

# Birds, Pigs, and People: The Rise of Pandemic Flu

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In early April 2009, a ten-year-old boy in San Diego County, California, showed up at an outpatient clinic with fever, severe cough, and vomiting. Suspecting flu, the health worker took a routine throat swab and sent it to the county laboratory.

The lab technician there confirmed influenza A but couldn't determine the subtype, or the "HN," of the virus. (The lab had reagents on hand to determine H3N2 and other common subtypes but not unusual ones.) "When we got a sample that we couldn't subtype, and that doesn't happen very often, we got concerned," said Anna Liza Manlucac, the supervisory microbiologist at the time. She sent the sample to the state lab in Sacramento—which forwarded it to the Centers for Disease Control and Prevention in Atlanta, Georgia—and then awaited the results. Meanwhile,

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an eight-year-old girl living in Imperial, California, more than 125 miles away, came down with similar symptoms.

On April 15, the CDC identified the virus from the first victim. It wasn't H3N2 or any other common seasonal flu variety but H1N1, or swine flu. This particular H1N1 strain had never before been seen in humans. That meant a potential pandemic. The CDC called it S-OIV, for "swine origin influenza virus," and began preparing for the worst.

Unlike pandemic flus, seasonal flu varieties bear some similarity year to year. Exposure one season leaves people with some immunity to the derivative strains the next. This tends to blunt the impact. But pandemic strains are new, so people carry little or no residual immunity. Pandemic strains can therefore spread faster and make people sicker than seasonal flu. If a pandemic strain happens to be highly virulent, it can fell young and old, healthy and infirm alike and kill far more than the hundreds of thousands seasonal flu kills each year around the globe.

The CDC soon determined that the boy in San Diego County and the girl in Imperial, 125 miles apart, had the same virus. Since they hadn't been infected by a common source, the virus must have been spreading from person to person. Two requirements for a pandemic had been met: a new virus and a contagious one. The question was whether it could sustain large outbreaks and spread worldwide. As for the first two victims, both recovered.

On April 12 Mexican authorities reported an outbreak of severe respiratory disease in the state of Veracruz. (In fact, it

turned out that more than 600 cases actually stretched back to early March, and the illness was soon to strike nearly one-third of the population of La Gloria.) Clusters also appeared in Mexico City and San Luis Potosí. Many victims were young adults, who usually are spared the worst effects of seasonal influenza but often are hit hard by pandemic strains. Many were hospitalized. When it turned out that SOIV was behind the outbreaks in Mexico and the United States, the CDC issued a travel health warning recommending that United States travelers postpone nonessential travel to Mexico. By that time, the virus had long since jumped the border.

Like the roots of invasive bamboo, H1N1 was sending up shoots in far-apart places. New cases emerged in Guadalupe County, near San Antonio, Texas; around Houston; and in Ohio and New York. By the end of April, New Zealand and Spain had reported cases. Secretary of Homeland Security Janet Napolitano proclaimed a public health emergency but likened the situation to predicting a hurricane: “The hurricane might not actually hit.”

It did. With the virus soon spreading to several countries, the World Health Organization raised the pandemic alert to Phase 4, meaning that the virus was igniting community-wide outbreaks and spreading globally. By the end of April, the CDC had confirmed cases on five continents. Still, WHO hesitated to elevate the alert to Phase 5—signifying an imminent pandemic—because influenza is so unpredictable. History is littered with lessons about crying “pandemic” too soon.

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In 1976 a mysterious respiratory outbreak hit Fort Dix, New Jersey, striking army recruit David Lewis, who was returning to town when he developed trouble breathing and collapsed. His commanding officer revived him, and Lewis was taken to the hospital on the base. He was pronounced dead on arrival. Lewis's death, along with the mounting victim toll, set off panic. Fearing a second coming of the 1918–1919 Spanish flu pandemic, the director of the CDC sent a memorandum to the US Department of Health and Human Services urgently recommending mass immunization. President Gerald Ford soon announced a crash program to “inoculate every man, woman and child in the United States.” Five months after the initial outbreak at Fort Dix, there was still no evidence of spread beyond the area. Not until seven months after the outbreak was the first vaccine administered. More than 45 million people eventually received it. But the feared pandemic never came.

