The Next Worldwide Pandemic - Avian Flu?

Scientists have long forecast the appearance of an influenza virus capable of infecting 40 percent of the world's human population and killing unimaginable numbers. Recently, a new strain, H5N1 avian influenza, has shown all the earmarks of becoming that disease. Until now, it has largely been confined to certain bird species, but that may be changing soon.

The havoc such a disease could wreak is commonly compared to the devastation of the 1918-19 Spanish flu, which killed 50 million people in 18 months. But avian flu is far more dangerous. It kills 100 percent of the domesticated chickens it infects, and among humans the disease is also proven to be lethal.

Since it first appeared in southern China in 1997, the virus has mutated, becoming heartier and deadlier and killing a wider range of species. According to the March 2005 National Academy of Science's Institute of Medicine flu report, the "current ongoing epidemic of H5N1 avian influenza in Asia is unprecedented in its scale, in its spread, and in the economic losses it has caused."

*In short, doom "**may**" loom.*

If the relentlessly evolving virus becomes capable of human-to-human transmission, develops a power of contagion typical of human influenzas, and maintains its extraordinary virulence, humanity could well face a pandemic unlike any ever witnessed. Or nothing at all could happen. Scientists cannot predict with certainty what this H5N1 influenza will do. Evolution does not function on a knowable timetable, and influenza is one of the sloppiest, most mutation-prone pathogens in nature's storehouse.

Such absolute uncertainty, coupled with the profound potential danger, is disturbing for those whose job it is to ensure the health of their community, their nation, and broader humanity.

The entire world could experience levels of viral carnage as never before, and those areas ravaged by HIV and home to millions of immunocompromised individuals might witness even greater death tolls. In response, some countries might impose useless but highly disruptive quarantines or close borders and airports, perhaps for months. Such closures would disrupt trade, travel, and productivity. No doubt the world's stock markets would teeter and perhaps fall precipitously. Aside from economics, the disease would likely directly affect global security, reducing troop strength and capacity for all armed forces, UN peacekeeping operations, and police worldwide.

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In a world where most of the wealth is concentrated in less than a dozen nations representing a distinct minority of the total population, the capacity to respond to global threats is, to put it politely, severely imbalanced. The majority of the world's governments not only lack sufficient funds to respond to a superflu; they also have no health infrastructure to handle the burdens of disease, social disruption, and panic.

The international community would look to the United States, Canada, Japan, and Europe for answers, vaccines, cures, cash, and hope. How these wealthy governments responded, and how radically the death rates differed along worldwide fault lines of poverty, would resonate for years thereafter.

WHAT ONCE WAS LOST

Nearly half of all deaths in the United States in 1918 were flu related. Some 675,000 Americans -- about 0.6 percent of the population of 105 million and the equivalent of 2 million American deaths today -- perished from the Spanish flu. The average life expectancy for Americans born in 1918 was just 37 years, down from 55 in 1917. Although doctors then lacked the technology to test people's blood for flu infections, scientists reckon that the Spanish flu had a mortality rate of just less than one percent of those who took ill in the United States. It would have been much worse had there not been milder flu epidemics in the 1850s and in 1889, caused by similar but less virulent viruses, which made most elderly Americans immune to the 1918-19 strain. The highest death tolls were among young adults, ages 20-35.

The Spanish flu got its name because Spain suffered from an early and acute outbreak, but it did not originate there. Its actual origin remains uncertain. The first strain was mild enough to prompt most World War I military forces to dismiss it as a pesky ailment. When the second strain hit North America in the summer of 1918, however, the virus caused a surge of deaths. First hit was Camp Funston, an army base in Kansas, where young soldiers were preparing for deployment to Europe. The virus then spread swiftly to other camps and on troop ships crossing the Atlantic, killing 43,000 U.S. military personnel in about three months. Despite the entreaties of the military's surgeons general, President Woodrow Wilson ordered continued shipments of troops aboard crowded naval transports, which soldiers came to call "death ships." By late September 1918, so overwhelmed was the War Department by influenza that the military could not assist in controlling civic disorder at home, including riots caused by epidemic hysteria. Worse, so many doctors, scientists, and lab technicians had been drafted into military service that civilian operations were hamstrung.

