 doesn't always kill. Some infections may even be so mild that they go unnoticed. But every hospital that has treated people seriously ill with avian flu has recorded shocking death rates.

It has been that way since 1997, when an H5N1 virus strain—a cousin of the one now plaguing Asia—first jumped to humans. Early that year an outbreak of the virus killed chickens in Hong Kong's rural New Territories. At that point, no one thought bird viruses threatened people directly. But this one broke the rules.

In May 1997 a three-year-old boy was admitted to a Hong Kong hospital with a cough and

COMES FROM THE ANIMAL WORLD

fever. His symptoms worsened rapidly and he had trouble breathing. He was given a flood of antibiotics and put on a ventilator, but within six days he was dead. Flu experts were astonished when secretions from the boy's windpipe yielded an H5N1 virus. It turned out to be the same one that had killed the chickens.

Still, his death looked like it might be a fluke until late in the year, when another 17 people checked into hospitals around Hong Kong with similar symptoms, and tests confirmed infection with H5N1. Five died. Many of the victims had visited one of the island's live-poultry markets.

Public health experts converged on Hong Kong, fearing that a 1918-style pandemic was about to explode. They persuaded the Hong

Kong government to kill every last bird—1.5 million of them—in the farms and markets. The mass slaughter worked. That particular H5N1 virus was never seen again, and a public health disaster had been averted.

But in 2001 another deadly strain of H5N1 cropped up in Hong Kong's markets, and the city again began killing poultry. This time the respite was shorter, and by the beginning of 2002 chickens were again dying of flu. The fact was, the drastic measures in Hong Kong had left the source of all these viruses untouched. They were coming from outside Hong Kong—just across the territorial border in southern China.

China's Guangdong Province teems with hundreds of millions of chickens, ducks, and geese,



BELOVED BIRDS Fear of bird flu is at war with tradition in Southeast Asia, where the chicken has a key place in culture and cuisine. In Ho Chi Minh City girls pose beside a giant straw rooster (opposite) during Tet, the Vietnamese New Year. The February 2005 festival ushered in the Year of the Rooster—and was followed by new bird-flu cases linked to holiday chicken meals. In Thailand worshippers bring statues of roosters to a shrine dedicated to a 16th-century national hero, who loved cock fighting.



DANGEROUS LIAISON *Tenderly reviving his champion, Ea Khamjean risks his own health as he sucks blood from his fighting cock's wounds after a match. Thousands of Thailand's fighting cocks have died of bird flu or been destroyed to stop its spread, and at least one man died after catching the virus from his prized birds.*

H5N1 IS ALL THE MORE FRIGHTENING

many wandering freely through gardens, farms, and ponds. Flu viruses that rain into this sea of poultry in wild-bird droppings can spread and swap genes with abandon. The result: new strains not found in the wild. Among them was the H5N1 virus that gave rise to the bird flu now plaguing Asia.

Year after year it swapped genes with other avian-flu viruses, generating a plethora of new H5N1 variants. Year after year they besieged Hong Kong, which imports poultry from the



mainland. By the end of 2003, they were infecting and killing birds across half of Asia.

Radiating from China, H5N1 strains reached South Korea and Japan in the north; they swept through Southeast Asia as far as Indonesia. Some experts and officials have suggested that the viruses traveled in the guts of wild waterbirds—geese, ducks, herons—which might have picked up the infection from farms. Governments embarrassed by their failure to halt the flu's spread welcome that idea. "They get a free lunch," says Yi Guan, a virologist at the University of Hong Kong. "Each time there's an outbreak, they say, 'It's migratory birds. I cannot control them. I cannot lock my sky!'"

This summer the virus killed thousands of wild geese and gulls at a nature reserve in western China. It was the largest known outbreak in wild birds and a warning that in the future they might spread the disease far and wide. But Guan isn't ready to blame migratory birds for the spread so far. He thinks the virus has killed

infected birds too quickly for them to fly long distances. Instead H5N1 probably hitchhiked across Asia in shipments of live poultry, in a disaster of our own making.