Sadly, more than five hundred people who had been vaccinated suffered a paralyzing nerve condition, according to research around the time. More than thirty died before the crash vaccination program was suspended. The influenza outbreak's final confirmed toll was 230 cases, with 13 hospitalizations and 1 death. The cure, it was widely believed, had been worse than the disease. (More than three decades later, an analysis using more modern tools called into question whether the vaccines had actually caused the paralysis.)

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In 1997, almost twenty-five years after the Fort Dix debacle, came the second pandemic scare. That year, eighteen people caught a deadly type of flu from live infected poultry in Hong Kong. Half of them died. But in contrast with the situation at Fort Dix, “bird flu” didn’t fade away. Warnings abounded that the second coming of Spanish influenza was really imminent this time. Fifteen years later, deadly bird flu continues to occasionally infect people around the world. Yet the dangerous H5N1 has not evolved into a pandemic—at least not yet.

If public health organizations hesitated to cry pandemic in 2009, it’s because they had learned from 1976 and 1997. But on April 29, 2009, with overwhelming evidence that the new H1N1 virus was about to explode, the World Health Organization raised the alert to Phase 5. A pandemic was imminent.

Whatever skepticism past flu scares had spawned, the vigilance had led to vastly improved flu surveillance. By 2009 more than 130 national influenza centers in 101 countries were conducting year-round surveillance for the appearance or spread of any new strains. After collection and initial analysis, the samples were sent to one of five World Health Organization (WHO) Collaborating Centers for Reference and Research on Influenza in Atlanta, Georgia; London; Melbourne, Australia; Tokyo; and Beijing. With data on the new virus pouring into databases accessible to scientists around the world, within weeks—sometimes even days—scientific reports and papers, facilitated by online peer review and

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publication, were appearing on sites such as Plos.org and updates on Nature.com. Real-time multicolored maps and charts were rapidly unfolding at flu.net and other database sites. The traditional plodding process of scientific review and publication had reached unprecedented speed—just what was necessary to keep up with fast-moving influenza. Yet the virus was leaving its high-tech trackers and scientific sleuths in the dust.

In the past, a pandemic strain took six to nine months to spread around the world, but H1N1 spread throughout the world from Mexico in a matter of weeks. This isn't surprising, given that during a typical flu season more than 2 million people typically fly from Mexico to more than a thousand destinations in over 160 countries. Eighty percent land in the United States or Canada, while others go to Central and South America and the Caribbean Islands. Nearly 10 percent fly to western Europe. And wherever travelers from Mexico went, H1N1 often followed. "Of the 20 countries worldwide with the highest volumes of international passengers arriving from Mexico, 16 had confirmed importations associated with travel to Mexico," according to a 2009 study in the *New England Journal of Medicine*.

Although many people were infected, not until late April did the first US victim of the disease die. Earlier that month, two-year-old Miguel Tejada Vazquez and his mother, vacationing from Mexico, had visited Houston's Galleria mall. (Miguel was the grandson of Mario Vazquez Raña, a press

baron from Mexico and former owner of the United Press International news service, who at the time owned forty-one newspapers in Mexico.) A few days later, Miguel came down with a severe respiratory illness and was rushed to Texas Children's Hospital. He died on April 27.

By May 1 Texas had twenty-eight confirmed cases, second only to New York, where the virus hit St. Francis Preparatory School in Fresh Meadows, Queens. Sixty-nine students became ill. More than thirty New York City schools soon closed. Of the city's 200 confirmed cases at the time, most involved only mild illness. Fifty-five-year-old Mitchell Wiener, an assistant principal at Intermediate School 238 in Hollis, Queens, was not one of them. He died within days of becoming infected.

The CDC's global map, meanwhile, was lighting up with new cases in Germany and Austria, in parts of Asia, and in eighteen other countries. The hundreds of confirmed cases suddenly exploded into 8,500, with 72 deaths, in thirty-nine countries. By the second week in June—barely a month after the ten-year-old boy became ill—there were 30,000 cases in 74 countries.