Under these conditions, influenza swept from the most populous U.S. cities to extraordinarily remote rural areas. Explorers discovered empty Inuit villages in what are now Alaska and the Yukon Territory, their entire populations having succumbed to the flu. Many deaths were never included in the pandemic's official death toll -- such as the majority of victims in Africa, Latin America, Indonesia, the Pacific Islands, and Russia (then still in the throes of revolution). What is known about the toll in these regions is staggering. For example, influenza killed 5 percent of the population of Ghana in only two months, and nearly 20 percent of the people of Western Samoa died. The official estimate of 40-50 million total deaths is believed to be a conservative extrapolation of European and American records. In fact, many historians and biologists believe that nearly a third of all humans suffered from influenza in 1918-19 -- and that of these, 100 million died.

In the last years of the nineteenth century and the early years of the twentieth, a series of important scientific discoveries spawned a revolution in biology and medicine and led pioneers such as Hermann Biggs, a New York City doctor, to create entire legal and health systems based on the identification and control of germs. By 1917, the United States and much of Europe had become enthralled by the hygiene movement.

Impressive new public health infrastructures had been built in many cities, tens of thousands of tuberculosis victims were isolated in sanatoriums, the incidences of child-killing diseases such as diphtheria and typhoid fever had plummeted, and cholera epidemics had become rare events in the industrialized world. There was great optimism that modern science held the key to perfect health.

Influenza's arrival shattered the hope; scientists still had virtually no understanding of viruses generally, and of influenza in particular. The hygienic precautions and quarantines that had proved so effective in holding back the tide of bacterial diseases in the United States proved useless, even harmful, in the face of the Spanish flu. As the epidemic spread, top physicians and scientists claimed its cause was everything from tiny plants to old dusty books to something called "cosmic influence." It was not until 1933 that a British research team finally isolated and identified the influenza virus.

Most strains of the flu do not kill people directly; rather, death is caused by bacteria, which surge into the embattled lungs of the victim. But the Spanish flu that circulated in 1918-19 was a direct killer. Victims suffered from acute cyanosis, a blue discoloration of the skin and mucous membranes. They vomited and coughed up blood, which also poured uncontrollably from their noses and, in the case of women, from their genitals. The highest death toll occurred among pregnant women: as many as 71 percent of those infected died. If the woman survived, the fetus invariably did not. Many young people suffered from encephalitis, as the virus chewed away at their brains and spinal cords. And millions experienced acute respiratory distress syndrome, an immunological condition in which disease-fighting cells so overwhelm the lungs in their battle against the invaders that the lung cells themselves become collateral damage, and the victims suffocate. Had antibiotics existed, they may not have been much help.

OOPS

In January 1976, 18-year-old Private David Lewis staggered his way through a forced march during basic training in a brutal New Jersey winter. By the time his unit returned to base at Fort Dix, Lewis was dying. He collapsed and did not respond to his sergeant's attempts at mouth-to-mouth resuscitation.

In subsequent weeks, U.S. Army and CDC scientists discovered that the virus that had killed Lewis was swine flu. Although no other soldiers at Fort Dix died, health officials panicked. F. David Matthews, then secretary of health, education, and welfare, promptly declared, "There is evidence there will be a major flu epidemic this coming fall. The indication is that we will see a return of the 1918 flu virus that is the most virulent form of flu. In 1918, a half million people died [in the United States]. The projections are that this virus will kill one million Americans in 1976."

At the time, it was widely believed that influenza appeared in cycles, with especially lethal forms surfacing at relatively predictable intervals. Since 1918-19, the United States had suffered through influenza pandemics in 1957-58 and 1968-69; the first caused 70,000 deaths and the second 34,000. In 1976, scientists believed the world was overdue for a more lethal cycle, and the apparent emergence of swine flu at Fort Dix seemed to signal that another wave had come. The leaders of the CDC and the Department of Health, Education, and Welfare (HEW) warned the White House that there was a reasonably high probability that a catastrophic flu pandemic was about to hit. But opinion was hardly unanimous, and many European and Australian health authorities scoffed at the Americans' concern.

Unsure of how to gauge the threat, President Gerald Ford summoned the polio-fighting heroes Jonas Salk and Albert Sabin to Washington and found the long-time adversaries in remarkable accord: a flu pandemic might truly be on the way.

On March 24, 1976, Ford went on national television. "I have just concluded a meeting on a subject of vast importance to all Americans," he announced. "I have been advised that there is a very real possibility that unless we take effective counteractions, there could be an epidemic of this dangerous disease next fall and winter here in the United States. ... I am asking Congress to appropriate $135 million, prior to the April recess, for the production of sufficient vaccine to inoculate every man, woman, and child in the United States."