AS IT ADVANCED, the virus began killing people again—by August the count stood at 40 in Vietnam, 12 in Thailand, 4 in Cambodia, and at least 1 in Indonesia. And it inflicted economic losses that, by one estimate, amounted to more than ten billion dollars in 2004 alone. Exports from Thailand's industrial chicken farms collapsed when the world learned of the outbreak there. In areas of Indonesia hit hard by the virus, more than 20 percent of the workers on commercial poultry operations lost their jobs.

Small farmers are suffering too. As one animal health official in Vietnam explains, "The birds are big treasures for the farmers." They scavenge for themselves, costing next to nothing to raise and putting good meat on the table. Vietnamese farmers lost some 40 million of these treasures in 2004, dead of flu or killed in control efforts. Even farms untouched by the disease were hit as fearful shoppers began avoiding poultry.

It may take a long time for Vietnam to regain its taste for chicken. At a riverside restaurant in the southern city of Can Tho, six veterinary officials—men responsible for keeping the district's poultry healthy—order prawns and a fish stew for lunch. They admit it: Not one of them will touch chicken these days.

H5N1 is all the more frightening because so much is unknown, starting with how it kills people. In a chicken, the virus spreads everywhere—gut, lungs, brain, muscle. In humans, like the 1918 flu, it devastates the lungs first and foremost.

Researchers at the University of Hong Kong have found that a victim's own immune system may be part of the problem. It reacts to the virus with a flood of chemical messengers that draw white blood cells into the lungs, where they trigger a massive inflammatory reaction. "It's kind of like inviting in trucks full of dynamite," says Malik Peiris, who led the work. Healthy tissue dies and blood vessels leak, filling the lungs with fluid.

But H5N1 may have more than one way to kill. This year researchers in Ho Chi Minh City,

BECAUSE SO MUCH IS UNKNOWN



HIGH STAKES Chickens are processed for export at a Thai plant (opposite), part of a billion-dollar industry devastated by bird flu in 2004, when outbreaks in Thailand led other countries to ban its poultry. In Hanoi, Anton Rychener of the United Nations Food and Agriculture Organization stabs the air in a meeting with Vietnamese and foreign officials as he urges quick changes in farming practices that raise the threat of a human pandemic. "The warning signs, the flags, are up," he says.

including Jeremy Farrar, detected H5N1 in a little boy who died in a coma, his brain inflamed but his lungs healthy until the very end. To Farrar it suggests that the virus can spread throughout the body. Others aren't sure.

It's one more bird-flu mystery.

Ask Keiji Fukuda and Tim Uyeki, flu epidemiologists at the Centers for Disease Control and Prevention (CDC) in Atlanta, what they would most like to know about the disease, and the questions come tumbling out. "How many people are infected? How many animals are infected?" asks Fukuda. Since 2004 only four countries have reported human illnesses. "Have there been no others?" Uyeki asks. "It's pretty likely there have

