

Week 12: Influenza

Recently the media has been in a frenzy about *influenza*. Nations are stocking up on Tamiflu, survivalists are stocking supplies. Why the pandemic panic? 2 reasons: Avian influenza H5N1, and the year 1918. H5N1 flu is moving with migratory wild birds. It is only a matter of time before the virus is found worldwide. Read this article from the New York Daily News, written in a sensational tabloid style, but remarkably comprehensive in its content.

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Big trouble

By LISA JONES

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Lou Marion is under quarantine. It isn't an official Health Department decree, but it might as well be. Ever since the boy's parents and three of his six siblings became deathly ill, none of his neighbors in Butler, N.J., will step inside the infected home. At least the doctors visit daily. Unfortunately, the only advice they have for the 11-year-old is to swallow Epsom salts to "help keep his system clean." See, Lou's family has a touch of the flu.

The year is 1918, and people throughout New Jersey are dying faster than carpenters can build caskets. As a result, all sorts of wooden boxes are being used for burial duty. And if a body doesn't fit, well, then you just have to break the limbs and fold them inside. It's different in Philadelphia. They're way beyond boxes. With 11,000 deaths in the month of October alone, and the danger that the corpses will act as incubators for other communicable diseases, the city has resorted to digging mass graves with steam shovels.

This was "America versus Influenza" 87 years ago, at the height of World War I. By the time the virus burned itself out in 1919, more than 500,000 people in the United States had died, making the Spanish flu more effective than the German army. Some victims died just days after being infected, probably as a result of a runaway immune reaction called a "cytokine storm," while others lingered for weeks as secondary viral pneumonia ravaged their lungs.

"I don't think anybody ever had that kind of flu before," says Lou, nearly 98 now and, despite his failing eyes and ears, still sharp and spirited. "It was something entirely new, and people were shocked and bewildered because they didn't know what to do about it."

As we chat inside Lou's retirement-community apartment — just a mile from where his family fought for their lives (and won) — I don't have the heart to tell him what I know: Despite nearly a century of scientific research, we may be no better prepared for a flu pandemic than when Epsom salts were our best defense.

Perhaps the best gauge of how worried we should be about a disease is whether terrorists would consider using it against us. If it isn't highly contagious, generally fatal, or both, Al Qaeda isn't going to bother trying to crop-dust a city with the stuff. That's why a scan of the list of Priority Pathogens put out by the biodefense-research branch of the National Institute of Allergy and Infectious Diseases (NIAID) is so disturbing: Right there, on the same page as "anthrax" and under "multi-drug-resistant TB," is "influenza."

Of course, the NIAID isn't referring to the A, B, or C seasonal strains of influenza that we're used to; those are viruses that infect the respiratory system and cause coughing, muscle aches and maybe nausea, but not death in people with healthy immune systems. Rather, the experts are afraid of something that's more on the order of the Spanish flu, a viral strain of influenza A that could make smallpox look like small potatoes.

"In our lifetime, we have not seen a disease sweep through a community and people die so fast that there's no one to take care of them at the hospital and there's no one to bury them," says Dr. Greg Poland, chief of the Mayo Vaccine Research Group at the Mayo Clinic College of Medicine in Minnesota. "That's what will happen in a pandemic. It would be more deaths than all the world's wars in all of human history. All within the space of six to 18 months."

You'd think that if something this dangerous existed, it would be locked up in a lab somewhere. Instead, it may now be hitchhiking its way across Southeast Asia. Since 2003, an avian influenza called H5N1 has killed at least 57 people and sickened twice that number in Vietnam, Thailand, Cambodia and Indonesia. While those numbers may seem small, especially considering that approximately 36,000 Americans (mostly elderly and children) die of flu-related complications every year, they're worrisome in context. Avian strains of influenza don't normally infect humans, but this

one has mutated and made the interspecies leap. What's more, the influenza viruses behind the last two pandemics were of avian origin. Yet another factor that has infectious-disease specialists scrambling is the toll H5N1 is taking on birds. There are basically two types of avian flu, as distinguished by their genetic makeup: "highly pathogenic" and "low pathogenic." A high-path virus kills nearly all the poultry it infects, and has the potential to produce a similarly impressive body count in humans, should it make the jump. A low-path strain is much less virulent all around. At this point, H5N1 has wiped out roughly 150 million birds, earning it the designation "high path."

Indeed, the accumulated evidence paints such a dire pathogenic picture that, earlier this year, the World Health Organization (WHO) issued an urgent warning that a flu pandemic could affect billions of people worldwide. Billions because, unlike with our annual flu outbreaks, practically every single one of us will be vulnerable.

