Preparing for a Pandemic

Influenza was first described by Hippocrates as early as 412 B.C., but the first pandemic was not recorded until 1580. The 1918 “Spanish flu” pandemic killed more people than died fighting World War I. This disaster was followed by epidemics of “Asian flu” in 1957, “Hong Kong flu” in 1968 (and again “bird flu” in 1997) and “Russian flu” in 1977.

Influenza is spread from person to person by coughs and sneezes, but the virus doesn't begin its journey in a human host. Instead, wild aquatic birds such as ducks and shore birds perpetuate the influenza viruses that cause human pandemics. Although these birds carry the genes for influenza in their intestines, they usually don't become sick from the virus. And because they can migrate thousands of miles, the healthy birds can spread the virus across the globe even before the microbe makes contact with the human population.

The form of the virus found in wild birds doesn't replicate well in human beings, and so it must first move to an intermediate host—usually domestic fowl or swine—that drinks water contaminated by the feces of aquatic birds. Horses, whales, seals and mink are also periodically infected with influenza. Although the intermediate hosts can sicken and die from the infection, swine can live long enough to serve as "mixing vessels" for the genes of avian, porcine and human forms of influenza. This occurs because swine have receptors for both avian viruses and human viruses.

Swine have probably played an important role in the history of the human disease. These animals appear to serve as living laboratories where the avian and mammalian influenza viruses can come together and share their genes (a *reassortment* of RNA segments) and create new strains of flu. When a strain of virus migrates into the human population, it changes into a disease-causing microbe that replicates in the respiratory tract. A sneeze or a cough spreads the virus in a contagious aerosol mist that is rich in virus particles. Despite their names, it is now thought that most influenza pandemics originate in China, where birds, pigs and people live in close proximity.

Type A influenzas are categorized by the structural variations of two glycoproteins, hemagglutinin (HA) and neuraminidase (NA), which protrude from the surface of the virus. HA's job is to attach the influenza virus to the receptors on the surface of the respiratory tract. After binding, the flu virus penetrates the host cell; there, viral RNA moves into the cell's nucleus. The viral RNA encodes messenger RNA and ultimately produces new virus particles. NA’s task is to enable the newly created virus to separate from the host cell and travel freely from one cell to another through the respiratory tract. Scientists have identified 16 HA and 9 NA subtypes, all of which are found in avian hosts. Epidemics occur when the HA or the NA proteins mutate. The subtypes of type A viruses are named according to the particular variants of the HA and NA molecules they contain—such as H1N1, the culprit in the 1918 Spanish flu; or H5N1, the "bird flu" of 1997.

The most fundamental thing to understand about serious pandemic influenza is that, except at a molecular level, the disease bears little resemblance to the flu that we all get at some time. An influenza pandemic, by definition, occurs only when the influenza virus mutates into something dangerously unfamiliar to our immune systems and yet is able to jump from person to person through a sneeze, cough or touch.

Some pandemics are mild. But some are fierce. If the virus replicates much faster than the immune system learns to defend against it, it will cause severe and sometimes fatal illness, resulting in a pestilence that could easily claim more lives in a single year than AIDS has in 25. Epidemiologists have warned that the next pandemic could sicken one in every three people on the planet, hospitalize many of those and kill tens to hundreds of millions. The disease would spare no nation, race or income group. There would be no certain way to avoid infection.

Rapid Response: Could a Pandemic Be Stopped?

Until 1999, WHO had a simple definition for when a flu pandemic began: with confirmation that a new virus was spreading between people in at least one country. Thereafter, stopping the flu's lightning-fast expansion was unthinkable--or so it then seemed.

But because of recent advances in the state of disease surveillance and antiviral drugs, the latest version of WHO's guidelines recognizes a period on the cusp of the pandemic when a flu virus ready to burst on the world might instead be intercepted and restrained, if not ***stamped out*** (eradicated).

Computer models and common sense indicate that a containment effort would have to be exceptionally swift and efficient. Flu moves with extraordinary speed because it has such a short incubation period—just two days after infection by the virus, a person may start showing symptoms and shedding virus particles that can infect others. Some people may become infectious a day before their symptoms appear. In contrast, people infected by the SARS coronavirus that emerged from China in 2003 took as long as 10 days to become infectious, giving health workers ample time to trace and isolate their contacts before they, too, could spread the disease.

Contact tracing and isolation alone could never contain flu, public health experts say. But computer-simulation results published in August showed when up to 30 million doses of antiviral drugs and a low-efficacy vaccine were added to the interventions a chance emerged to thwart a potential pandemic.

Conditions would have to be nearly ideal. Modeling a population of 85 million based on the demographics and geography of Thailand, Neil M. Ferguson of Imperial College London found that health workers would have at most 30 days from the start of person-to-person viral transmission to deploy antivirals as both treatment and preventives wherever outbreaks were detected.

But even after seeing the model results earlier this year, WHO officials expressed doubt that surveillance in parts of Asia is reliable enough to catch a budding epidemic in time. In practice, confirmation of some human H5N1 cases has taken more than 20 days, WHO flu chief Stöhr warned a gathering of experts in Washington, D.C., in April 2005. That leaves just a narrow window in which to deliver the drugs to remote areas and dispense them to as many as one million people.