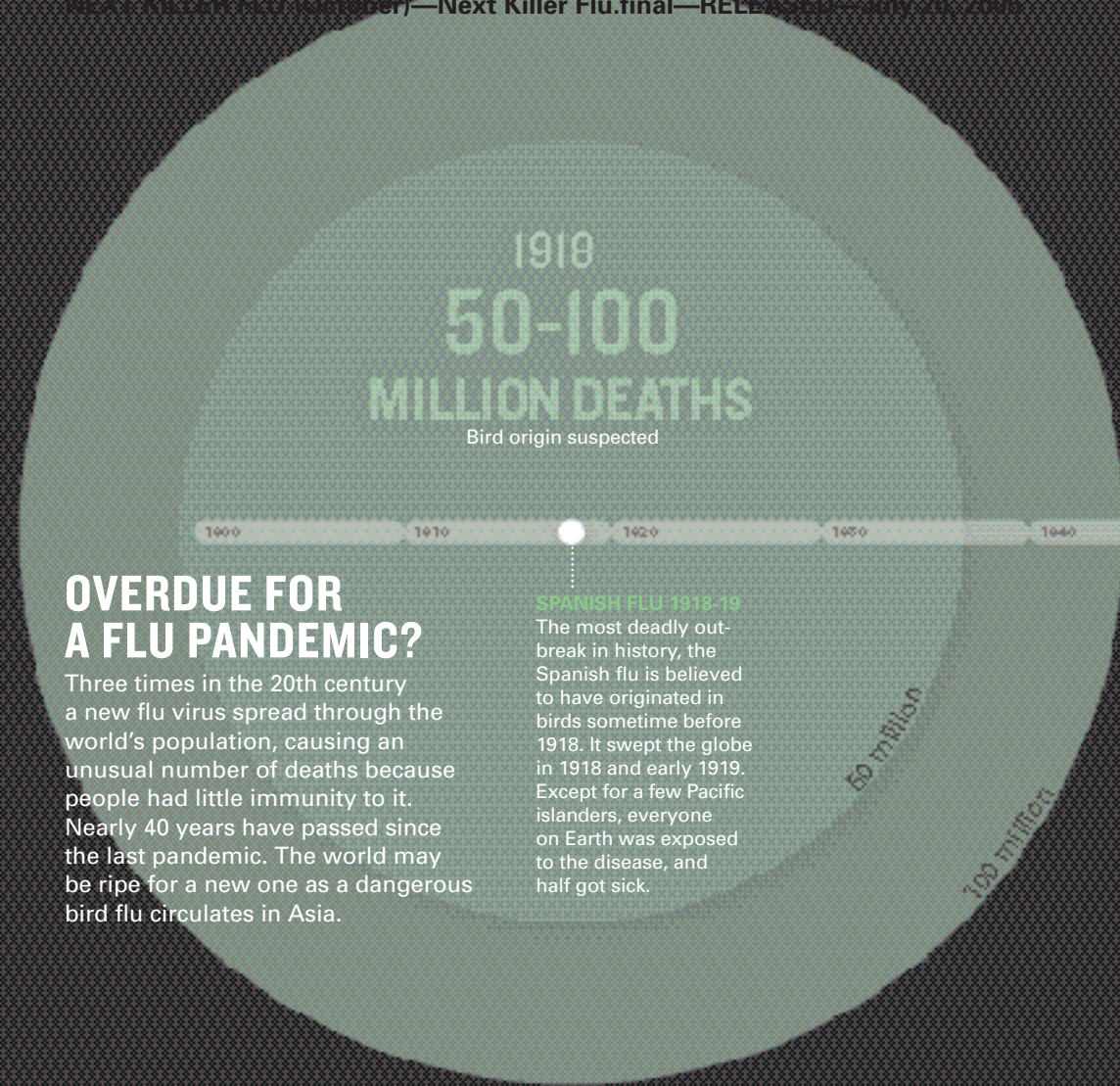
been, but we have no information about that."

Then there's the mystery of exactly how people get infected. "Right now we believe that most cases are related to people somehow being exposed to sick or dying or dead poultry," says Fukuda. "Well, what does that mean?" he asks, ticking off possibilities. Does that mean people touched it? Did they eat it? Did they breathe in dust containing chicken feces? He's frustrated at the often sketchy reports from Asia. "What is really going on?" he asks. "This has very practical implications" for fighting the disease.

The biggest question is whether the virus will start spreading like ordinary human flu. "Human to human—that's the one (Continued on page 26)