On June 11, WHO Director-General Dr. Margaret Chan called a news conference and declared that a pandemic was officially under way. It was the first in almost forty years—since the Hong Kong flu of 1967–1968. “The virus is entirely new,” she said. “Further spread is considered inevitable. We are all in this together, and we will all get through this, together.”

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“The virus that has caused these infections is actually very interesting,” Dr. Nancy Cox, director of the CDC Influenza Division, said at an earlier press briefing. The virus had gene segments from bird, human, and pig flu viruses—what scientists call a “triple reassortant.” The pig component had come from both North American swine influenzas and one from Eurasia. Although Dr. Cox found the new virus interesting, she probably hadn’t found it completely surprising.

For more than eighty years, a familiar strain of H1N1 had been coursing through American hog farms, causing periodic outbreaks of “swine influenza” in the animals and occasionally minor infections in people who had been in contact with them. Around 1998 this familiar H1N1 virus underwent a major genetic change and emerged in pigs as a triple reassortant. This new three-headed virus—part pig, part bird, part human—caused a rash of outbreaks in North American swine. Then it continued to silently evolve. By 2005 descendants of the triple-headed virus had begun spilling more frequently into people who worked with pigs.

Between 2005 and 2009, eleven triple-reassortant swine flu infections were documented in people. The victims had come in direct contact with the pigs through butchering, at fairs, on a farm, or in live animal markets in the Midwest or Texas. Symptoms included fever, cough, headache, and diarrhea. Four of the victims ended up in the hospital, and two had to be put on ventilators. One of those infected was a previously healthy seventeen-year-old boy from Wisconsin

who, a week before falling ill, had helped his brother-in-law slaughter pigs. The boy had pulled a slaughtered pig's front legs forward while his brother-in-law gutted the animal. After a few days with a headache, low back pain, and a cough, the boy recovered. The pigs had no apparent illness, but researchers concluded the boy had most likely been infected by inhaling aerosolized secretions from the slaughtered animal's lungs or airway. All eleven victims ultimately survived.

A three-headed virus that could jump to people was still something fairly new, and such a quirk of viral evolution had not come about without a lot of inadvertent human help. Certain conditions had to be met for it to occur—conditions that would probably not have occurred naturally. First, the three types of flu viruses creating it—bird, human, and pig—had to converge on the same host.

Enter the versatile pig.

Pigs are hospitable to both human and bird flu viruses—not to mention hosting their own strains. In a pig, different viruses can co-infect the same cells. Once cohabiting a single cell, the viruses split apart, exchange genetic material, and replicate. The spun-off virus could have parts of all of them. The idea of the pig as a flophouse for influenza viruses isn't new. A century ago, veterinarian J. S. Koen, an inspector with the US Bureau of Animal Industry, pointed out that flu jumps back and forth between people and pigs. What people didn't know at the time was that cells in the airways of a pig have surface features that happen to fit the landing ports of human flu viruses. (This landing port is what the "H" of a

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viral subtype refers to, as in H1N1.) Swine tracheal cells not only host human flu viruses; they also host the H portion of bird flu viruses. The pig is therefore something of a biological boudoir for the meeting and mating of flu viruses.

If the pathway that human and pig flus travel between the two species is understood, exactly how the avian strains became part of the three-headed virus is much less so. What is known is that birds—especially aquatic ones—are the natural reservoir of all the influenza A viruses. In fact, only from wild waterfowl and seabirds have all the known subtypes of influenza A been isolated. They are a continuing wellhead of dangerous diversity for the seasonal influenzas that infect people and feed pandemics.

The ecological pathways by which avian flu genes regularly move into humans were probably established long ago. For centuries farmers in southern China and along the rice belt of Vietnam, Thailand, and Cambodia have grown rice in a system that uses domesticated ducks to feed on weeds and insect larvae, snails, and other pests in the paddies. When the rice blooms, the ducks are moved. After the harvest, they are welcomed back to feed on any remaining grain. The rice belt is along major migration routes for waterfowl. Drawn to the artificial wetlands, the wild birds, which are natural carriers of influenza A, land in the paddies and shed the virus in their feces. The domesticated poultry feeding in the paddies pick up flu viruses from the wild birds.

