What Will the Next Influenza Pandemic Look Like?
Predicting pandemics might still be impossible, but with millions of lives at stake, researchers are using the latest and lessons from history to best prepare for the next big one

By Katherine Harmon | Monday, September 19, 2011 | 9 comments

MALTA—Contagion, a film released earlier this month, depicts a gruesome outbreak of an exotic and deadly new virus. In the world, a not-so foreign infection is circulating among animals every day of every year. If it picks up just a handful of certain mutations, it could start spreading among people, with a mortality rate as high as 60 percent. What is this potent virus? The flu.

Although the 2009 pandemic of influenza A H1N1 ended up being relatively mild—killing about one in 10,000 people who came with it—it still claimed more than 14,000 lives across the globe. The relatively low mortality rate was a relief to forecasters because the outbreak’s origin in Mexico and type had taken many by surprise.

Such surprises have turned out to be one of the few constants in the virus world: "Expect the unexpected," Ab Osterhaus, a professor of virology at the Erasmus Medical Center in Rotterdam, said here Tuesday at the fourth European Scientific Working Group on Influenza (ESWI) conference.

The uncertainty factor makes global preparedness particularly challenging. And given the basic questions that remain to be answered such as why some healthy people die of the flu and others do not—researchers are using new technologies to look for leads in victims as well as in the virus itself.

Because, as scientists and public health experts seemed to agree: "What is clear is that it is when, not if," Frederick Hayden, of University of Virginia School of Medicine, said here on Tuesday, referring to the next influenza pandemic—one of many proclamations of coming plague during the meeting that was tinged with just enough urgency to generate attention (and research funding) but not ignite an all-out panic.

Ongoing research is providing some new clues about what type of virus might become pandemic, where it might emerge and who it is most likely to kill.

Mysterious mutations
Topping the worst-case scenario list for most flu experts is a pandemic of H5N1, the "bird flu" which has killed about six in 10 who have gotten it—a total of at least 550 people since 2003—and has laid to waste hundreds of millions of domestic fowl and wild birds.

Fortunately, so far, it has not been transferred from human to human and has passed to us only via direct contact with animals. But any flu can change rapidly, mutating in each new host. So researchers wonder: Could the dreaded H5N1 ever morph into a disease that could spread among people, via a cough or sneeze, to attach to nasal or tracheal membranes, as the seasonal flu does every year?

To help answer this question, Ron Fouchier, also of Erasmus Medical Center, and his team "mutated the hell out of H5N1" and how readily it would bind with cells in the respiratory tract. What they found is that with as few as five single mutations it gains ability to latch onto cells in the nasal and tracheal passageways, which, Fouchier added as understated emphasis, "seemed to be news."
The variety that they had created, however, when tested in ferrets (the best animal model for influenza research) still did not very easily just through close contact. It wasn't until "someone finally convinced me to do something really, really stupid," Fouchier said, that they observed the deadly H5N1 become a viable aerosol virus. In the derided experiment, they let the virus itself evolve that killer capacity. To do that, they put the mutated virus in the nose of one ferret; after that ferret got sick, they put infected from the first ferret into the nose of a second. After repeating this 10 times, H5N1 became as easily transmissible as the season.

The lesson from these admittedly high-risk experiments is that "the H5N1 virus can become airborne," Fouchier concluded—a "re-assortment with mammalian viruses is not needed" for it to evolve to spread through the air. And each of these mutations already been observed in animals. "The mutations are out there, but they have not gotten together yet," Osterhaus said.

The exact likelihood of an H5N1 pandemic moving into humans is still unknown, pointed out Derek Smith, a professor of infectious disease informatics at the University of Cambridge in the U.K. From a scientific perspective, he noted, "one expects that's a low probability, but it's a really high-impact thing to prepare against—it's like preparing against terrorism."

Despite all of the concern about H5N1, scientists are also keeping an eye out for other emerging varieties. With 16 known forms influenza hemagglutinin (the "H" in the strain name), nine known varieties of neuraminidase enzyme (the "N" in the name), and different subtypes within each type, the potential for new enzymatic combinations—and recombinations—is great.

