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Preparing for pandemic flu

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The 2004-2005 influenza season thus far has been relatively mild in the United States, and public health officials hope current trends will persist through the end of the season.

However, a much greater flu threat worries world scientists and health officials -- a possible influenza pandemic caused by an emerging, highly virulent avian influenza virus.

What is pandemic influenza and how does it differ from the more familiar "interpandemic" or seasonal influenza we confront each year? Pandemic influenza is caused by an influenza virus so dramatically changed it is completely unfamiliar to our immune systems and can massively devastate immunologically "naive" populations. In contrast, seasonal influenza viruses change only slightly from year to year and most people harbor some residual immunity from prior exposure to identical or similar influenza viruses, which may be boosted by vaccination.

In the 20th century, mankind faced three influenza pandemics: the devastating 1918 "Spanish Flu" pandemic, as well as two less severe influenza pandemics in 1957 and 1968.

Today, health officials throughout the world fear the first influenza pandemic of this century is possible, because deadly new strains of avian influenza have emerged in Southeast Asia.

Most worrisome is the H5N1 influenza virus that first emerged in Hong Kong in 1997, infecting 18 people -- virtually all of whom had direct contact with domestic fowl. A massive culling of live birds prevented its further spread.

In the last two years, H5N1 has re-emerged with a vengeance. More than 50 confirmed human cases of H5N1 avian influenza have been reported since January 2004 in Vietnam, Thailand and Cambodia, and have resulted in the deaths of more than 40 people. In addition, the virus has killed millions of chickens and has expanded its host range by infecting other birds, pigs, tigers, leopards and domestic cats.

Unfortunately, we can only estimate the risk and timing of an influenza pandemic caused by the H5N1 virus by considering an escalating scale of what can best be described as "compounding probabilities."

To start with, there is no probability of a pandemic caused by H5N1 influenza if the virus does not exist in birds or other animals. It becomes slightly more probable if the virus appears in birds in a single country. It becomes slightly more probable again if it spreads to birds in many countries. Probability increases again if the virus begins to jump from birds to humans. A major increment in threat emerges in any human-to-human transmission. This is greatly compounded if the virus can efficiently spread from human to human.

In 2004, the H5N1 influenza virus spread to bird populations in 10 countries in Asia. Though the virus has jumped from birds to humans, it thus far has not acquired the ability to spread efficiently from human to human, though isolated cases of person-to-person transmission have been reported. If this form of transmission becomes widespread, a worldwide influenza pandemic is likely. Prevention will require a coordinated, multifaceted effort by agriculture and public health agencies, industry and biomedical researchers throughout the world.

Experts at the World Health Organization, the Centers for Disease Control and Prevention (CDC) and other health agencies have carefully monitored the recent H5N1 influenza outbreaks. In addition to ongoing surveillance of H5N1 outbreaks and the evolution of the virus, scientists throughout the world, including those supported by the CDC and the National Institutes of Health (NIH), are developing techniques for rapidly isolating and identifying new viral strains and cell-culture methods for more predictably and reliably growing the virus and upgrading vaccine production capacity. Several important projects are under way to improve production and use of influenza vaccine and to develop new treatments.

For example, by a technique called reverse genetics, researchers developed an H5N1 "seed virus" for vaccine production in a matter of weeks, a process that usually requires several months. NIH has contracted with vaccine manufacturers using this reference virus to produce pilot lots of inactivated H5N1 vaccine for phase 1 and phase 2 clinical trials. Trials are expected to begin in the next few months.

Several projects also are under way to rapidly sequence influenza genomes derived from multiple sources to understand how the viruses evolve, spread and cause disease, with the long-term goal of improved prevention and treatment. In addition, researchers are working to understand, at a molecular level, why the 1918 virus was so deadly and if any of the emerging avian viruses such as H5N1 share these characteristics. Such studies may help scientists identify molecular targets for new drugs and vaccines.

Strategies also are being evaluated to extend vaccine supplies by "dose-sparing approaches" such as diluting stocks, immunizing people directly into the skin rather than in muscle, or adding, substances that increase vaccine potency. Scientists are investigating the possibility of reducing influenza infection rates by immunizing healthy children and adults not at high risk for complications but likelier to spread virus to others.

As efforts advance to develop and produce vaccines against a potential pandemic virus, other research focuses on antiviral medications to prevent and treat influenza.

The H5N1 virus is resistant to two common influenza drugs, rimantadine and amantadine, but newly developed drugs such as oseltamivir (Tamiflu) and zanamivir (Relenza) appear to be effective in fighting the H5N1 virus. The Department of Health and Human Services and CDC have created a stockpile of Tamiflu for use during a possible influenza pandemic. New anti-influenza drugs are in the research pipeline.

Again, we do not yet know when the next influenza pandemic will occur, but the situation in Asia is alarming.

It is difficult to predict if H5N1 will be the virus that ultimately triggers the next influenza pandemic. Clearly, without a robust research program to develop the technology to rapidly detect and monitor evolving pathogens, to understand their disease-causing mechanisms, and to develop measures to block transmission, we are doomed to relive the pandemics of the past. As a result of recent research advances, we are far better prepared to produce vaccines and antivirals to contain the virus than we were just a year ago.

But even if another virus emerges with pandemic potential, our efforts will not be wasted. In developing the tools and infrastructure to identify and study H5N1, and rapidly produce and scale up vaccine production, we are developing the capabilities to respond to any novel virus that may emerge.

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