In many regions, pigs have been integrated into this system of seeming ecological beauty and efficiency. But the

high agricultural yield hides the messy viral cross contamination behind it. In Thailand, some rice paddies are connected to fish ponds, which are “enriched” with pig manure. Nutrient-rich water from the fish ponds is sometimes used to fertilize the rice paddies. All the while, humans frequent the areas and sometimes live adjacent to them. Little wonder southern China and other parts of Asia have become known as global “flu generators,” seeding outbreaks of influenza with new genetic material while occasionally propelling the rise of new and potentially deadly pandemic strains.

More recently, the rising affluence of many in China has increased the numbers of poultry and pigs. “No question. Today there is more of what we need for the virus to move from one host to the other,” said the CDC’s Nancy Cox. “Poultry is relatively inexpensive to grow to supplement needs and desires of the human population. Swine farms have also grown.” What’s more, the disposal of pigs that inevitably die from disease outbreaks is a growing challenge to farmers. Prohibited in certain cases from burying the animals, farmers throw them into nearby rivers. In March 2013 thousands of dead pigs festered in the major river flowing through Shanghai.

Expanding markets in cities, where animals of every conceivable type are kept live, butchered, or sold among crowds of shoppers, have created major microbiological thoroughfares for cross contamination, evolution, and human infections with flu and other diseases such as SARS. According to a 2009 study in the *Journal of Molecular and Genetic Med-*

icine, “commercial poultry farms, ‘wet markets’ (where live birds and other animals are sold), backyard poultry farms, commercial and family poultry slaughtering facilities, swine farms, human dietary habits and the global trade in exotic animals have all been implicated in the spread of influenza A viruses. The ‘wet markets’ of Southeast Asia, where people, pigs, ducks, geese and chickens (and occasionally other animals) are in close proximity pose a particular danger to public health.” Traditional agriculture, expanding pig and duck culture spurred by increasing affluence, and the growth in live animal markets may all have helped to generate new strains of influenza.

In theory, any place where wild and domesticated birds intermingle with humans can create a bridge for a flu virus to cross. In 1996 the *Lancet* reported that a housewife in England, who kept a duck house next to a pond frequented by Canada geese, mallards, and other wild birds, appeared to be among the first cases on record in which a particular type of bird flu jumped directly to humans. Fortunately, she came down with only a bad case of conjunctivitis. Such isolated cases have probably occurred for centuries. But the vast scale of live animal agriculture today, especially in China and Southeast Asia, has become central to the maintenance of seasonal flu and the creation of pandemics.

Large hog farms in the United States, Mexico, and elsewhere probably also give viruses ample chance to meet and mix in their favorite host before inflicting the human caretakers. Genetic analysis of the 2009 H1N1 outbreak

showed that swine can give rise to pandemics and that factory farm workers' occupational exposure to pigs vastly increases that risk.

It may not have been coincidental that five-year-old Edgar Hernandez of La Gloria, Mexico, was one of the earliest confirmed cases of H1N1. La Gloria, ground zero for the 2009 pandemic, is located in a major hog-farming area, not far from the town of Perote, home of the massive hog-farming company Granjas Carroll de México. A later survey of the hog farm failed to turn up the virus, and lack of sampling in the years before the virus emerged would make pinpointing its origins impossible—beyond knowing that it emerged in swine, where it had been circulating undetected for a decade before spinning off triple-headed strains whose descendants ultimately sparked the 2009 epidemic.

Nevertheless, Texas resident Steven Trunnell was convinced that a Mexican hog-farming operation gave rise to the flu virus that killed his wife, Judy. On April 14 Judy, who was eight months pregnant, developed achiness, dry cough, and a slight fever. The next day she visited her obstetrician-gynecologist. A rapid diagnostic test showed that she had the flu. Five days later she went to a local emergency room with a fever and gasping for air. Her lungs were filling with fluid, so she was intubated and put on a respirator. Later that day, a healthy baby daughter was born by an emergency cesarean delivery. But it was too late for Judy, who passed away on May 4—the first American citizen to die from H1N1.

