

Researchers have no way of knowing what the next influenza pandemic will look like. But models and educated guesses are disconcerting

Looking the Pandemic in the Eye

Ask flu experts about their worst nightmare and they may tell you something like this. Somewhere in Asia, a new flu virus is born that's able to jump from one human to the next, yet is cloaked in avian proteins that human immune systems have never seen before. Laying low at first, the virus sickens and kills a small number of people, while it's getting better at the human-to-human transmission game. When authorities finally notice the expanding cluster of flu cases, the virus has already moved on. It takes advantage of flights that connect Asia's major cities to the rest of the world, popping up simultaneously in Sydney, Los Angeles, and London.

Hundreds begin to die, literally drowning as fluid fills their lungs. A stunned public demands a vaccine, drugs—anything—but no vaccine will be available for months, and antivirals are in short supply; the question is, who gets them? Panic and riots erupt while schools, businesses, and transportation systems are shutting down. Overcrowded hospitals start turning away desperate patients. There aren't nearly enough doctors and nurses to take care of the sick and dying, nor enough coffins. When the outbreak finally peters out 18 months later, more than 2 billion people have become ill, and more than 40 million are dead—twice the number claimed by AIDS in 25 years.

True, that's a worst-case scenario—but few experts dismiss it out of hand. After years of neglect, the threat of a new pandemic is back on the world's radar screen, beeping noisily. Public health experts, virologists, and disease modelers are struggling to envisage how fast it would spread, how many it would kill, what it would cost, and most of all, how best to fight it.

The efforts were spurred in part by severe acute respiratory syndrome (SARS), the planet's close brush with pandemic disaster last year. The SARS virus wasn't all that contagious, striking fewer than 9000 people before it was brought under control. But the world may not be so lucky next time. Nor does it take

a newcomer like the SARS virus for a pandemic to occur. Most experts agree that flu strains now circulating can, and eventually will, spawn a new pandemic.

Predicting what it will look like means going out on a limb, however, because everything depends on which flu strain is the culprit and how virulent it is—two questions no one can answer. Still, researchers can crunch the numbers for a range of assumptions. They end up with a series of scenarios—from something quite benign to an “overwhelming and potentially catastrophic event,” says Martin Meltzer, an economist and disease modeler at

This happens when one or both of the virus's envelope proteins (hemagglutinin and neuraminidase, the H and N in names like H5N1) have never before circulated in humans.

By far the most terrifying example is the 1918–19 “Spanish flu” pandemic, during which at least 20 million people, and perhaps as many as 100 million, are believed to have perished. Most of that virus's genetic baggage has been reassembled from preserved tissue scraps and an Alaska victim's frozen body. In a paper published in last week's issue of *Nature*, researchers reported that a modern flu strain equipped with the 1918 hemagglutinin is highly pathogenic to mice—a finding that may help clarify why the 1918 virus was so deadly. It's still unclear where the virus came from, however; nor are researchers sure about the origins of two subsequent, milder pandemics that struck in 1957 and 1968.

For decades, the dominant theory was that new pandemic viruses arise when avian and human flu viruses reassort, or hybridize, inside pigs, which can be infected with both. (Chinese farms, where ducks, humans, and pigs mingle, were seen as plausible locales.) But since 1997, three avian flu viruses—including H5N1, the virus that has infected poultry in 10 Asian countries—have been found to infect humans directly. Now, the predominant worry is that humans infected with both avian and human viruses may be mixing vessels.

Fortunately, chances of this happening still seem low, says Neil Ferguson, an epidemiologist at Imperial College in London. Even if you assume that reassortment occurs in each and every patient infected with the two viruses—which is unlikely—more than 600 people would have to be infected with H5N1 to create a 50% chance of reassortment, Ferguson and his colleagues wrote ear-



Put to bed. A ballroom was turned into an emergency infirmary at the University of Massachusetts during the 1957 “Asian flu” pandemic.

the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

Even trickier to predict are a pandemic's social, political, and economic fallout. “Go ask the fiction writers what could happen,” Meltzer says. It seems certain, though, that a pandemic will raise agonizing dilemmas about who should be first to receive drugs, vaccines, and medical care—an issue that most countries haven't even begun to debate.

