

In pandemics of the past, caution for the future

May 24 2009, By Don Sapatkin

A novel flu circulated in some American cities in April and May of 1918, causing mild illness and going largely unnoticed. It returned in September, and again in January, eventually killing more than 500,000 people nationwide.

Another new flu appeared in Louisiana schoolchildren in early summer 1957 and smoldered for several months before turning virulent; more than 60,000 people died.

While the public may be over the initial scare from Mexico last month, it is these longer-term scenarios that keep pandemic experts up at night. A seeming resurgence of swine flu in New York over the past several days and its continuing spread worldwide haven't helped.

"This one may or may not come back in September or October. It may or may not come back in December. It may or may not come back at all," said Howard Markel, a medical historian at the University of Michigan and author of "When [Germs](#) Travel: Six Major Epidemics That Have Invaded America and the Fears They Have Unleashed."

Influenza, as experts repeat like a mantra, is unpredictable.

Despite an explosion of [genetic information](#) over the past decade, strikingly little is known not just about pandemic flu but about the seasonal variety as well.

Scientists don't even understand why it is seasonal. Indoor crowding, humidity and temperature are all possible explanations for the November-to-April season in North America; some tropical countries have year-round, low-level flu with two peaks rather than one.

But an out-of-season appearance is a red flag for public health officials -- and one that, in hindsight, was not heeded amid the chaos of World War I.

"The epidemics which occurred in the spring," Army Sanitary Corps Major George A. Soper wrote in the Nov. 8, 1918, issue of the [journal Science](#), near the peak of the pandemic, "were like those which are taking place now, except that the disease was milder and there was less pneumonia. ... Something seems to have occurred during the summer greatly to increase the virulence of the disease."

That so-called Spanish flu turned out to unfold in four major waves in the United States: February to May 1918, September to December 1918, January to April 1919 and December 1919 to March 1920.

The first wave was the weakest, and until recently was largely unnoticed by scientists and historians who focused on the far more deadly second wave. Death data from that era are abundant, but illness statistics are not.

Stephen S. Morse, a professor of clinical epidemiology at Columbia University's Mailman School of Public Health, co-authored a 2005 paper that analyzed death records for different age groups -- pandemics disproportionately hit young adults -- to show that an early wave had hit New York City in the spring of 1918.

"But why very often the subsequent waves are more virulent," Morse said in an interview, "is unknown."

What is known is that influenza A circulates around the world, constantly undergoing small mutations known as "drift." People who are exposed retain some immunity depending on the extent of the drift, but it is enough to require new vaccines every year.

Every once in a while, a major change -- usually a genetic reassortment, known as a "shift" -- creates a form of virus that is virulent, highly contagious and novel enough that people have little immunity. This causes a pandemic, often in several waves. The population gradually builds immunity and it persists as the seasonal flu until the next pandemic comes along to displace it.

All viruses require a host cell to reproduce, and influenza A strains are broadly named according to versions of two proteins that are key to the process: hemagglutinin (H) controls how the virus binds to a host cell, and neuraminidase (N) dictates how its resulting progeny are released.

The [influenza](#) A(H1N1) of 1918 settled into seasonal flu until it was displaced in the pandemic of 1957-58 by H2N2, which in turn was pushed out in the pandemic of 1968-69 by H3N2, which remains the main seasonal flu.

Species preferences and other differences are not reflected in the H and N designations. The current H1N1 is believed to be a distant relative of what began in 1918.

The link may help explain the current pattern of disease among younger people since anyone born before 1957 would have residual immunity. Some protection may also be conferred by forms of H1N1 that have been circulating for unknown reasons since 1977.

Scientists speculate that, unlike the seasonal flu, pandemic flu might first appear in any season because people have little or no immunity; it strikes

an immediately susceptible population.

"I think we already know that this virus has pandemic potential," said Edwin D. Kilbourne, an emeritus professor of microbiology and immunology at New York Medical College who has written extensively about pandemics.

Laboratory analysis has officially confirmed at least 5,764 cases of swine flu in the U.S. as of Friday, but so many illnesses are now being treated as seasonal flu that the U.S. Centers for Disease Control and Prevention says the actual number could be more than 100,000. At least nine people have died.

So far, though, the new H1N1 has proven only slightly more deadly than the seasonal flu, Anne Schuchat, a CDC infectious-disease expert, told reporters Monday. Yet it's an unusual season, with particularly late outbreaks in schools.

"We wonder whether this strain will continue during the summer," Schuchat said. "This is certainly a possibility. It's not something that I can predict."

Whether it becomes more dangerous depends largely on what other viruses it meets, and possibly reassorts with, in the coming months.

The new strain responds to the drug oseltamivir (sold as Tamiflu), for example, but a predominant strain of the recent seasonal flu is resistant. And a far more virulent strain of bird flu is circulating in the world but currently is not transmissible among humans.

Public health officials will be looking for signs of change in the Southern Hemisphere as its winter -- the north's summer -- approaches. But there is no guarantee that any more serious version would show up

there.

"Where does the virus go when it goes away?" said Harvey Rubin, a professor of medicine and director of the Institute for Strategic Threat and Response at the University of Pennsylvania. "You know what? We don't really know."

And if the spring of 2009 is a first wave, the timing of the second is another unanswered question.

"The interval between successive waves," the World Health Organization notes in a pandemic preparedness document, may be "as short as a month."

Although that would be too soon to distribute a vaccine, [pandemic-flu](#) experts interviewed in the past week were generally pleased that this novel flu, which they all expected to come along sooner or later, had shown up in the spring.

"The good news is it's a heads-up, 'Hello, this virus is out there,' and you better learn as much about it and make some decisions because of the possibility that it will come back big-time in the fall," said Jim Hughes, a former director of the CDC's National Center of Infectious Diseases and now a professor at Emory University.

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