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Avian influenza

Sense of urgency required to minimize effects of potential pandemic

When the National Hurricane Center warns coastal communities that a tropical storm is approaching, governments designate shelters and residents rush to purchase supplies. Upgrade the threat sufficiently, and evacuations will be ordered. As television and newspaper images of highways packed with fleeing residents testify, few choose to “ride out the storm.”

Since time began, human beings have learned to heed warning signs they are given and to prepare for emergencies. The projected threat may not materialize, but comfort is taken in knowing one is ready for whatever may happen.

However, such preparations are not being made in response to a major threat looming in the near future. The skies have been darkening since 1997, and very few people are heeding the signs of the gathering storm: H5N1, a strain of avian influenza that many experts consider the biggest health threat facing the world today.

This edition of The Lipman Report takes a look at recent developments in research regarding H5N1, the threat it poses and what steps are needed to mitigate the threat.

‘A Trojan horse’

Since it first surfaced in 1997 in China, the H5N1 virus that causes avian influenza has been found only in Asia, where it has resulted in the death or slaughter of hundreds of millions of birds and has killed at least 55 people in Vietnam, Thailand, Cambodia and Indonesia. Usually, human infection comes from contact with infected poultry such as chickens, but there have been three documented clusters of human-to-human transmission, including one that did not involve any contact with chickens. It is the possibility – some say inevitability – that H5N1 will mutate and become easily transmitted person-to-person that has scientists concerned about a global pandemic.

Avian influenza viruses are known for mutating. They reproduce rapidly, changing form, building resistance to drugs and infecting a broad range of species. That is why influenza is impossible to eradicate. Each year, the annual influenza vaccine is developed and administered based on which flu viruses experts view most likely to be prevalent.

According to Laurie Garrett, Senior Fellow for Global Health at the Council on Foreign Relations and an award-winning journalist who covers medical issues, the fact that initial tests suggest an experimental human vaccine may be effective against avian influenza cannot be met with a sigh of relief and a belief that the threat of a global pandemic will be averted. Unfortunately, favorable test results occurred only in volunteers who received the highest vaccine doses, meaning that limited supplies could not be diluted for use in a large number of people. History shows no indication that the world could mass-produce the millions of vaccine doses required in a timely manner. In addition, the strain of H5N1 for which the vaccine was created may not resemble the form of virus that ultimately becomes transmitted from person-to-person, thereby rendering it ineffective. As a result, it is necessary to continue monitoring the virus for genetic changes and to modify treatment and vaccine preparations accordingly. Proactive planning must also address how to effectively distribute vaccine supplies to those in need, taking into consideration the fact that the vaccine would be prohibitively expensive to many countries.

Another effort by three pharmaceutical companies focuses on developing a “universal” vaccine that targets M2e, a protein found in all type A influenza viruses. If successful, this vaccine would eliminate the need for a new and different flu vaccine every year. However, this concept is only in the development stage and if successful, still faces several years of research, testing and regulatory approval.

H5N1 has mutated several times and has become resistant to amantadine, one of two classes of antiviral medications that appear to lessen its severity. In June 2005, researchers concluded that at least part of the reason that drug is no longer effective is because Chinese farmers had for years been using it to suppress avian flu outbreaks among chickens, even though the drug is intended for humans. That leaves only one other

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antiviral medication that is effective against the virus: oseltamivir, or Tamiflu®. Many countries are stockpiling the drug, but the length of time required to manufacture it and the cost involved mean that national stores will never come close to what is needed to manage a global pandemic.

Chinese authorities in late April 2005 reported that more than 6,000 waterfowl at a nature reserve in the remote western province of Qinghai were infected. In May 2005, two more outbreaks were reported in Xinjiang among domestic geese and ducks.

The outbreaks are regarded as alarming and unusual because waterfowl have been generally unaffected by avian flu viruses unless they came into contact with infected domesticated birds. Avian flu spreads via migratory birds, which have already begun circulating on routes that extend from South Asia to India, Australia and Europe.