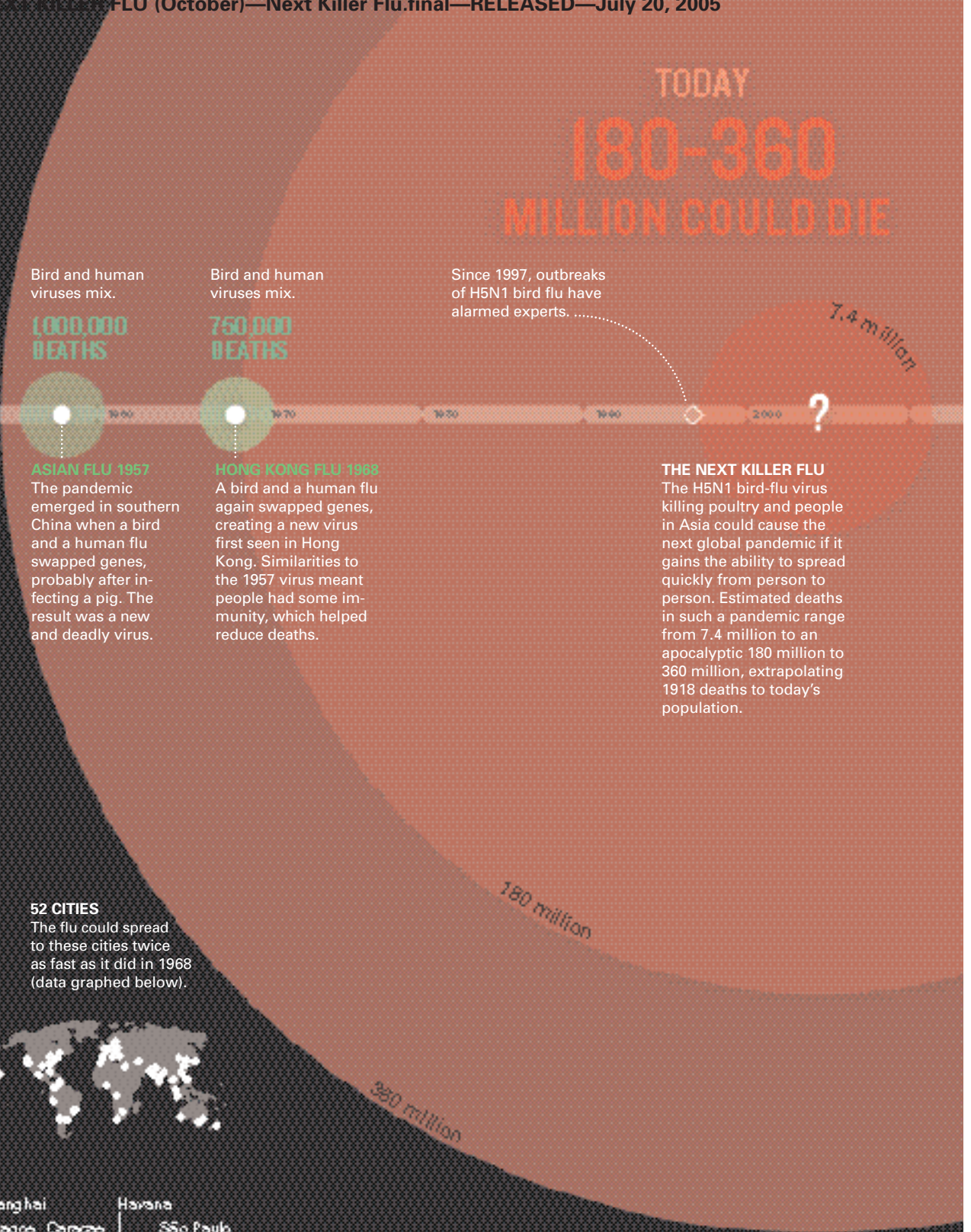
TOUCH AND GO Comatose and hooked to a ventilator at Bach Mai Hospital in Hanoi last March, bird-flu patient Nguyen Si Tuan was not expected to live. The young man rallied and went home two months later—a lucky survivor. “It’s a phenomenally destructive infection in the cases we’ve seen,” says one doctor.



OVERDUE FOR A FLU PANDEMIC?

Three times in the 20th century a new flu virus spread through the world's population, causing an unusual number of deaths because people had little immunity to it. Nearly 40 years have passed since the last pandemic. The world may be ripe for a new one as a dangerous bird flu circulates in Asia.

SPANISH FLU 1918-19
The most deadly outbreak in history, the Spanish flu is believed to have originated in birds sometime before 1918. It swept the globe in 1918 and early 1919. Except for a few Pacific islanders, everyone on Earth was exposed to the disease, and half got sick.



Bird and human viruses mix.

1,000,000 DEATHS

ASIAN FLU 1957

The pandemic emerged in southern China when a bird and a human flu swapped genes, probably after infecting a pig. The result was a new and deadly virus.

Bird and human viruses mix.

750,000 DEATHS

HONG KONG FLU 1968

A bird and a human flu again swapped genes, creating a new virus first seen in Hong Kong. Similarities to the 1957 virus meant people had some immunity, which helped reduce deaths.