Vaccine producers immediately complained that they could not manufacture sufficient doses of vaccine in such haste without special liability protection. Congress responded, passing a law in April that made the government responsible for the companies' liability. When the campaign to vaccinate the U.S. population started four months later, there were almost immediate claims of side effects, including the neurologically debilitating Guillain Barré Syndrome. Most of the lawsuits -- with claims totaling $3.2 billion -- were settled or dismissed, but the U.S. government still ended up paying claimants around $90 million.

Swine flu, however, never appeared. The head of the CDC was asked to resign, and Congress never again considered assuming the liability of pharmaceutical companies during a potential epidemic. The experience weakened U.S. credibility in public health and helped undermine the stature of President Ford. Subsequently, an official assessment of what went wrong was performed for HEW by Dr. Harvey Fineberg, a Harvard professor who is currently president of the Institute of Medicine.

Fineberg concluded:"In this case the consequences of being wrong about an epidemic were so devastating in people's minds that it wasn't possible to focus properly on the issue of likelihood. Nobody could really estimate likelihood then, or now. The challenge in such circumstances is to be able to distinguish things so you can rationally talk about it. In 1976, some policymakers were simply overwhelmed by the consequences of being wrong. And at a higher level [in the White House] the two -- likelihood and consequence -- got meshed."

Fineberg's warnings are well worth remembering today, as scientists nervously consider H5N1 avian influenza in Asia. The consequences of a form of this virus that is transmittable from human to human, particularly if it retains its unprecedented virulence, would be disastrous. But what is the likelihood that such a virus will appear?

DEVOLUTION

Understanding the risks requires understanding the nature of H5N1 avian flu specifically and influenza in general. Influenza originates with aquatic birds and is normally carried by migratory ducks, geese, and herons, usually without harm to them. As the birds migrate, they can pass the viruses on to domesticated birds -- chickens, for example -- via feces or during competitions over food, territory, and water. Throughout history, this connection between birds and the flu has spawned epidemics in Asia, especially southern China. Aquatic flu viruses are more likely to pass into domestic animals -- and then into humans -- in China than anywhere else in the world. Dense concentrations of humans and livestock have left little of China's original migratory route for birds intact. Birds that annually travel from Indonesia to Siberia and back are forced to land and search for sustenance in farms, city parks, and industrial sites.

For centuries, Chinese farmers have raised chickens, ducks, and pigs together, in miniscule pens surrounding their homes, greatly increasing the chance of contamination: influenza can spread from migrating to domestic birds and then to swine, mutating and eventually infecting human beings.

Ominously, as China's GDP grows, so do the expensive appetites of the country's 1.3 billion people, more of whom can afford to eat chicken regularly. Today, China annually raises about 13 billion chickens, 60 percent of them on small farms. Chicken farming is quickly morphing into a major industry, with some commercial poultry plants rivaling those in Arkansas and Georgia in scale -- but lagging behind in hygienic standards. These factors favor rapid influenza evolution. By the close of the twentieth century, at least two new types of human-to-human flu spread around the world every year.

Influenza viruses contain eight genes, composed of RNA and packaged loosely in protective proteins. Like most RNA viruses, influenza reproduces sloppily: its genes readily fall apart, and it can absorb different genetic material and get mixed up in a process called reassortment. When influenza successfully infects a new species -- say, pigs -- it can reassort, and may switch from being an avian virus to a mammalian one. When that occurs, a human epidemic can result. The transmission cycles and the constant evolution are key to influenza's continued survival, for were it to remain identical year after year, most animals would develop immunity, and the flu would die out. This changing form explains why influenza is a seasonal disease. Vaccines made one year are generally useless the following.

Among the eight influenza genes there are two, dubbed H and N, that provide the code for proteins recognized by the human immune system. Scientists have numbered the many types of H and N proteins and use this system to classify a virus. A different viral combination of H and N proteins will trigger a different human immune response. For example, if a strain of H2N3 influenza circulates one year, followed by a different variety of H2N3 the next year, most people will be at least partially immune to the second strain. But if an H2N3 season is followed by an outbreak of H3N5 influenza, few people will have any immunity to the second virus, and the epidemic could be enormous. But a widespread epidemic need not be a severe or particularly deadly one: a virus' virulence depends on genes other than the two that control the H and N proteins.