Think back to last year's flu-vaccine shortage: Remember how health officials told us that only children and the elderly should stand in line for flu shots? That was because they knew nearly everyone else's immune system would be strong enough to weather an infection. Not so with H5N1. If a high-path avian flu hits, we will all, in effect, be like the very young and the very old.

"In normal flu years, most of us have immunity, either from the vaccine or from having the flu in previous years," explains Marc Lipsitch, Ph.D., an associate professor of epidemiology, immunology and infectious diseases at the Harvard School of Public Health. "But in pandemics, we have no prior immunity, and it's just like being hit with a completely new disease that we've never built up any ability to fight. That's why the mortality tends to be high even in the age groups that don't usually get very sick from flu."

Even athletic, twenty- and thirtysomething men will be susceptible, despite having what are arguably the most vigorous immune systems of all.

"People basically — and particularly [physically fit young males] — are highly likely to become infected and develop complications, possibly even die," says Poland. "Why do I say that? In 1918, the people who more frequently died were in their teens to 40s. No one knows why."

Witness what unfolded during the 1918-19 Stanley Cup finals. The championship series between the Montreal Canadiens and the Seattle Metropolitans had been tied at 2-2-1 when the NHL abruptly canceled Game 6. The reason: George Kennedy, the Canadiens' manager, and five players, including "Bad" Joe Hall, were severely stricken with "La Grippe." Hall, 37, died four days after the cancellation, and the series was subsequently abandoned.

The problem with influenza is that it's really a bridesmaid disease," says Dr. Scott Harper, a medical officer with the flu team created by the Centers for Disease Control and Prevention's National Center for Infectious Diseases. "It always gets lumped into the phrase 'cold and flu.'" Young men, in particular, see the flu as nothing more than a severe case of the sniffles," he says. But while it's rare for men in this demographic to die in a normal flu season, that's not the case with H5N1. "What we're seeing in Vietnam is that young, healthy people are getting it and dying," says Harper, adding that the current mortality rate is 50%.

I'm sitting in Harper's office at the CDC headquarters in Atlanta, though "office" is really a bit of a stretch. There's only one window, and it's high up on the door, a layout that could be used as a police-station interrogation room. Or, as I later find out, a holding pen for lab animals.

Harper, 39, with a boyish face and slate blue eyes, joined the flu team a few years ago, soon after a stint battling another bug: Ebola. For three months, Harper went from hut to hut in villages across Uganda, searching for infected people — all the while dodging rebel soldiers who would have killed him quicker than the virus. By the end of what turned out to be the largest recorded Ebola outbreak, 428 people had been infected, and nearly half of them died.

One similarity between the Ebola virus and avian influenza (aside from their capacity for carnage) is that both diseases initially move from animal hosts to humans. So far, all the reported human cases of H5N1 have occurred in people who were in close proximity to domestic birds, such as farmers who raise chickens and men who bet on cockfights. In order for the virus to become a pandemic strain, says Harper, it needs to spread quickly and easily from human to human. That hasn't happened yet. But if there's an "antigenic shift" — an abrupt and major change of the proteins inside the virus that results in a brand-new subtype — everything could change.

Such a shift could occur if a person who's harboring human influenza simultaneously becomes infected with H5N1. His

lungs would then turn into a lab experiment in which the two viruses could "reassort," meaning that a chunk of the genome from the human influenza would insert itself into the genome of the avian flu. The resulting Frankenflu would be a mutated strain of H5N1 capable of spreading easily among humans.

"It's purely contact time," says Harper. "The more people who have an opportunity to be in contact with infected birds, the more opportunities two viruses have to get together. That's what we're really worried about."

As Harper ends my visit with a tour of the CDC buildings, including the Biosafety Level 4 laboratory, where scientists handle highly infectious viruses like Marburg and Ebola, I begin to wonder whether "really worried" is government-speak for "totally screwed."

There are two ways we can dodge a pandemic: Destroy every H5N1-infected bird before the antigenic shift can occur, or develop a vaccine against the disease and inoculate everyone. Health officials in Southeast Asia have been trying the first approach since 1997, cooking more chickens than KFC. But so far, the virus has managed to remain one carrier ahead of annihilation.

By comparison, the second strategy should be a cinch to pull off, considering that scientists already tailor each season's flu vaccine to the human strain that's most likely to strike. Their actual progress, however, has been slow — some critics say catastrophically so.