Even H1N1 is not yet in the clear. Since the 2009 outbreak in humans, H1N1 has become much more prevalent in pig populations currently, "we are seeing quite large numbers of re-assortments," Malik Peiris, of the University of Hong Kong, said at ESWI. A swine-origin triple re-assortment of the H3N2 strain had recently infected two children in the U.S., the Centers for Disease Control and Prevention in Atlanta reported earlier this month.

But the basic dynamics of how these diseases spread are still being worked out. "We don't know enough about how they transn human to human—whether re-assortments in pigs makes it more likely or less likely" to spread among humans, Smith said.

In addition to shifts in virulence and method of spread, slight mutations in the virus can also lead to major changes in how easily treated. A single-point mutation, for example, can render it resistant to commonly used antiviral medications, such as Tamiflu.

**The body enigmatic**

One of the most disconcerting things about influenza pandemics, as opposed to the seasonal flu, is their tendency to sicken—the young and seemingly healthy. Underlying risk factors, such as heart disease and neurological conditions, have been linked to fatality rates. But as Maria Van Kerkhove, of the Imperial College London's (I.C.L.) School of Public Health, found in a survey of global data following the H1N1 pandemic, no chronic conditions were reported among some 40 percent of people who were hospitalized for the flu and then died.

There is a "massive difference in the way people respond" to the same strain of influenza, noted Peter Openshaw, director of the Center for Respiratory Infection at I.C.L. He and his colleagues are studying samples from hundreds of people, many of whom became ill from the H1N1 pandemic strain, to look for clues as to why one apparently healthy 40-year-old might wind up in intensive care whereas another will fight the virus off just fine at home. But because too little is known about these varied reactions, the team everywhere: in human and viral genetics, for traces of bacterial infections, and elsewhere for hints about what might release the "cytokine storm" that kills some people, now seemingly at random, Openshaw said.

**Unknown origins**

The 2009 outbreak of H1N1 caught most people off guard—not in the least, those charged with tracking new flu strains and out. Especially after the 2003 emergence of SARS in Asia, most pandemic plans were centered on a Southeast Asian or Asian emergence of the next flu epidemic.
Modeling had predicted that a Southeast Asia–based strain would take some two to four months to spread extensively and arrive in Europe and North America about one to three months after that. That delay would give Western countries three to seven months to develop comprehensive treatment and vaccination plans.

When the flu emerged in Mexico, instead, North America endured the peak of the epidemic without a vaccine.

An outbreak’s point of origin can also play a large role in determining how quickly a pandemic is detected. Regions such as Africa and some places in Southeast Asia are still lagging in surveillance capabilities, noted Maria Zambon, of the U.K. Health Protection Agency.

To the advantage of epidemiologists and the public, "the severity of a virus will determine how quickly we detect it," Neil Ferguson, professor of mathematical biology of infectious diseases at I.C.L., said on Tuesday. The 2009 H1N1 virus had already been circulating in Mexico for some months before the full scope of its potential came to light. "We detected the 2009 virus as late as we did just because it was as mild as it was," he noted. And lingering immunity in the older population further reduced its spread. But if the next virus is more virulent and more rapidly transmitted, "we will detect it earlier," he said.

Subsequent analysis of the spread of the 2009 pandemic showed that it matched up with commercial air traffic from Mexico—spreading more rapidly into the U.S. and Spain, which are strongly socially connected to the Latin American country. If an outbreak were in Asia, however, South America is "a great place to be," because there is very little direct air traffic from Asia to the region, Smith said on Monday. So by the time the pandemic would arrive in force, a vaccine would likely already be available.

Asia is still at the focus of pandemic watchfulness, especially for hints of H5N1 spread. The virus is relatively common among migratory birds, which it usually does not sicken. As Osterhaus noted, "dead birds don't fly," so the well ones that still carry the disease travel, infecting other flocks—and domestic poultry as well. It can also be spread via human activity, with exports of birds, feathers, and other related products.