Scientists first started saving flu virus samples in the early twentieth century. Since that time, an H5N1 influenza has never spread among human beings. According to the World Health Organization (WHO), "No virus of the H5 subtype has probably ever circulated among humans, and certainly not within the lifetime of today's world population. Population vulnerability to an H5N1-like pandemic virus would be universal." As for virulence, within about 48 hours of infection, H5N1 avian influenza kills 100 percent of infected chickens -- although the virulence of a potential human-to-human transmissible H5N1 is impossible to predict.

A team of Chinese scientists has been tracking the H5N1 virus since it first emerged in Hong Kong in 1997, killing 6 people and sickening 18 others. The strain came out of southern China's Guangdong Province, where it apparently was carried by ducks, and hit Hong Kong's chicken population hard. After authorities there killed 1.5 million chickens -- almost every single one in Hong Kong -- the outbreak seemed to stop. But the virus had not disappeared; rather, it had retreated to China's Guangdong, Hunan, and Yunnan provinces, spreading once again to aquatic birds.

From 1998 to 2001 the virus went through multiple reassortments and moved back to domestic birds, spreading almost unnoticed in Chinese chicken flocks. It continued to evolve at high speed: 17 more reassortments occurred, and in January 2003 the "Z" virus emerged, a mutant powerhouse that had become tougher, capable of withstanding a wider range of environmental challenges. The Z virus spread to Vietnam and Thailand, where it evolved further, becoming resistant to one of the two classes of antiflu drugs, known as amantadines, or M2-inhibitors.

In early 2004, it became supervirulent and capable of killing a broad range of species, including rodents and humans. That permutation of the virus was dubbed "Z+." In the first three weeks of January 2004, Z+ killed 11 million chickens in Vietnam and Thailand. By April 2004, 120 million chickens in Asia had died of flu or been exterminated to slow the influenza brushfire. The avian epidemic stopped for a while, but in July another 1 million chickens died from the disease. The Z+ virus was causing massive internal bleeding in the birds. By the beginning of 2005, with chickens dying and customers shying away from what remained, the Asian poultry industry had lost nearly $15 billion.

By April 2005, the H5N1 virus had also moved to pigs. Scientists isolated the disease from swine in a part of Indonesia where pigs are raised underneath elevated wood-slatted platforms that house chickens. Less rigorous investigations had previously indicated that pigs in China and Vietnam may also have been infected by H5N1 influenza. The discovery in Indonesia provided disturbing evidence that the virus was infecting mammals, although it was not yet known how widely the swine disease had spread or how lethal it was for the animals.

HARD TO KILL

Over the course of this brief but rapid evolution, the H5N1 virus developed in ways unprecedented in influenza research. It is not only incredibly deadly but also incredibly difficult to contain. The virus apparently now has the ability to survive in chicken feces and the meat of dead animals, despite the lack of blood flow and living cells; raw chicken meat fed to tigers in Thailand zoos resulted in the deaths of 147 out of a total of 418. The virus has also found ways to vastly increase the range of species it can infect and kill. Most strains of influenza are not lethal in lab mice, but Z+ is lethal in 100 percent of them.

It even kills the very types of wild migratory birds that normally host influenza strains harmlessly. Yet domestic ducks, for unknown reasons, carry the virus without a problem, which may explain where Z+ hides between outbreaks among chickens.

Traditional Asian methods of buying, slaughtering, and cooking meat make it hard to track the spread of an influenza virus -- and tracking it is critical to preventing the disease from spreading. In Asia, consumers prefer to buy live chickens and other live animals at the market, slaughtering them in home kitchens. Asians thus have a high level of exposure to potentially disease-carrying animals, both in their homes and as they pass through the markets that line the streets of densely packed urban centers. For someone trying to trace a disease, Asia is a nightmare: with people daily exposed to live chickens in so many different environments, how can a sleuth tell whether an ailing flu victim was infected by a chicken, a duck, a migratory heron -- or another human being?

Although most of the 109 known human H5N1 infections have been ascribed to some type of contact with chickens, mysteries abound, and many cases remain unsolved. "The virus is no longer causing large and highly conspicuous outbreaks on commercial farms," a 2005 WHO summary of the human Z+ cases states.

"Nor have poultry workers or cullers turned out to be an important risk group that could be targeted for protection. Instead, the virus has become stealthier: human cases are now occurring with no discernible exposure to H5N1 through contact with diseased or dead birds."

