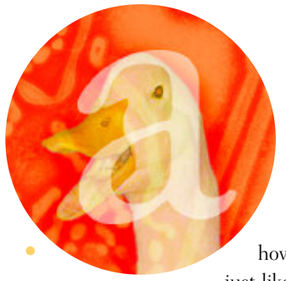
ON ALERT

IF AVIAN FLU LEADS TO A PANDEMIC — AS MANY EXPERTS BELIEVE IT WILL — THE DEATH TOLL COULD BE WELL OVER 100 MILLION IN SIX MONTHS. CAN WE DO ANYTHING TO STOP IT?

BY JEFF MORTIMER



THE TITLE OF THE ALL-DAY SYMPOSIUM WAS "PANDEMIC INFLUENZA: COULD HISTORY REPEAT ITSELF?"

It was presented in January by the School of Public Health's Michigan Center for Public Health Preparedness and the Michigan Department of Community Health. And if people in attendance didn't already know the answer when they arrived, they did by the time they left.

"We're overdue," says SPH Associate Dean for Practice Matthew Boulton, former chief medical executive and state epidemiologist for the Michigan Department of Community Health. "If you look at the periodicity of pandemics that have occurred, and you combine that with the epidemiological picture of avian influenza, almost all the components necessary for the next pandemic are in place. We now have confirmed but very limited person-to-person transmission of avian flu, so the only variable missing is more efficient spread among people—at which point all the criteria for the next pandemic will have been met."

Influenza pandemics swept around the globe in 1918–19, 1957, and 1968. The first, the so-called Spanish Flu, was easily the worst, killing what is currently estimated at 50 million people, including upwards of half a million in the United States. (If the same percentage of the population were to perish today, the domestic death toll would be close to 1.4 million.) Death was swift and grisly. The virus caused massive hemorrhaging in the lungs, and its victims essentially drowned in their own body fluids, often within hours of first showing symptoms.

Moreover, unlike "normal" flus, which mostly kill the very young and the very old, the highest mortality rates for the Spanish Flu were among those aged 16 to 50, peaking at around age 27.

In one chilling respect, however, the 1918–19 flu was just like the much milder pandemics of 1957 and 1968: all were caused by a novel Type A virus of avian origin, like the one that appeared in humans for the first time in Hong Kong in 1997. All three adjectives are significant: humans are less likely to have developed any resistance to a novel strain, Type A viruses are the most virulent and the least likely to respond to immunization, and bugs that come from birds have been particularly devastating to our species.

"Based on some of the epidemiological evidence we have on how severe avian flu has been in southeast Asia, it's possible that a pandemic resulting from avian influenza could approach what we saw in 1918," says Boulton.

As if the toll on individuals weren't bad enough, such mind-numbing levels of morbidity and mortality would wreak havoc on social systems. Entire cities shut down all their public functions, including schools, for months at a time in 1918–19 in an attempt to stem the tide of infection. World Health Organization officials estimate that the next pandemic would affect about 30 percent of the population, and a third of the work force would be laid up for two to four weeks. Perversely but predictably, public health workers and clinicians would be the most vulnerable sector.

The death toll could be well over 100 million in six months. By comparison, AIDS has killed an estimated 22 million since 1981. "You're really talking about the potential for governmental destabilization," says Boulton. "You wouldn't have the necessary infrastructure to provide public health and medical services, and at the same time you would be faced with this overwhelming level of morbidity and mortality in the population."

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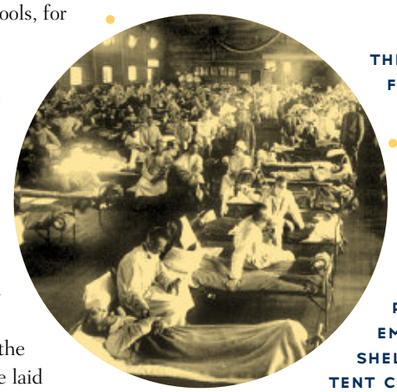
The real question is how *much* of history will repeat itself. The extent of the next influenza pandemic's effects will depend on the extent to which we are ready for it.

"I think this should be an alert, not an alarm," says Arnold Monto, SPH professor of epidemiology, founding director of the University of Michigan Bioterrorism Preparedness Initiative, and one of the world's leading experts on influenza.



THE 1918–19 FLU PANDEMIC OVERWHELMED HOSPITAL FACILITIES ALL OVER THE COUNTRY, FORCING THOUSANDS OF INFECTED PATIENTS INTO EMERGENCY SHELTERS AND TENT CITIES.

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While increases in population density, global travel, and migration make us more vulnerable than our ancestors were, we also have vastly better tools than they did. Surveillance systems, however imperfect and insufficient, improve our chances of detecting an outbreak early enough to make a difference. The Internet enables scientists and clinicians to communicate in real time, as they did so productively during the SARS epidemic in 2003. We have antiviral medications, at least one of which is known to work against avian influenza.