Since 1997, outbreaks of H5N1 bird flu have alarmed experts.

THE NEXT KILLER FLU

The H5N1 bird-flu virus killing poultry and people in Asia could cause the next global pandemic if it gains the ability to spread quickly from person to person. Estimated deaths in such a pandemic range from 7.4 million to an apocalyptic 180 million to 360 million, extrapolating 1918 deaths to today's population.

A VIRUS MOVES TWICE AS FAST NOW

The last pandemic, in 1968, took a year to spread around the world. More than three decades later, increased jet travel could halve that time—limiting the opportunity for slowing the spread with a vaccine.

KEY

In each city, flu cases rise to a peak several weeks after the first reported infection, then gradually taper off.

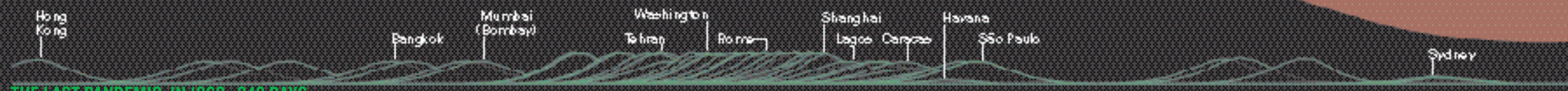
Flu cases per city

52 CITIES

The flu could spread to these cities twice as fast as it did in 1968 (data graphed below).



HYPOTHETICAL PANDEMIC: 180 DAYS (MODELED FOR 2000)



THE LAST PANDEMIC, IN 1968: 342 DAYS

RESPONSE: DAY 1

As soon as a pandemic begins, countries with stockpiles of antiviral drugs can begin distributing them.

DAY 100

If a vaccine were developed and tested in advance, distribution could begin within three months of the start of the pandemic.

DAY 250

It normally takes about this long to develop a vaccine, test it, amass the millions of fertilized eggs needed to make it, and get it to market.

PANDEMIC MORTALITY RATES (TOP): MICHAEL T. OSTERHOLM, UNIVERSITY OF MINNESOTA; WORLD HEALTH ORGANIZATION. SPREAD MODELS (BOTTOM): REBECCA F. GRAIS, J. HUGH ELLIS, GREGORY E. GLASS, JOHNS HOPKINS UNIVERSITY. NGM ART

NO ONE WANTS TO SIT AND WAIT FOR



that we don't want to see," says Robert Webster. But already, H5N1 has given experts a few scares.

NGUYEN THANH HUNG, a cement trader in Hanoi, says he feels well these days. He works, tends a small forest of potted plants, and spends hours a day jogging and doing breathing exercises. In his living room one day in February he shows off his hospital discharge papers as if they were his new lease on life. It's been just a month since Hung got over a serious bout of avian flu. "The doctor told me if I had been taken to the hospital one or two days later—no way," he says. His older brother, also infected, was not so lucky.

If Hung's survival is remarkable, so is the way he seems to have caught the disease. On a visit to their home village outside Hanoi he and his brother had shared a pudding made of raw duck blood, a Vietnamese delicacy. The duck must have been infected with H5N1, because Hung's brother came down with the flu a few days later. But Hung did not get sick for more than two weeks—not until the day after his brother died.

That's too late for the pudding to be the cause, Tim Uyeki believes. Hung probably got infected while caring for his brother in his final days.

H5N1 is also thought to have jumped from a girl dying of avian flu in Thailand to her mother and aunt, who nursed her. Several other cases of human-to-human transmission are suspected. But one step beyond the initial victim is all the virus seems to have managed. So far, sustained transmission—the chain-reaction spread of ordinary flu—is not in its repertoire.

It might gain that ability on its own, by mutating. Or it might swap genes with a human-flu virus. That could take place in an infected person who also catches ordinary flu, or in the classic flu mixing vessel, the pig. Still, no one knows whether the exchange would yield a nightmare virus or a dud.

Flu researchers at the CDC and in the Netherlands hope to find out in advance, by artificially breeding new viruses. In high-containment labs they are deliberately mixing and matching genes from H5N1 and human-flu viruses. Then they will test the hybrids to see whether any have inherited both the bird virus's virulence and the human virus's ability to spread. In effect, they are trying to create a pandemic flu strain in the lab.