If proximity to infected animals is the key, why have there been no deaths among chicken handlers, poultry workers, or live-chicken dealers? The majority of the infected have been young adults and children. And there has been one documented case of human-to-human transmission of the Z+ strain of the H5N1 virus -- in late 2004, in Thailand. Several more such cases are suspected but cannot be confirmed. According to the WHO, there is "no scientific explanation for the unusual disease pattern."

Assessing and understanding H5N1's virulence in humans has also proved elusive. When it first appeared in Hong Kong in 1997, the virus killed 35 percent of those it was known to have infected. (Less severe cases may not have been reported.) The Z strain of the disease, which emerged in early 2003, killed 68 percent of those known to have been infected. In H5N1 cases since December 2004, however, the mortality has been 36 percent. How can the fluctuation over time be explained? One disturbing possibility is that H5N1 has begun adapting to its human hosts, becoming less deadly but easier to spread. In the spring of 2005, in fact, H5N1 infected 17 people throughout Vietnam, resulting in only three deaths. Leading flu experts argue that this sort of phenomenon has in the past been a prelude to human influenza epidemics.

The medical histories of those who have died from H5N1 influenza are disturbingly similar to accounts of sufferers of the Spanish flu in 1918-19. Otherwise healthy people are completely overcome by the virus, developing all of the classic flu symptoms: coughing, headache, muscle pain, nausea, dizziness, diarrhea, high fever, depression, and loss of appetite. But these are just some of the effects. Victims also suffer from pneumonia, encephalitis, meningitis, acute respiratory distress, and internal bleeding and hemorrhaging. An autopsy of a child who died of the disease in Thailand last year revealed that the youth's lungs had been torn apart in the all-out war between disease-fighting cells and the virus.

BAD MEDICINE

According to test-tube studies, Z+ ought to be vulnerable to the antiflu drug oseltamivir, which the Roche pharmaceuticals company markets in the United States under the brand name Tamiflu. Yet Tamiflu was given to many of those who ultimately succumbed to the virus; it is believed that medical complications induced by the virus, including acute respiratory distress syndrome, may have prevented the drug from helping. It is also difficult to tell whether the drug contributed to the survival of those who took it and lived, although higher doses and more prolonged treatment may have a greater impact in fighting the disease. A team of Thai clinicians recently concluded that "the optimal treatment for case-patients with suspected H5 infection is not known." Lacking any better options, the WHO has recommended that countries stockpile Tamiflu to the best of their ability. The U.S. Department of Health and Human Services is doing so, but supplies of the drug are limited and it is hard to manufacture.

What about developing a Z+ vaccine? Unfortunately, there is only more gloom in the forecast. The total number of companies willing to produce influenza vaccines has plummeted in recent years, from more than two dozen in 1980 to just a handful in 2004. There are many reasons for the decline in vaccine producers. A spate of corporate mergers in the 1990s, for example, reduced the number of major international pharmaceutical companies. The financial risk of investing in vaccines is also a key factor. In 2003, the entire market for all vaccines -- from polio to measles to hepatitis to influenza -- amounted to just $5.4 billion.

Although that sum may seem considerable, it is less than two percent of the global pharmaceutical market of $337.3 billion. Unlike chemical compounds, vaccines and most other biological products are difficult to make and can easily become contaminated. There is also a large and litigious antivaccine constituency -- some people believe that vaccines cause harmful side effects such as Alzheimer's disease and autism -- adding considerable liability costs to manufacturers' bottom lines.

The production of influenza vaccines holds particular drawbacks for companies. Flu vaccines must be made rapidly, increasing the risk of contamination or other errors. Because of the seasonal nature of the flu, a new batch of influenza vaccines must be produced each year. Should sales in a given year prove disappointing, flu vaccines cannot be stockpiled for sale in a subsequent season because by then the viruses will have evolved. In addition, the manufacturing process of flu vaccines is uniquely complex: pharmaceutical companies must grow viral samples on live chicken eggs, which must be reared under rigorous hygienic conditions. Research is under way on reverse genetics and cellular-level production techniques that might prove cheaper, faster, and less contamination-prone than using eggs, but for the foreseeable future manufacturers are stuck with the current laborious method. After cultivation, samples of the viruses must be harvested, the H and N characteristics must be shown to produce antibodies in test animals and human volunteers, and tests must prove that the vaccine is not contaminated. Only then can mass production commence.

The H5N1 strain of avian flu poses an additional problem: the virus is 100 percent lethal to chickens -- and that includes chicken eggs. It took researchers five years of hard work to devise a way to grow the 1997 version of the H5N1 virus on eggs without killing them; although there have been technological improvements since then, there is no guarantee that an emerging pandemic strain could be cultivated fast enough.