On May 11 Steven, a paramedic, filed a petition in the

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district court of Cameron County, Texas, seeking to depose officials of Smithfield Foods, part owner of the hog operation in Perote. The petition claimed that “it is likely that the creation and spread of this lethal strain of swine flu may have been caused, in part, by historically unsanitary conditions which Smithfield Foods knowingly caused to occur in Mexico in connection with the operation of the largest pig farm business in the world.” The petition stated that “it is reasonable to expect that this area around La Gloria is ‘ground zero’ for the H1N1-2009 swine influenza virus.” Ultimately, the petition went nowhere.

A year and a half after it began, the worst of the 2009 swine flu pandemic had passed, and on August 10, 2010, the World Health Organization announced that the world had entered the “post-pandemic period.” “The new H1N1 virus has largely run its course,” WHO said. “This time around, we have been aided by pure good luck. The virus did not mutate during the pandemic to a more lethal form.” Although it was far from another “pandemic that never was,” it was, by many accounts, far milder than most had predicted.

According to Marc Lipsitch of Harvard School of Public Health, it was probably “the mildest pandemic on record—compared to the three that happened in the 20th century,” although it had a disproportionate impact on children and young adults. The CDC’s director, Thomas Frieden, on the other hand, said that “any flu season that kills at least three times more children than a usual flu season—I think it would be very misleading to describe that as mild.”

By the time it was over, the pandemic had affected over 214 countries and caused more than 18,000 laboratory-confirmed deaths—including more than 250 children. A study in the *Lancet* cautioned that “this number is likely to be only a fraction of the true number of the deaths associated with 2009 pandemic influenza A H1N1.” The study concluded that between April 2009 and August 2010, more than 200,000 people had been infected—80 percent of them adults under the age of sixty-five. More than half of the infections occurred in Southeast Asia and Africa.

Probably never before had so much been learned so quickly about a virus. Three years after H1N1 appeared, a search of medical literature showed that more than 2,500 papers on it had been published, making it among the most studied pandemics in history—and generating an enormous amount of data that would help scientists to better understand future outbreaks.

The good news was that the pandemic had come—and gone—with far less damage than many had anticipated. The bad news was that H1N1 wasn’t even the pandemic everyone had been predicting and preparing for. The original suspect—the feared H5N1 bird flu from Asia—had been on the loose since 1997 and was considered far more lethal.

#### 4.

This most feared pandemic—H5N1, or “bird flu”—began in Hong Kong in 1997. Bird flu first came to light when a three-year-old boy in Hong Kong was hit with a fever, sore throat,

and cough. He was admitted to the hospital's pediatric intensive care unit, where he soon died of severe respiratory distress. Like the later H1N1, bird flu had never before been seen in humans. Of the eighteen people infected in Hong Kong during the initial outbreak, six died.

Today, fifteen years later, bird flu is still traveling, having spread widely in poultry. And where poultry outbreaks began, human infections weren't long in following. In almost all human infections the virus jumped directly from birds to people, but there may be some limited person-to-person transmission, according to the CDC. Between 1997 and 2013, more than 600 people were infected. More than half died. The situation harkens back to the days when H1N1 also had limited human transmission. But fortunately, when it comes to influenza the past does not always predict the future.

If the "sudden" appearance of swine flu in 2009 misled the public to believe that pandemics seem to explode out of nowhere, the lingering bird flu from 1997 taught that, in reality, they almost never do. And if H1N1 tricks us into believing that influenza is a medical issue best addressed by physicians, H5N1 tells us that the real cause is ecological.

In some ways the ecological trajectories of swine flu and bird flu were similar. But whereas H1N1 was mostly at home in pigs, H5N1 has been most at home in birds, which gave it birth. The year before the 1997 Hong Kong outbreak, H5N1 was isolated from a flock of sick geese in Guangdong Province, China. No one can say exactly how the virus first arose, only that it had probably been carried there by birds. But the

virus may already have been widely dispersed in wildfowl, and it may have been only by chance that it was detected in Guangdong instead of elsewhere.