Partial immunity in the population could buy more time, however, according to Ira M. Longini, Jr., of Emory University. He, too, modeled intervention with antivirals in a smaller community based on Thai demographic data, with outcomes similar to Ferguson's. But Longini added scenarios in which people had been vaccinated in advance. He assumed that an existing vaccine, such as the H5N1 prototype version some countries have already developed, would not perfectly match a new variant of the virus, so his model's vaccinees were only 30 percent less likely to be infected. Still, their reduced susceptibility made containing even a highly infectious flu strain possible in simulations. NIAID director Fauci has said that the U.S. and other nations with H5N1 vaccine are still considering whether to direct it toward prevention in the region where a human-adapted version of that virus is most likely to emerge--even if that means less would remain for their own citizens. "If we're smart, we would," Longini says.

Based on patterns of past pandemics, experts expect that once a new strain breaks loose, it will circle the globe in two or three waves, each potentially lasting several months but peaking in individual communities about five weeks after its arrival. The waves could be separated by as long as a season: if the first hit in springtime, the second might not begin until late summer or early fall. Because meaningful amounts of vaccine tailored to the pandemic strain will not emerge from factories for some six months, government planners are especially concerned with bracing for the first wave.

Once a pandemic goes global, responses will vary locally as individual countries with differing resources make choices based on political priorities as much as on science. Prophylactic use of antivirals is an option for a handful of countries able to afford drug stockpiles, though not a very practical one. No nation has enough of the drugs at present to protect a significant fraction of its population for months. Moreover, such prolonged use has never been tested and could cause unforeseen problems. For these reasons, the U.K. declared that it would use its pandemic stockpile primarily for treating patients rather than for protecting the uninfected. The U.S., Canada and several other countries are still working out their priorities for who will receive antivirals and when.

For most countries there will be no choice: what the WHO calls nonpharmaceutical interventions will have to be their primary defense. Although the effectiveness of such measures has not been extensively researched, the WHO gathered flu specialists in Geneva in March 2004 to try to determine which actions medical evidence does support. Screening incoming travelers for flu symptoms, for instance, "lacks proven health benefit," the group concluded, although they acknowledged that countries might do it anyway to promote public confidence. Similarly, they were skeptical that public fever screening, fever hotlines or fever clinics would do much to slow the spread of the disease.

The experts recommended surgical masks for flu patients and health workers exposed to those patients. For the healthy, hand washing offers more protection than wearing masks in public, because people can be exposed to the virus at home, at work and by touching contaminated surfaces—including the surface of a mask.

Traditional "social distancing" measures, such as banning public gatherings or shutting down mass transit, will have to be guided by what epidemiologists find once the pandemic is under way. If children are especially susceptible to the virus, for example--as was the case in 1957 and 1968—or if they are found to be an important source of community spread, then governments may consider closing schools.

What Can Be Expected for the Sick?

If two billion become sick, will 10 million die? Or 100 million? Public health specialists around the world are struggling to quantify the human toll of a future flu pandemic. Casualty estimates vary so widely because until it strikes, no one can be certain whether the next pandemic strain will be mild, like the 1968 Hong Kong flu that some flu researchers call a "wimp"; moderately severe, like the 1957 Asian flu; or a stone-cold killer, like the 1918 Spanish flu (during this pandemic, some victims felt a bit sick in the morning, went to bed in the afternoon and were dead by nighttime).

For now, planners are going by ***rules of thumb*** (ways of proceeding based on experience): because no one would have immunity to a new strain, they expect 50 percent of the population to be infected by the virus. Depending on its virulence, between one third and two thirds of those people will become sick, yielding a clinical attack rate of 15 to 35 percent of the whole population. Many governments are therefore trying to prepare for a middle-ground estimate that 25 percent of their entire nation will fall ill.

Ordinarily, those hardest hit by annual flu are people who have complications of chronic diseases, as well as the very young, the very old and others with weak immune systems. The greatest cause of seasonal flu-related deaths is pneumonia brought on by bacteria that invade after flu has depleted the body's defenses, not by the flu virus itself.

In contrast, the 1918 pandemic strain was most lethal to otherwise healthy young adults in part because they had robust immune systems. Researchers studying that virus have discovered that it suppresses early immune responses, such as the body's release of interferon, which normally primes cells to resist attack. At the same time, the virus provokes an extreme immune overreaction known as a cytokine storm, in which signaling molecules called cytokines lead a ferocious assault on the lungs by immune cells. Doctors faced the same problem in SARS patients. If this devastating attack was not stopped in time, their lungs became increasingly inflamed and so choked with dead tissue that pressurized ventilation was needed to get enough oxygen to the bloodstream.

Nothing about the H5N1 virus in its current form offers reason to hope that it would produce a moderate pandemic, according to Frederick G. Hayden, a University of Virginia virologist who is advising WHO on treating avian flu victims. "Unless this virus changes dramatically in pathogenicity," he asserts, "we will be confronted with a very lethal strain." Many H5N1 casualties have suffered acute pneumonia deep in the lower lungs caused by the virus itself, Hayden says, and in some cases blood tests indicated unusual cytokine activity. But the virus is not always consistent. In some patients, it also seems to multiply in the gut, producing severe diarrhea. And it is believed to have infected the brains of two Vietnamese children who died of encephalitis without any respiratory symptoms. (***American Scientist***, 2003; ***Scientific American***, 2005)