Virgin territory

Flu pandemics occur when a new virus emerges that's easily transmissible between people and also finds virgin territory in the human population because no one is immune.

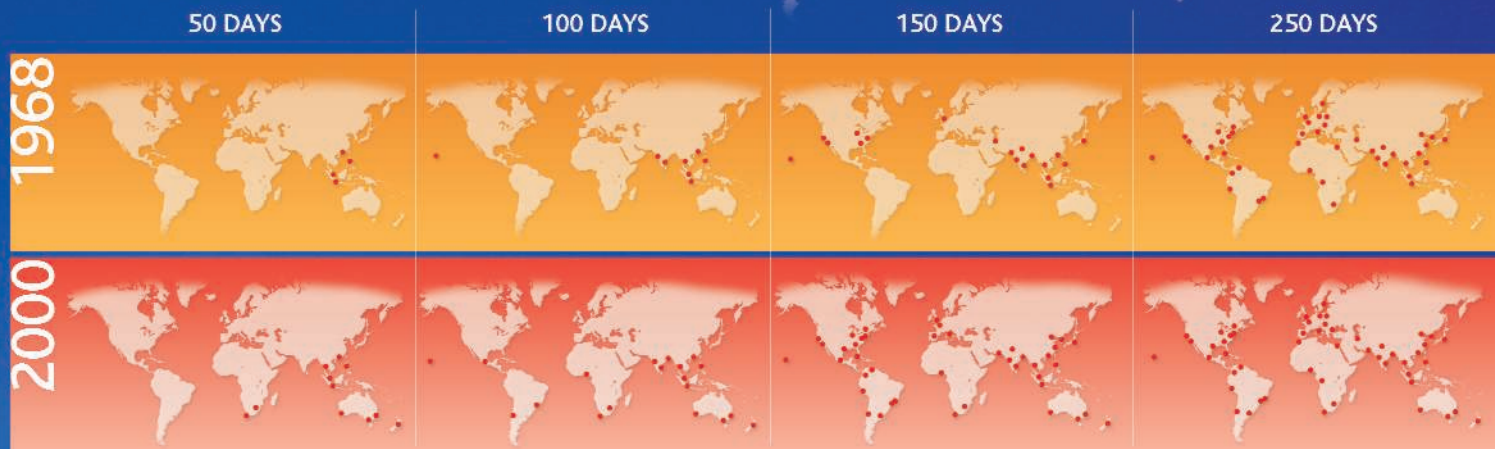
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Frequent-Flyer Virus



DAY ZERO

Models based on airline travel data show that the 1968 pandemic flu virus, which originated in Hong Kong, would have circled the globe much faster if it had erupted in 2000.



lier this year in *Science* (14 May, p. 968). So far, fewer than 50 people in Vietnam and Thailand are confirmed to have been infected with H5N1. What's more, most reassortants are likely to pose no threat.

Assuming a new pandemic virus emerges, how might it behave? Epidemics can be modeled several ways, but mathematicians always need a number of key parameters, such as the basic reproductive number (R_0), which denotes the number of secondary infections resulting from one patient, the attack rate (the percentage of people who get sick after being exposed to the virus), the chance of becoming infected when in close contact with a patient, the incubation period, and the mortality rate.

For many diseases, those variables are reasonably well known and more or less constant. Not pandemic flu; even year-to-year changes in the influenza virus make for difficult modeling, says Ira Longini, an expert at Emory University in Atlanta—which is why modelers have tended to stay away from flu.

But faced with what many perceive as a gathering threat and using past pandemics as a rough guide, modelers are beginning to tackle the problem. The Models of Infectious Disease Agent Study (MIDAS), for instance, a network funded by the U.S. National Institutes of Health that includes Longini's group, this summer made work on flu pandemics its top priority. The U.S. government is keenly interested in the results, Longini says, because models can help decide how best to deploy drugs and vaccines.