In the current system, all influenza vaccines must be quickly made following a WHO meeting of flu experts held every February. At that gathering, scientists scrutinize all available information on the flu strains known to be circulating in the world. They then try to predict which strains are most likely to spread across every continent in the next six to nine months. (This year the WHO committee chose three human flu strains, of types H3N2 and H1N1, to be the basis of the next vaccine.) Samples of the chosen strains are delivered to pharmaceutical companies around the world for vaccine production, and the vaccines are hopefully available to the public by September or October -- a few months after influenza typically strikes Asia, in the early summer. Europe and the Americas are usually hit shortly after, in September. Because viruses constantly change themselves, the process cannot be executed earlier in the year.

Although new technology may allow an increase in production capacity, manufacturers have never made more than 300 million doses of flu vaccine in a single year. The slow pace of production means that in the event of an H5N1 flu pandemic millions of people would likely be infected well before vaccines could be distributed.

GLOBAL REACH

The scarcity of flu vaccine, although a serious problem, is actually of little relevance to most of the world. Even if pharmaceutical companies managed to produce enough effective vaccine in time to save some privileged lives in Europe, North America, Japan, and a few other wealthy nations, more than six billion people in developing countries would go unvaccinated. Stockpiles of Tamiflu and other anti-influenza drugs would also do nothing for those six billion, at least 30 percent of whom -- and possibly half -- would likely get infected in such a pandemic.

Resources are so scarce that both wealthy and poor countries would be foolish to count on the generosity of their neighbors during a global outbreak. Were the United States to miraculously overcome its vaccine production problems and produce ample supplies for U.S. citizens, Washington would probably deny the vaccine to neighbors such as Mexico, since governments tend to reserve vaccine supplies for their own citizens during emergencies. Were the United States to falter, it would probably not be able to rely on Canadian or European generosity, as it did just last year. When the United Kingdom suspended the license for the Chiron Corporation's U.K. production facility for flu vaccine due to contamination problems, Canada and Germany bailed the United States out, supplying additional doses until the French company Sanofi Pasteur could manufacture more. Even with this assistance, however, the United States' vaccine needs were not fully met until February 2005 -- the tail end of the flu season.

In the event of a deadly influenza pandemic, it is doubtful that any of the world's wealthy nations would be able to meet the needs of their own citizenry -- much less those of other countries. Domestic vaccine purchasing and distribution schemes currently assume that only the very young, the elderly, and the immunocompromised are at serious risk of dying from the flu. That assumption would have led health leaders in 1918 to vaccinate all of the wrong people. Then, the young and the old fared relatively well, while those aged 20 to 35 -- today typically the lowest priority for vaccination -- suffered the most deaths from the Spanish flu. And so far, H5N1 influenza looks like it could have a similar effect: its human victims have all fallen into age groups that would not be on national vaccine priority lists, and because H5N1 has never circulated among humans before, it is highly conceivable that all ages could be susceptible.

Every year, trusting that the flu will kill only the usual risk groups, the United States plans for 185 million vaccine doses. If that guess were wrong -- if all Americans were at risk -- the nation would need at least 300 million doses. That is what the entire world typically produces each year.

There would thus be a global scramble for vaccine. Some governments might well block foreign access to supplies produced on their soil and bar vaccine export. Since little vaccine is actually made in the United States, this could prove a problem for Americans in particular. Facing such limited supplies, the U.S., European, and Japanese governments might give priority to vaccinating heads of state around the world in hopes of limiting social chaos. But who among the elite would be eligible? Would their families be included? How could such a global triage be executed justly?

A similar calculus might be necessary for countries engaged in significant military operations. Troop movements would certainly help spread the disease, just as World War I aided the growth of the 1918-19 Spanish flu. Back then, the flu wreaked havoc on combatant nations. In the summer of 1918, influenza killed far more soldiers than did bombs, bullets, or mustard gas. By October, some 46 percent of the French army was off the field of battle -- ailing, dying, or caring for flu victims. Influenza death tolls among the various military forces generally ranged from 5 to 10 percent, but some segments fared even worse: historian John Barry has reported that 22 percent of the Indian members of the British military died.