H5N1 is a type of poultry disease called highly pathogenic avian influenza, or HPAI. This flu virus and other flu viruses that infect birds have caused among the largest outbreaks of animal disease ever recorded, with several hundred million wild birds, geese, chickens, turkeys, and ducks having died from it. Long before the flu virus was identified in these massive outbreaks, the disease it caused was known as “fowl plague,” first identified in Italy in 1878. The virus was spread through the transport of fowl to poultry exhibitions and shows in Europe in the late 1800s and early 1900s. But not until 1955 was it determined to be an influenza A virus. Although avian influenza is now controlled in the United States, in 1983 and 1984 an outbreak in the northeastern United States led to the destruction of more than 17 million birds and cost \$65 million, causing the retail price of eggs to jump by nearly 30 percent at the time. A 2004 outbreak in Canada led to several hundred million dollars in losses.

Although mostly limited to birds, avian influenzas such as HPAI have long been known to cause occasional mild illness in humans. Their versatility in infecting other species is also well documented. In 1986 two different flu viruses from gulls were found to have infected a pilot whale. Avian influenza viruses have also caused periodic die-offs of seals near New England.

Not long after the 1997 H5N1 outbreak in Hong Kong,

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the virus began spreading to mainland China and elsewhere in Southeast Asia, sowing occasional human infections along the way. Then, in 2003, new human H5N1 infections emerged in Vietnam, followed by sporadic cases in Europe, Africa, and the Middle East. Reports of human infections in Thailand soon followed. The virus was also killing 100 percent of the poultry it infected there and in Vietnam. Wherever there were human cases, they seemed to follow outbreaks in poultry.

Although spread in part by migrating birds, the virus had become so entrenched in poultry throughout regions of China that distinct regional variations of the bug evolved. Detached from wild birds, where it arose, it is now mapping its own evolutionary course. The movement of poultry has reintroduced these regional variations from one region or country to the next, adding further momentum.

Bird flu's forays into other species didn't stop, and it seemed to run rampant across interspecies borders. In late 2003 cases of H5N1 were reported in dogs, cats, pigs, and weasels. In December of that year, two tigers and two leopards in a Thai zoo died after being fed carcasses of slaughtered chickens that had been having respiratory problems. At about the same time the tigers and leopards died, there was an outbreak of H5N1 on nineteen poultry farms in Korea. Just before the outbreak, the owner had on many occasions seen magpies entering an area where chicken feces were disposed of. Dead magpies later found on the farm had been infected by the virus.

In Japan, dead crows found near chicken pens had also been infected with the same virus originally found in Guangdong Province, or one closely related to it. The virus decimated poultry wherever it struck. Over 100 million domesticated birds were culled in a futile effort to contain the first wave of the virus. A second wave swept through poultry in China, Indonesia, Thailand, and Vietnam in late 2004. And another outbreak at a Thai zoo led to the deaths of 147 tigers.

By 2005 a third wave of H5N1 was sweeping through Southeast Asia. Human cases were also being reported every month in Asia, eastern Europe, Africa, and the Far East. Still, there was little, if any, transmission from one person to the next. In October 2005, 276 smuggled songbirds died en route to Taiwan from mainland China. Later tested for disease, the birds were found to be infected with H5N1. It wasn't the first time that contraband could have contributed to the spread. The year before, two eagles hidden in tubes and smuggled into Brussels from Thailand were found to be infected. Although showing no symptoms, both birds were euthanized.

In 2005 three civet cats died of H5N1 in Vietnam. Often bought and sold in street markets in China, civet cats were double-crossed: they had also spread SARS—severe acute respiratory syndrome—to people during that outbreak in 2003.

In April 2005, H5N1 killed more than six thousand bar-headed geese, gulls, shelducks, cormorants, and other wild birds at Qinghai Lake in central China—the first time the

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virus had shown sustained transmission in waterfowl. It had probably been carried there by wild birds that picked it up from poultry in southern China.

After the Qinghai Lake outbreak, dead migratory birds were found in western Siberia and in Kazakhstan and Tibet, as well as in Mongolia. H5N1 continued to spread among poultry in Turkey and Romania and in mute swans in Croatia and Hungary. Birds fell ill from H5N1 at a zoo in Jakarta, a dead flamingo was found in Kuwait, and dead swans were found in Iraq and Egypt; in Bulgaria, Greece, Italy, Austria, Hungary, Germany, Slovakia, Poland, and Denmark; and elsewhere in Europe. Poultry were infected in Afghanistan, Pakistan, Jordan, and Israel and in several other North African countries. By 2006 human cases were beginning to surge again, with most of them in Indonesia and Egypt. Sporadic human infections continue to this day.