Some critics think that's reckless, but Erich Hoffmann, a St. Jude researcher who helped develop a genetic engineering technique for flu, says the experiments are key to learning what we may eventually face. "It's basically the best simulation one could have in the lab of what possibly could happen in nature."

If we're lucky, he says, all the hybrid viruses will be harmless or won't thrive, suggesting that H5N1 may never spawn a pandemic. "That of course would be good news," says Hoffmann. And if the news is less reassuring? Then scientists monitoring H5N1 in Asia would have a clue about what to watch for—what genetic changes in the virus might signal big trouble ahead.

THAT KNOWLEDGE might buy some warning time, but no one wants to sit and wait for H5N1 to make its move. And everyone agrees on the best way to head it off: Eradicate H5N1 in poultry, so people can't catch it. It's simple—but not easy.

Howard Wong, a senior veterinary officer in Hong Kong, knows what it takes. Since 2003, after multiple outbreaks and two wholesale poultry slaughters, the territory has kept its farms and markets free of H5N1. Wong is proud of his success. "We were very happy in 2004, when it was everywhere else, and we managed to hold it back."

Here are some steps Wong and other officials took: vaccinating every chicken in Hong Kong against H5N1; regularly testing chickens, pet birds, even wild birds; shutting down the hundreds of live-poultry stalls twice a month to

THE VIRUS TO MAKE ITS MOVE

disinfect them; and inspecting farms and markets obsessively. "We're almost at the limit of what we can do," says Wong. "It's like holding up this wall, and this wall just gets heavier all the time."

And as one aid official in Vietnam puts it, Hong Kong is rich, and an island. Vietnam is neither. In the winter of 2003-04, H5N1 broke out in most of the country's 64 provinces. To fight it, the country slaughtered tens of millions of chickens. The epidemic seemed to decline, and in March the government declared victory.

But in late 2004 avian flu roared back, infecting birds and people along the length of the country. Cooler weather, which favors the survival and spread of the virus, had apparently

brought it out of hiding. By February of this year Anton Rychener, the representative of the United Nations Food and Agriculture Organization (FAO) in Hanoi, was beside himself. "Why the hell are we sitting here a year later with literally the same pattern of outbreak?" he asked a roomful of officials. A year of meetings and emergency initiatives had done little to change the conditions that made Vietnam ripe for viral spread.

In the countryside, chickens peck in yards and stalk through underbrush, mingling with birds from other farms. Poultry markets act as viral swap meets, and unsold birds are taken back home with any viruses they picked up. Farmers with sick birds have little incentive to speak up and see their flocks destroyed: The government



OUR BEST SHOT Lisa Chrisley at the University of Maryland Medical Center in Baltimore injects volunteer Christopher Tate with a trial vaccine against the H5N1 flu virus. In August the U.S. government announced that the vaccine appeared effective. Flu vaccines are made from virus grown in fertilized chicken eggs like those at Charles River Laboratories in Connecticut (opposite), where workers harvest virus-rich tissue from eggs to produce a test for detecting flu infections in poultry.

WITNESSES Dorothy Horsch, 91, and Gertrude Fitzpatrick, 98, at right, were girls when the 1918 flu swept through their hometown of Buffalo, New York. At Beechwood Residence near Buffalo, they share memories of a fearful time. “We would never have been this close in the flu time—we were all too afraid,” says Horsch.



IN A FEW WEEKS A NEW PANDEMIC

can afford to pay less than half of a bird's market value as compensation. And then there are the ducks.

The duck, says Webster, is “the Trojan horse of this outbreak.” His group has found that unlike chickens, infected ducks often seem healthy, able to waddle, swim—and spread the virus in their droppings. In Vietnam and other parts of Southeast Asia, they spread it far and wide because duck herders drive their flocks from one rice field to the next, following the harvest, so the birds can fatten on leftover grains.

Inefficiency, tradition, and scarce funds have all slowed Vietnam's efforts to change such practices. And although officials gamely declare that they are making progress, last year's confidence

has faded. When asked whether he expects his district to be hit by bird flu again next year, a veterinary officer in Can Tho says, “It's not my expectation, but I think it will happen.”