In the event of a modern pandemic, the U.S. Department of Defense, with the lessons of World War I in mind, would undoubtedly insist that U.S. troops in Iraq and Afghanistan be given top access to vaccines and antiflu drugs. About 170,000 U.S. forces are currently stationed in Iraq and Afghanistan, while 200,000 more are permanently based elsewhere overseas. All of them would potentially be in danger: in late March, for example, North Korea conceded it was suffering a large-scale H7N1 outbreak -- taking place within miles of some 41,000 U.S. military forces. It is impossible to predict how such a pandemic influenza would affect U.S. operations in Iraq, Afghanistan, Colombia, or any other place.

Armed forces throughout the world would face similar issues. Most would no doubt pressure their governments for preferential access to vaccine and medications. In addition, more than a quarter of some African armies and police forces are HIV positive, perhaps making them especially vulnerable to influenza's lethal impact. Social instability resulting from troop and police losses there would likely be particularly acute.

Such a devastating disease would clearly have profound implications for international relations and the global economy. With death tolls rising, vaccines and drugs in short supply, and the potential for the virus to spread further, governments would feel obliged to take drastic measures that could inhibit travel, limit worldwide trade, and alienate their neighbors. In fact, the Z+ virus has already demonstrated its disruptive potential on a limited scale. In July 2004, for example, when the Z+ strain reemerged in Vietnam after a three-month hiatus, officials in the northern province of Bac Giang charged that Chinese smugglers were selling old and sickly birds in Vietnamese markets -- where more than ten tons of chickens are smuggled daily. Chinese authorities in charge of policing their side of the porous border, more than 1,000 kilometers long, countered that it was impossible to inspect all the shipments.

Such conflicts are now limited to the movement of livestock, but if a pandemic develops they could well escalate to a ban on trade and human movement.

Although there is little evidence that isolation measures have ever slowed the spread of influenza -- it is just too contagious -- most governments would likely resort to quarantines in a pandemic crisis. Indeed, on April 1, 2005, President George W. Bush issued an executive order authorizing the use of quarantines inside the United States and permitting the isolation of international visitors suspected of carrying influenza. If one country implements such orders, others will follow suit, bringing legal international travel to a standstill. The SARS (severe acute respiratory syndrome) virus, which was less dangerous than a pandemic flu by several orders of magnitude, virtually shut down Asian travel for three months.

As great as they would be, the economic consequences of travel restrictions, quarantines, and medical care would be well outstripped by productivity losses. In a typical flu season, productivity costs are ten times greater than all other flu-related costs combined. The decline in productivity is usually due directly to worker illness and absenteeism. During a pandemic, productivity losses would be even more disproportionate because entire workplaces -- schools, theaters, and public facilities -- would be shut down to limit human-to-human spread of the virus. Workers' illnesses also would likely be even more severe and last even longer than normal. Frankly, no models of social response to such a pandemic have managed to factor in fully the potential effect on human productivity. It is therefore impossible to reckon accurately the potential global economic impact.

AILING

The potential for a pandemic comes at a time when the world's public health systems are severely taxed and have long been in decline. This is true in both rich and poor countries.

The Bush administration recognized this weakness following the anthrax scare of 2001, which underscored the poor ability of federal and local health agencies to respond to bioterrorism or epidemic threats.

Since that year, Congress has approved $3.7 billion to strengthen the nation's public health infrastructure. In 2003, the White House also took several steps to improve the nation's capacity to respond to a flu pandemic: it increased funding for the CDC's flu program by 242 percent, to $41.6 million in 2004; gave the National Institutes of Health an additional 320 percent in funds for flu-related research and development, for a total of $65.9 million; increased spending on the Food and Drug Administration's licensing capacity for flu vaccines and drugs by 173 percent, to $2.6 million; and spent an additional $80 million to create new stockpiles of Tamiflu and other anti-influenza drugs. On August 4, 2004, the Department of Health and Human Services also issued its pandemic flu plan, detailing further steps that would be taken by federal and state agencies in the event of a pandemic. Several other countries have released similar plans of action.

But despite all this, a recent event underscored the United States' tremendous vulnerability. In October 2004, the American College of Pathologists mailed a collection of mystery microbes prepared by a private lab to almost 5,000 labs in 18 countries for them to test as part their recertification.

The mailing should have been routine procedure; instead, in March 2005 a Canadian lab discovered that the test kits included a sample of H2N2 flu -- a strain that had killed four million people worldwide in 1957. H2N2 has not been in circulation since 1968, meaning that hundreds of millions of people lack immunity to it. Had any of the samples leaked or been exposed to the environment, the results could have been devastating. On learning of the error, the WHO called for the immediate destruction of all the test kits. Miraculously, none of the virus managed to escape any of the labs.