"Are we adequately prepared?" asks Poland. "No. We do not yet have a vaccine ready to go. If the pandemic happened next week, the public would be outraged that we waited and ignored the concerns and now people in every neighborhood were dying."

So just how far away are we? In March 2005, the National Institutes of Health began clinical trials of an experimental H5N1 vaccine in 450 people. Researchers at three sites are vaccinating healthy men and women, ages 18 to 65, and then administering a booster shot a month later. After that, blood samples will be taken and placed in test tubes, where they'll be exposed to H5N1.

"It's called a neutralization test, and it generally reflects the presence of antibodies that can attach to the bird-flu virus and immobilize it," says Dr. John Treanor, the lead investigator of the trial at the University of Rochester. When a neutralization test was performed during this trial, the preliminary results showed that the vaccine produced a positive immune response.

Still, even if researchers hit the biological bull's-eye with the vaccine, it will be impossible to produce a supply large enough to protect the entire country by this fall. Part of the problem is that one of America's three vaccine suppliers, Chiron, is still awaiting final FDA approval because of its well-publicized contamination problems. And while the company could receive the okay at any time, the CDC isn't counting on it.

"Right now, we can make roughly 60 million doses domestically of a normal flu vaccine in a normal year," says Lipsitch. "But according to recent research, the total amount of antigen required to immunize a person against H5N1 is four times as much as the total amount in a normal flu shot. In a pandemic, nearly everyone would need flu vaccines, but with the current version, we could immunize only 15 million Americans, just over 5% of the country."

There is, however, a pandemic plan B: antiviral medications. Of the existing antivirals, one, oseltamivir phosphate, aka Tamiflu, has been shown to be effective against H5N1. According to Dr. Arnold Monto, a professor of epidemiology at the University of Michigan, Tamiflu could be used not only to treat and shorten the duration of H5N1 infections, but to prevent the virus from spreading.

"Tamiflu inhibits the protein neuraminidase, which enables the virus to spread to other cells," he says. "If the virus can't escape from its host cell, it can't spread to other people."

It's for this reason that the World Health Organization (WHO) has advised certain countries to immediately start stockpiling Tamiflu. (Fortunately, it has a five-year shelf life.) But here again, we're lagging. While England has already ordered enough Tamiflu to treat 25% of its population, the U.S. has requested a mere 2.3 million treatments — enough for less than 1% of the country's inhabitants.

"We're way behind," says Jeffrey Levi, a senior policy adviser at the nonprofit organization Trust for America's Health.

"The United States cannot come close to that 25% level. For us, that would be at least 75 million treatments. We have to hope that the pandemic doesn't strike before we've ordered enough and received enough that it will provide some kind of protection."

An additional order of 20 million treatments of Tamiflu has already been planned, and that number could still be adjusted upward. Unfortunately, as with the H5N1 vaccine, filling an America-size order could be problematic — there's only one company, Roche, that makes Tamiflu, and the line to its door wraps around the world. Our best hope may turn out to be the Tamiflu that Roche is giving away: In a recent surprise announcement, the company said it would donate 3 million treatments to the WHO, so that if H5N1 erupts in Southeast Asia, the supply could immediately be flown to the region to try to stem the outbreak. Or at least slow it down.

If we were to have a pandemic of H5N1, it would be bad for two or three years," says Harper. "But eventually, the population gains immunity. And the virus probably changes itself to become less dangerous and circulate in humans from year to year."

Two or three years. With the near-certain shortage of vaccine and antivirals, surviving that period will depend on taking the same types of precautions used against another wildfire virus: SARS. "That would mean wearing masks and not shaking hands," says Poland. "Mass gatherings would be canceled. School would be canceled." And in such an atmosphere, adds Harper, the biggest challenge of all would be keeping our cool. "What we really don't want to see is an epidemic of panic."

There is, of course, the chance that this flu season will turn out to be more hype than horror. Nature, after all, is capricious. "It could be that we wake up in a few weeks and H5N1 is not the concern anymore," says Harper. "It might be a whole different virus that surprises us."

Questions.

1. What year did the so-called "Spanish flu" rip around the world, killing more than 500,000 people in the U.S. (and *at least* 20,000,000 worldwide)?
2. In what part of the world did avian influenza H5N1 originate?
3. Normally, the flu that strikes every winter kills mainly the very old and the very young. Was this also true for the Spanish flu?
4. So far, all reported human cases of H5N1 influenza have occurred in people who do what?
5. Which American flu vaccine manufacturer stopped producing vaccine because of contamination problems?
6. What does viral protein does Tamiflu inhibit?