Thailand has made more headway. Wealthier and more developed than Vietnam, it reimburses farmers more generously when birds are slaughtered. It tests ducks for H5N1 and allows only virus-free flocks to move around the countryside. And it has enlisted nearly a million village volunteers to watch for unusual chicken die-offs. By early this year it had driven the virus back into just a handful of provinces.

Even so, Wantanee Kalpravidh, the FAO's regional coordinator for avian influenza in Southeast Asia, says the country cannot rest easy. It has



LIFE IN THE BALANCE Thai farmer Noi Tritanasombat waits for health workers to test his ducks for the H5N1 virus. Such measures have checked the spread of bird flu in Thailand, but outbreaks elsewhere in Asia pose a continuing threat. The virus could evolve into a form that passes easily from person to person—and could spread around the world by jet (opposite). “We know what we should do,” says flu expert Yoshihiro Kawaoka. “Eradicate the virus in Asia. Identify infected poultry, and kill it all.”

WOULD HIT MAJOR CITIES

long borders with Laos and Cambodia, destitute lands struggling with their own avian-flu outbreaks. Thailand's efforts could quickly be undone if a crate or two of infected poultry slipped in. As Kalpravidh points out, “Birds need no visa or passport.”

NOR DO VIRUSES. Suppose H5N1 lives up to the fears and picks up a new talent for contagion. Somewhere, probably deep in the countryside, a pandemic spark would ignite. A person sick with bird flu would infect his family, who would pass the disease to friends and neighbors. Exponential spread might follow.

Computer simulations suggest that public health officials just might be able to douse the spark by flooding the region with antiviral drugs, treating the hundreds of thousands of people who are at highest risk for infection. But the strategy could succeed only if the outbreak were detected within a few weeks and the virus spread slowly at first. And the infrastructure and skills required are lacking in much of Asia.

If containment failed, in a few more weeks the newborn pandemic would hit major cities. There it would infect people with passports and plane tickets. The rest of the world would be hours away.

Richer countries are scrambling to prepare. Because Tamiflu can protect against H5N1 as well as treat it, governments are building up stockpiles, and drugmaker Roche is hard-pressed to keep up with demand. The U.K. has ordered enough for 15 million people, a quarter of its population, and France almost as much. The U.S. has opted for a smaller stockpile—just 2.3 million treatments so far. It is also pinning its hopes on a vaccine.

Ordinary flu vaccines contain flu virus, grown in fertilized chicken eggs, then killed and split into pieces. But because it's so deadly, H5N1 requires expensive safety measures and tends to kill the eggs needed to grow it.

So Webster's group turned to genetic engineering, altering one gene to tame the virus and splicing in others to speed its growth. By August human tests of a vaccine made from the altered virus showed early signs of success. The U.S. government has already ordered two million doses.

Two million doses would be scant protection



for a country of nearly 300 million. But officials hope the vaccine formula will be fully tested and ready before it is ever needed. Makers would know how to produce it and could boost production fast, says Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases. At the first sign of a pandemic, “We'll be able to say: Go, take off the brakes and make millions and millions of doses.”

BUT AGAIN COMES THE REFRAIN, no one knows. No one knows whether an H5N1 pandemic strain—if it ever emerges—will be similar enough to the virus now stalking Asia for this vaccine to offer full protection. No one can even be sure H5N1 is the right threat to focus on. Several other bird-flu viruses have recently shown signs of infecting humans, though none has proved as deadly as H5N1.

Here is what we know for sure. One day a new flu pandemic will come, and one day it will pass. And then the killer strain, tamed by our immune systems and the passage of time, will fade into the background of nuisance flus.

It even happened to the worst of them all. Did you catch the flu last winter? There's a chance it was a direct descendant of the Spanish flu. If so, you were lucky. The heir to 1918 is one of the milder flu strains around today. □

WHEN WILL IT STRIKE? What should we do to prepare for a global pandemic? Share your thoughts in our forum. Then travel across Southeast Asia with photographer Lynn Johnson in a special multimedia show at ngm.com/0510.