But just as the inevitability of the crisis was clear to those at the January symposium, so was the fact that having the tools is not the same as having enough of them, much less a deployment system. While the world is better prepared than it was for the outbreaks of 1918 or 1957 or 1968, it's not nearly as well prepared as it could and should be.

At least, we got a warning this time: an unprecedented increase in avian flu among birds in southeast Asia, and the unprecedented direct transmission from avians to humans eight years ago.

"We know that at least one of our antivirals will work against this virus," says Monto. "Why don't we use this antiviral as our first line of defense? The supplies will be exhausted very rapidly."

Sixty-one million courses of the medication would be needed just for prophylaxis for health care workers, Scott Harper of the National Center for Infectious Diseases told the symposium. And as Sandro Cinti, clinical assistant professor of internal medicine at the UM Medical School, pointed out that day, there is "no way the state or federal government can stockpile enough to take care of them."

"In an attempt to address this very fundamental problem we're facing—a pandemic without a vaccine—we're much more likely to use certain types of these antiviral drugs," says Boulton, for both prevention and treatment. "The problem is that they're not produced in large enough quantities, nor have we really put plans into place to increase production. And there are very few antivirals included in the Strategic National Stockpile."

Even if supplies were adequate, "there are really no substantive plans in place right now for mass distribution," he says. "The federal government has just started to address that."

As Monto mildly puts it, "There are logistic problems in using antivirals for control of the pandemic before we have vaccine. That's the ideal for prevention but if we have a new virus, it's going to take some time before we have vaccine even in limited quantities."

First, the vaccine would have to be developed. Because the virus mutates, even the vaccine for seasonal flu must be reformulated every year; Monto is among those who determine the recipe.

"The virus outwits us a lot of the time," he says. "Just when we think we've learned all we can about flu, something new comes along. It is a moving target, and we have to use fancy footwork to be able to stay ahead, because all we can do is try to stay ahead." In two years out of the last eight, the panel was wrong.

Once the vaccine was formulated, the same drug industry that now makes 300 million doses a year for the regular flu season would have to manufacture billions within weeks. But conventional methods, which require growing influenza viruses in specially cultivated chicken eggs, take months—and don't work in this case anyway: the avian virus is so lethal that it kills the developing chicks before they can grow enough virus to be worth harvesting.

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Two large vaccine manufacturers and the National Institute of Allergy and Infectious Diseases are experimenting with genetic techniques that alter the strain so it can be grown in fertilized eggs, which could also shorten the production schedule. But even if a new vaccine were available today, the industry would be unlikely to divert so much capacity to what amounts to a gamble.

It all sounds like a prescription for panic, and that's a concern in and of itself. Last fall's flu shot shortage was "a warning shot over the bow," says Monto.

"When the pandemic does come, we're not going to have enough antivirals, we're not going to have enough vaccine," he says. "We need to make recommendations about what we're going to do. We really need to look right now, in the inter-pandemic period, at things like closing schools, face masks, hand washing—which is advocated by many people without a whole lot of evidence—and try to figure out what works and what doesn't work, because we want to be able to inform the public about positive steps that they can take, rather than just say it's a big problem and we really don't know how to deal with it."

Not that the School of Public Health has ever done that. Far from it: "The school has been a site of work on influenza and other respiratory viruses since Dr. Thomas Francis Jr. came here to found the Department of Epidemiology," Monto says. "There's a long history in respiratory disease in general and influenza in particular."

Francis was the first researcher to isolate the influenza virus, and he developed the killed virus flu vaccine in the 1940s. His former student John Massaab, now professor emeritus of epidemiology at the School of Public Health, developed FluMist™, a live attenuated influenza vaccine that received FDA approval in 2002.

Today, Monto is leading clinical trials to determine the relative effectiveness of both inactivated vaccine and FluMist.

Boulton notes that Monto's work also was of assistance in planning the state of Michigan's disease surveillance system, "an important area of intersection between the practice community and the academic community."

There are many others. "Various faculty across all departments have been involved with the state public health department in public health preparedness," says Boulton. "They have conducted research and are involved in various components of practice that attend on catastrophic health event response and planning, whether it's mental health aspects, how to educate the public, risk communication, or surveillance for these pathogens."

Indeed, the Michigan Center for Public Health Preparedness is a national model for the training of front-line responders. Now, says Boulton, it's time for preparedness to be an internal priority as well.

"What's new in all this is thinking of preparedness as a foundational public health competency that we need to teach to students, public health workers and others who will need to respond to catastrophic health events," he says. "I think a lot of public health people haven't thought about preparedness in this way as, and it's critically important they do."

"It's only been in the last five years or so that public health was invited to the table around planning for large-scale health events. I think that was a very important acknowledgement. Now that we've been included, there are tremendous expectations of public health and how we'll perform."

In what has since become an infamous comment, U.S. Surgeon General William H. Stewart told Congress in the late 1960s that "it is time to close the book on infectious diseases. The war against pestilence is over."

We know better now. And we need to know even more. ■

Reuters/Corbis

Millions of ducks, chickens, and other domestic fowl have been slaughtered in efforts to contain the spread of avian flu in Asia and other parts of the world.

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