A recent study of the H5N1 virus in Laos found that some 0.6 percent of ducks sampled showed traces of the infection. And in Laos, where local poultry markets facilitate the movement of fowl around the country, the spread of the infection is of great concern to local and foreign health officials. The country has seen a documented outbreak of H5N1 every year since 2006.

Surveillance of the virus has been ramping up throughout Southeast Asia. In Bangladesh, for example, backyard farms predominate, putting fowl in close contact with both humans and migratory birds, so spread to the dense human population is of particular concern. "Bangladesh is in the front line now," explained Syed Ahmed, of the University of Southern Denmark.

Preventing the unpredictable

With the virus mutating in the dark, hidden cells in billions of birds, pigs and other animals, tracking their changes might seem impossible. "If we're going to [create] the best interventions that we can, we need to understand how they circulate around the world," Smith said of flu viruses. Surveillance of animal populations worldwide has improved vastly in the past decade, boosting the chance that scientists will spot new potentially dangerous mutations early.

But researchers are not simply watching and waiting. Scientists are continually developing new seed vaccines, or so-called seed vaccines, to test against newly emerging strains of the flu.

And there is plenty to do on the logistics side. The H1N1 pandemic hit Europe later than it did South and North America. And even though the outbreak was milder, thanks to the arrival of the vaccine during the pandemic peak, as I.C.L.'s Openshaw pointed out, many places were still running out of respirators, hospital beds and nursing staff.

"We know that it takes at least four to six months to have a vaccine," noted Sylvie Briand, of the World Health Organization (WHO) for countries that receive the early waves of a pandemic, a vaccine will likely not come in time to protect people against the virus very important to improve clinical response," by having ample medication and facilities to treat those at risk and reduce overall
Advancing preparedness in one fell swoop, however—even within the comparatively well-equipped European Union—has proved difficult, as Cambridge’s Smith pointed out, because countries that are less prepared are so for different reasons—making a one-size-fits-all approach to improving preparedness impractical. And when countries the world-over are thrown into the mix—many of which far fewer scientific, medical and infrastructural resources—the task is even more of a challenge.

At the end of the day, much of the preparation lays in the hands of policymakers—withint "the realpolitik of the department of health," Openshaw noted, adding that he realized that science was only part of the equation that politicians and governmental officials consider.

In addition to battling the mercurial virus and any political roadblocks, those trying to mitigate a future pandemic face another unpredictable force: public behavior.

In the first days of a pandemic, scientists and policymakers are forced to make consequential decisions—about containment, treatment, prophylaxis—with relatively limited information, "based on a perception," Briand said. And communicating the appropriate message to the public, which might not be well versed in risk and uncertainty, is a difficult task. Cry wolf, and it is likely to cause panic as w subsequent criticism of overreacting. But fail to instill adequate caution, and the reaction—and mortality rate—will be even worse.

Ill-advised
In 2009, for example, the WHO eventually declared the H1N1 pandemic a level 6—the highest designation possible. But that, Briand pointed out, was not indicative of the disease’s severity, but rather the extent of its spread. This distinction, which is great in the eyes of epidemiologists, was typically unaddressed in the media and thus in public perception, leading to later claims that officials had oversold the virus’s danger.

So, in addition to lab work on the viruses, some scientists are hard at work "thinking about how best to communicate the uncer that is undoubtedly going to arrive with the first wave of the next outbreak, I.C.L.'s Van Kerkhove said. "We learned that from pandemic, and we can expect that from the next one."

Unlike other human plagues, such as polio or smallpox, however, "eradication of the flu is impossible," Osterhaus said. The latest scientific and social research has pointed to three important steps to best meet the next pandemic head on, Briand said. Official make a variety of plans based on different scenarios; they must remain flexible to respond to rapidly changing situations; and t keep plans up to date—refreshing stockpiles and reevaluating plans based on the latest science.