The models all suggest that pandemic flu is unlikely to be contained using the old-fashioned public health measures that put the SARS genie back into the bottle, such as isolating patients and tracing and quarantining contacts. SARS has an incubation pe-

riod of about 6 days during which infected people don't seem to infect others—precious time health authorities could use to trace those exposed but still healthy. With flu, they'd have only about 2 days on average. Moreover, SARS's severe symptoms helped identify patients, whereas flu can be as mild as the sniffles.

The only exception may be very early on, notes Ferguson. When the virus is still struggling to replicate among humans, surveillance and quarantine, perhaps helped by aggressive use of antiviral drugs, might nip a pandemic in the bud—which is why the World Health Organization is exploring a plan to ship antivirals to the cradle of a potential pandemic (see p. 394).

Once a virus was on the loose, jumbo jets would likely spread pandemic flu faster than ever in history. In a model published last year, Rebecca Grais and her colleagues at Johns Hopkins University in Baltimore, Maryland, collected data on the number of passengers traveling daily among 52 major cities around the globe and then calculated how fast the 1968 strain would have spread had it surfaced in 2000. Although the model has its limits, the trend is clear: The outbreak would peak in most of the 52 cities within 6 months (see graphic above). In the same model fed with travel data from 1968—as well as in the actual pandemic—almost a year passed before the virus made it around the globe. The difference is crucial, because developing and mass-producing a vaccine may take as long as 6 months. Few countries can hope to be spared that long.

Two waves

The toll of the pandemic would depend largely on the attack rate and the mortality rate—two unpredictable factors that can

change during an outbreak. Spanish flu, for instance, came in two waves: One, in the spring and summer of 1918, caused widespread disease but few deaths; another, much more vicious wave the following autumn and winter killed half a million people in the United States alone. Presumably, the virus had evolved to become more virulent.

When trying to predict the course of the next pandemic, however, most modelers look more to 1957 and 1968 than to 1918. That's in part because much more is known about the virology and epidemiology of those epidemics, which makes modeling easier. Still, Longini admits that the later pandemics make for rosier outlooks, and the MIDAS group is now collecting data to tackle the 1918 pandemic.

When Meltzer and two CDC colleagues estimated the economic impact of a pandemic on the United States in a 1999 study, they used conservative attack and mortality rates comparable to those in the milder pandemics. Even then, a pandemic could cause between 314,000 and 734,000 hospitalizations and claim between 89,000 and 207,000 lives, they found. Even the lower figures would overwhelm the U.S. health system, says Meltzer: Hospitals were under severe stress when the 1999–2000 flu season was worse than usual.

The team put the economic cost of a 1968-style pandemic for the United States at somewhere between \$71.3 billion and \$166.5 billion. Using a different set of assumptions, including lower health care costs, Jeroen Medema of Solvay, a vaccine company in the Netherlands, arrived at about \$167 billion for all developed countries combined. Both studies, however, included only direct medical costs and lost productivity as a result of disease and

death. A pandemic would almost certainly cause economic disruption that would multiply the cost several-fold. (Asian economies suffered incalculable losses from the SARS outbreak.)

Vaccines would curb the toll, but supplies would be short in the beginning, Meltzer says—as would drugs and attention from doctors and nurses. “Who will get a hospital bed—a 90-year-old grandmother or a 30-year-old mother of two children? People in America are not used to that kind of rationing,” Meltzer says, although they’re getting a taste of it now that manufacturing problems have abruptly cut the yearly flu vaccine supply in half (see p. 385).

In an as-yet-unpublished paper, Longini and his colleagues show that, when a vaccine is in short supply, different objectives can lead to radically different strategies dur-

ing relatively mild pandemics. When reducing mortality is the primary goal, for instance, it’s best to vaccinate the elderly. When trying to reduce the number of cases or reduce the economic fallout, it would be better to start with schoolchildren.