In 2006 influenza researcher Robert Webster declared that “the likelihood of an H5N1 influenza pandemic seems high, and the consequences could be catastrophic. Recent findings suggest that the 1918 ‘Spanish flu’ pandemic may have resulted from a similar interspecies transmission event in which a purely avian virus adapted directly to human-to-human transmission.”

Several years after Webster’s warning, studies suggested that the virus could be only a few simple mutations away from contagiousness. In one study, scientists inserted into the 2009 swine flu virus a mutant version of a key viral protein from bird flu. A mere four mutations later, the hy-

brid strain was able to strongly bind to mammalian cells and replicate enough to saturate respiratory droplets—the beginnings of aerosol transmission—that is, it developed the ability to spread easily from one person to the next. Technical details of the research were so worrisome to the terrorism-sensitive US National Science Advisory Board for Biosecurity that it recommended researchers withhold key details when publishing their work. After a heated six-month debate between government officials and scientists, two papers detailing the results were finally published in their entirety in *Nature* and *Science*.

Even as public health officials at the World Health Organization and the Centers for Disease Control and Prevention wrote swine flu into the history book, the catastrophic potential of bird flu weighed heavily on their minds. One might have hoped that pandemic scares would end there. They didn't. In 2012 yet a third contender for the title of Next Pandemic arose.

## 5.

The third “pandemic” begins in early April 2013 when a sixty-year-old woman from Zhejiang Province, China, is hospitalized, barely able to breathe. Fourteen other cases of severe respiratory difficulty quickly come to light in Zhejiang Province, Shanghai, and Anhui Province. All of the victims are hospitalized. Six die. The virus identified, H7N9, has never been seen before in humans. Because it is new to people, it has “potential pandemic” written in its H surface protein.

Setting H7N9 ominously apart from even H5N1 are genetic changes, according to authors of a 2013 study, that “probably facilitate binding to human-type receptors and efficient replication in mammals . . . highlighting the pandemic potential.”

With H5N1, H1N1, and now H7N9—all new to human experience—the earth seems to be passing through a meteor shower of new flu viruses. H1N1 has already struck, bird flu appears to be a near miss, and H7N9 is passing somewhere between. The genetic makeup of H7N9 suggests it probably originated from Eurasian avian influenza viruses. Other components echoed duck, chicken, and even pigeon ancestry.

So the story goes.

The cases are initially limited to Shanghai and neighboring regions. By the third week in April two people are infected in Beijing, to the north, and two more in Henan Province—with live poultry shipped from Shanghai the likely source of the spread. But with some 6 billion domesticated birds shipped annually throughout China, the viral trail is almost impossible to follow. There’s still no evidence of the virus spreading widely among people, but the scattered reports are worrisome. Jeremy Farrar, director of the Oxford University Clinical Research Unit in Ho Chi Minh City, Vietnam, told the journal *Nature*, “I think we need to be very, very concerned.”

Because H5N1 leaves a trail of dead poultry, the virus’s whereabouts are known. But H7N9 can silently infect birds, flying under the radar, spreading through flocks undetected

and in turn infecting people in poultry markets, far from where the last human cases were seen. By mid-April there are 63 infections and 14 reported deaths—up from 24 cases in a single week. Within the first two weeks of its appearance, H7N9 virus is infecting more people than H5N1 has since 1997.

In April 2013, the first asymptomatic case of H7N9 is detected in humans—a four-year-old girl who had been in contact with a seven-year-old who fell seriously ill. The occurrence of silent cases among humans, as among poultry, means the virus may be evading surveillance. US Secretary of Health and Human Services Kathleen Sebelius declares that the avian influenza virus has a “significant potential to affect national security.”

Shortly after H7N9’s emergence, studies show it has already mutated in people since jumping from birds—a mutation that allows the virus to grow well at a temperature similar to that of the human upper respiratory tract.

By August 2013 it has infected more than 130 people in China, with more than 40 deaths. As with its dangerous cousin H5N1, which continues to evolve, no one can say where the new virus will end.

The rest remains to be seen.