China has been slow to provide information on these outbreaks, which may be due in part to an internal dispute regarding whether the virus is widespread and what risk it poses to humans. One Chinese scientist published evidence in the journal *Nature* that contradicted the Chinese government by suggesting that avian flu did not originate outside China as the government has stated. The Chinese government issued an edict to scientists that nothing can be published or reported regarding avian influenza research without approval from a central clearinghouse. It is not clear if this move is to reduce the risk of panic over the potential for a pandemic or an example of China's reluctance to share information.

Late last month, Russian officials reported H5N1 had been identified as the virus that killed large numbers of ducks, geese, chickens and turkeys in the Novosibirsk region of Siberia, where migrating birds stop at the lakes. More recent research bolsters experts' suspicions that the virus is on the verge of breaking out of Asia. In July 2005, a team of researchers in the United

States reported that mutations have made the virus less deadly to ducks, which means these migratory birds can host the virus without getting sick and then pass it on to other birds and people.

"These results suggest that the duck has become the Trojan horse of Asian H5N1 influenza viruses," stated the team's report, published in the journal *Proceedings of the National Academy of Sciences*.

The virus has already shown an ability to jump species, going from birds to pigs, tigers, cats and other mammals. The virus absorbs genetic material from each species it circulates through, but the point at which it can become easily transmissible among humans is not known.

Frequent comparisons are made between the threat posed by H5N1 and the 1918 Spanish flu pandemic, which killed millions worldwide. During that pandemic, influenza circulated between the United States and Europe via the movement of troops fighting in World War I.

There was far less commercial travel then. In today's global economy, the spread of disease will happen much more quickly. Consider the 2003 outbreak of Severe Acute Respiratory Syndrome (SARS). SARS was spread from China to 26 other countries virtually overnight. Scientists were able to isolate the virus and develop a treatment, but not before more than 8,000 people were infected and 774 died.

Another frightening aspect of the H5N1 virus is that it has a reported 55 percent mortality rate among humans. A virus of the H5N1 combination has never circulated among humans. When it comes to the H5N1 virus, no one has immunity. If the virus becomes transmissible between humans, it will lose some of its potency, but even with a 5 percent mortality rate, it will still be the most lethal flu the world has seen.

Economic impact of a pandemic

In the United States, the garden-variety seasonal influenza costs the national economy more than

\$10 billion a year in lost productivity and direct medical expenses. More than 200,000 people are hospitalized, and 36,000 to 40,000 people die. Studies cited by the U.S. Centers for Disease Control and Prevention (CDC) indicate that a “medium-level” pandemic would cause 89,000 to 207,000 deaths in the United States, 314,000 to 734,000 hospitalizations, 18 million to 42 million outpatient visits and another 20 million to 27 million people sick. About one third of the U.S. population could be affected. Estimates of the economic impact of such a pandemic are between \$71.3 billion and \$166.5 billion. Already, avian influenza has cost regions in Asia some \$8 billion to \$12 billion, mainly in lost revenues from poultry and related industries.

The last pandemic occurred in 1968-1969, when the “Hong Kong flu” killed about 34,000 in the United States. Experts believe that the H5N1 virus is far more severe than the 1968 virus and would result in far more hospitalizations.

The CDC notes that a pandemic is different from other health threats for which the public health system prepares. A pandemic will last longer than other emergency events and may include waves of influenza activity. But, there is no clear way to predict how the virus will behave.

The number of health-care workers and first responders available to work could be reduced because they are at high risk of illness from exposure in health-care settings. The widespread nature of an influenza pandemic will cause resources to be spread thin in most locations.

The interdependent nature of the world economy means the effect on the United States would be felt immediately, regardless of where the pandemic first developed. Supply shortages in the health-care system would result from international shipping restrictions. To lessen the spread of the virus, limits on travel and public events would be imposed.