But the snafu raises serious questions: If billions have been spent to improve laboratory capabilities since 2001, why did nobody notice the H2N2 flu until about six months after the kits had been shipped? Why did a private company possess samples of the virulent flu? Why was the sample included in the kits? In the aftermath of the September 11, 2001, attacks and the anthrax scare, many countries reclassified 1957-58 and 1968-69 influenza strains as Level 3 pathogens, requiring extreme care in their handling, distribution, and storage -- why did the United States still consider H2N2 to be a mere Level 2 pathogen, a type frequently mailed and studied? Finally, around the world, what other labs -- public and private -- currently possess samples of such lethal influenza viruses? The official CDC answer to these questions is, "We don't know."

Even with all of these gaps, probably the greatest weakness that each nation must individually address is the inability of their hospitals to cope with a sudden surge of new patients. Medical cost cutting has resulted in a tremendous reduction in the numbers of staffed hospital beds in the wealthy world, especially in the United States. Even during a normal flu season, hospitals located in popular retirement areas have great difficulty meeting the demand. In a pandemic, it is doubtful that any nation would have adequate medical facilities and personnel to meet the extra need.

National policymakers would be wise to plan now for worst-case scenarios involving quarantines, weakened armed services, and dwindling hospital space and vaccine supplies. But at the end of the day, effectively combating influenza will require multilateral and global mechanisms. Chief among them, of course, is the WHO, which since 1947 has maintained a worldwide network that conducts influenza surveillance. The WHO system oversees laboratories all over the world, chases (and sometimes refutes) rumors of pandemics, pushes for government transparency regarding human and avian flu cases, and acts as an arbiter in negotiations over vaccine production, trade embargoes, and border disputes. Its companion UN agency, the Food and Agriculture Organization (FAO), working closely with the World Organization for Animal Health, monitors flu outbreaks in animal populations and advises governments on culling flocks and herds, cross-border animal trade, animal husbandry and slaughter, and livestock quarantine and vaccination.

All of these organizations have published lengthy guidelines on how to respond to a pandemic flu, lists of answers to commonly asked questions, and descriptions of their research priorities -- most of which have been posted on their Web sites.

The efforts of these agencies should be bolstered, both with expertise and dollars. The WHO, for example, has an annual core budget of just $400 million, a tiny increment of which is spent on influenza- and epidemic-response programs. (In comparison, the annual budget of New York City's health department exceeds $1.2 billion.) An unpublished internal study estimates that the agency would require at least another $600 million for its flu program were a pandemic to erupt.

It is in every government's interest to give the WHO and the FAO the authority to act as impartial voices during a pandemic, able (theoretically) to assess objectively the epidemic's progress and rapidly evaluate research claims. The WHO in particular must have adequate funding and personnel to serve as an accurate clearinghouse of information about the disease, thereby preventing the spread of false rumors and global panic. No nation can erect a fortress against influenza -- not even the world's wealthiest country.

Few members of the U.S. Congress or its legislative counterparts around the world were alive when the great Spanish flu swept the planet. There may be some who lost parents, aunts, or uncles to the 1918-19 pandemic, and perhaps even more have heard the horror stories that were passed down. But politics breeds shortsightedness, and for decades the threat of an influenza pandemic has been easily forgotten, and therefore ignored at budget time. Politicians and health leaders made many serious errors in 1918-19; some historians say that President Wilson sent 43,000 soldiers to their deaths by forcing them aboard crowded ships to join a war he had already won. But in those days, human beings had no understanding of their influenza foe.

In 1971, the great American public health leader Alexander Langmuir likened flu forecasting to trying to predict the weather, arguing that "as with hurricanes, pandemics can be identified and their probable course projected so that warnings can be issued. Epidemics, however, are more variable [than hurricanes], and the best that can be done is to estimate probabilities."

Since Langmuir's time a quarter of a century ago, weather forecasting has gained a stunning level of precision. And although scientists cannot tell political leaders when an influenza pandemic will occur, researchers today are able to guide policymakers with information and analysis exponentially richer than that which informed the decisions of President Ford and the 1976 Congress. Whether or not this particular H5N1 influenza mutates into a human-to-human pandemic form, the scientific evidence points to the potential that such an event will take place, perhaps soon. Those responsible for foreign policy and national security, the world over, cannot afford to ignore the warning.