But so far, there’s been little discussion about such priorities and even less consensus. When CDC and other organizations convened a meeting of more than 125 public health experts from 46 states in 2002, participants were asked which of five goals should get top priority during a pandemic: reduce disease, reduce deaths, ensure that essential services continue, limit the economic impact, or ensure “equitable” distribution of scarce resources. None received more than 50% of the votes. “We need a national debate now about these questions,” Meltzer says.

“When you have a pandemic, it’s not a good time to have a discussion with your doctor about the ethics of rationing.”

If handled badly, such choices may increase the risk of social upheaval, says Monica Schoch-Spana, a senior fellow at the University of Pittsburgh’s Center for Biosecurity. Today’s public is likely to become disillusioned when it finds that the government can’t offer protection. “There’s always the operating assumption that some expert somewhere knows what to do,” she says. Clearly explaining the choices as well as the uncertainties is going to be essential, she says.

Retired historian Alfred Crosby, an expert on the 1918 pandemic, is worried about panic, too. But it needn’t happen, he notes—the next pandemic may be of the mild rather than cataclysmic variety. Says Crosby: “I wish us all luck.”

—MARTIN ENSERINK

Facing Down Pandemic Flu, the World’s Defenses Are Weak

A lack of interest in developing pandemic flu vaccines and a dearth of antiviral drugs have left the world vulnerable to a global outbreak

At a hotel meeting room outside Quebec last March, 35 health officials and others from the world’s seven leading industrialized countries and Mexico passed around a vial of bitter-tasting white powder. If Asia’s potent H5N1 bird flu assumes a form transmitted between humans, this drug, oseltamivir, would be the world’s only initial defense against a pandemic that could kill millions of people. But oseltamivir, sold as Tamiflu, is made by only one company, Roche, at a single plant in Switzerland. “We are living in a brave new world where we only have one drug,” says flu expert Arnold Monto of the University of Michigan, Ann Arbor, who spoke before the working group meeting of the G7+ Global Health Security Action Group.

That grim assessment is one indicator of the world’s vulnerability to pandemic influenza. Most virologists say a pandemic is a virtual certainty within the next few decades, if not from H5N1 then from another avian flu strain (see p. 392). When that happens, public health officials will have two tools to battle the disease: antiviral drugs and vaccines. But although research has produced effective new antivirals, they are expensive, and global supply falls far short of need. And a promising genetically engineered vaccine against H5N1 is still an experimental product only just now being tested in people.

After years of warning from flu experts,

governments are finally beginning to respond. Some countries are starting to stockpile antivirals. The United States in August unveiled a draft pandemic flu plan; it is also



Priority list. Pandemic vaccines and antivirals will likely have to be rationed to protect the vulnerable, such as children and the elderly.

launching clinical trials of an H5N1 vaccine and will pay Aventis Pasteur \$13 million to manufacture 2 million doses. “There’s a lot of momentum,” says virologist Robert Webster of St. Jude Children’s Research Hospital in Memphis, Tennessee.

But even that is not enough, say global flu experts. Of the world’s 12 major flu vaccine manufacturers, so far only two are willing to tackle the financial, regulatory, and patent issues involved in making a new pandemic vaccine, mainly for the U.S. market. Companies in other countries also need to be developing emergency products, flu experts say. Moreover, only 15 countries have pandemic flu preparedness plans that lay out how scarce vaccines and antivirals will be distributed, notes World Health Organization (WHO) virologist Klaus Stöhr.

As worries intensify, flu experts are exploring a controversial alternative: pooling available supplies of antiviral drugs to stamp out an incipient pandemic in Asia. But whether countries will voluntarily ship their own precious stockpile overseas to fight a faraway plague remains to be seen.

A clear and present danger

The United States last geared up for pandemic flu in 1976, after swine flu broke out in Fort Dix, New Jersey. Within 10 months, the country produced 150 million doses of vaccine and vaccinated 45 million people. But the virus didn’t spread, and critics said the government had jumped the gun. That led to the first U.S. pandemic flu plan.

The need to rethink such plans became apparent in 1997, when an outbreak of H5N1 avian flu in Hong Kong killed six people. Unlike previous pandemic strains, H5N1 did not first combine with a human flu virus in

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