Some countries would certainly enforce quaran-

tines or border closings that would further disrupt travel, trade and productivity. Developing nations with uncertain political and economic environments would be further destabilized. The extent to which states and nations enforce border restrictions could result in lingering diplomatic and political fallout.

The WHO predicts that an H5N1 flu pandemic would affect about 25 percent of countries’ populations. CDC projections for the United States put that number at nearly 67 million individuals. As of May 2005, the United States had stockpiled 2.3 million courses of the antiviral medication Tamiflu® and was planning on ordering 3 million more. **At that level, the U.S. stockpile would only contain enough to treat 5.3 million people, leaving 61.5 million Americans likely to be infected but unable to receive antiviral medication.**

Even if increased supplies were ordered, with the present production capacity, additional doses of Tamiflu® would not be available until 2007. And since air travel would likely be restricted in the event of a pandemic, transporting Tamiflu® from the only factory that makes it, located in Switzerland, would be extremely difficult.

If a pandemic were to occur, the countries that can afford to stockpile the vaccine will want to keep it for their own citizens, regardless of where it could be best put to use. Of the 19 largest cities with populations greater than 10 million, only four are in the developed world.

Laurie Garrett noted that it is difficult to convince the nation to build up stockpiles of medications and supplies because everyone assumes health organizations will be able to identify a pandemic when it starts. “We don’t know how this virus, if it does make a jump, will behave,” she said.

Any vaccine, if developed, will be of little help if other countries are devastated by the pandemic

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and the world economy shuts down. The impact of a pandemic will be global, and it needs to be planned for accordingly.

Preparation is vital

“Clearly these are problems that have not been adequately addressed or considered,” said Garrett, author of *Betrayal of Trust: The Collapse of Global Public Health* and *The Coming Plague: Newly Emerging Diseases in a World Out of Balance*. While the WHO and many nations have been planning for a pandemic, not nearly enough has been done. Most scientists say the coming pandemic – whether this year, next year or years from now – cannot be avoided. They do say, however, that its impact can be lessened.

Leaders on the global, national and local level must realize the importance of investing in preparation. World leaders must pressure all countries for cooperation in sharing information and research about this disease and outbreaks that are affecting their countries. The speed with which a virus can travel today makes timely dissemination of information vitally important.

Private and public sectors should work together to develop emergency plans to maintain critical domestic supply chains as well as manufacturing and distribution. Communities will need to identify the commodities and services they need to survive 12 to 36 months. There will be an increased need for medical equipment and supplies, rendering some items unattainable. For example, only two companies in the world manufacture respiratory protection masks. Neither may be able to meet the demand caused by a pandemic, and even if they did, if all major transport systems shut down, they will have no way to ship them. Stockpiles of key materials need to be warehoused in strategic locations where they can be easily distributed even if most methods of transport are unavailable.

Companies need to develop a plan for protecting employees and ensuring business continuity.

Experts recommend that individuals receive flu vaccinations to protect against the more common strains of the virus. Companies should consider providing employees with information on the benefits of vaccination, as well as information on proper methods of hand washing – a key means of preventing the spread of disease. Businesses also need to rethink human resources policies to contend with a pandemic. In particular, executives need to evaluate the tendency of some employees to try to “tough it out” and come to work when ill. If a pandemic is raging, it may not be in a business’ best interest financially to have employees, either ill and contagious themselves or carrying a virus passed to them by a sick family member, come to work and infect the rest of the work force. Companies also should develop emergency response plans for a pandemic that include access control management

A worst-case scenario has the avian flu virus beginning its global spread in October or November 2005. A best-case scenario is that the virus never makes that jump between animals and humans that would lead to a pandemic.

The U.S. Secretary of Health and Human Services may have summarized it best in his remarks before a Ministerial Meeting on Avian Influenza held during the World Health Organization’s annual World Health Assembly in Geneva, Switzerland, on May 16, 2005:

“There is a time in the life of every problem when it is big enough to see and small enough to solve. For flu preparedness, that time is now.”



The Lipman Report Editors