# Pandemic Paradox: New Flu Virus Keeps Researchers and Health Officials Guessing

Chandra Shekhar
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When avian flu jumped the species barrier to claim human victims in the late 1990s, scientists warned that it could evolve further and trigger a pandemic. And now, a decade later, a pandemic has indeed struck—but from an entirely different and unexpected source. Carrying a mishmash of genetic parts from human, avian, and swine influenza viruses, the new pathogen appears to have crossed over to us from pigs, not birds. In a matter of weeks, it has spread to practically every region on the globe, claiming an estimated one million infections in the United States alone and triggering an unprecedented global effort to track and ascertain its behavior. Despite its spectacular progress, however, this swine flu pandemic has so far caused only a few hundred cases of severe illness or death, and its potential long-term impact remains unclear. "As of now, neither from point of view of spread nor virulence can the virus be considered severe," says virologist William Gallaher, PhD, of Louisiana State University in New Orleans. "But all bets are off as to what will happen when the classic flu season begins in the northern hemisphere where most people live. If the virus gets cracking, 25% attack rates are not out of the realm of possibility."

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The current outbreak has ominous similarities to "the mother of all pandemics," the 1918 Spanish Flu virus that infected nearly a third of the world population and killed approximately 100 million people. Then, as now, the infectious agent was an influenza A virus of the H1N1 subtype. Then, as now, a mild but widespread wave of infection struck the northern hemisphere in summer, well before the normal flu season. (The devastating wave that followed in the fall of 1918 did most of the damage). Then, as now, the elderly were spared and young adults disproportionately affected; the opposite of what happens with routine seasonal flu. "I don't want to cry wolf, but whenever you see a pattern like that, you've got to keep your eyes peeled," says epidemiologist Lone Simonsen, PhD, of George Washington University.

A key feature of influenza A pandemics is "antigenic shift": the appearance of a virus with such a significantly different set of surface proteins that most people have no immunity to the infection. From an immune standpoint, the two key viral proteins are hemagglutinin, which comes in 16 varieties (H1–H16), and neuraminidase, which comes in nine (N1–N9). The agents of the three major pandemics of the last century—in 1918, 1957, and 1968—each sported such an "antigenic shift" in their surface proteins. In each case, as the population developed "herd" immunity, the viruses evolved under selective pressure into seasonal strains or disappeared altogether. (Currently, seasonal flu is mostly caused by the H1N1, H3N2, or influenza B subtypes. The H2N2 subtype that caused the 1957 pandemic has not been detected in humans since 1968.) How does the 2009 swine flu strain rate on the antigenic scale? Sequence data indicate that its hemagglutinin and neuraminidase differ by about 27% and 18% in amino acid sequence from the corresponding proteins in the seasonal H1N1 strain. "That amounts to a major antigenic shift," says Gallaher.

Some researchers such as Peter Palese, PhD, a microbiologist at the Mount Sinai School of Medicine in New York, feel that the change is not significant enough to qualify as antigenic shift, but is instead a case of antigenic "drift." Palese points out that the novel virus is still part of the H1N1 subtype, whereas prior pandemics were caused by entirely new subtypes, such as the H3N2 virus that caused the 1968 pandemic. "In the old days, we wouldn't have called this a pandemic," he says.

Some clues lie in the novel virus's intriguing lineage. Central to the influenza A virus's success as a pandemic agent is its unique ability to swap one or more of its eight genome segments with other viruses of this family to continually reinvent itself. Thus, a pair of genetically distinct viruses could recombine in as many as 256 different ways; one of these new versions may have just the right genetic mix to evade the human immune system and/or cause severe disease. The 2009 swine flu virus is a so-called triple reassortant, carrying a novel mix of one human, two avian, and five swine flu gene segments. Its hemagglutinin and neuraminidase proteins seem well adapted for human infection, studies show. But other features of the pathogen suggest lower virulence. Compared to the viruses involved in the 1957 and 1968 pandemics, the novel pathogen has several more genes from nonhuman flu strains. This may make it less adapted for human disease. Further, it lacks a virulence factor present in all prior pandemics: PB1-F2, a small viral protein that makes patients sicker and more likely to catch bacterial pneumonia. These factors may explain why the virus has so far caused mostly mild disease, with a case fatality rate comparable to seasonal flu. "I would argue that it is actually a fourth seasonal influenza strain," says Palese. "But if you insist on calling it a pandemic strain, it's a very mild one."

The virus could of course turn nastier with further mutation or reassortment; for

instance, it could acquire the coding sequence for PB1-F2 from another flu virus infecting the same patient. "Only a few tweaks and changes separate a mild virus from a virulent one," says Gallaher. "A single case of mixed infection could help the virus become 'humanized' and pose a much greater threat." However, as Palese points out, a virus that turns more virulent in one aspect may become less effective in other aspects. Avian flu, for instance, is extremely virulent both in humans and chickens, but doesn't transmit easily between humans; if it does manage to acquire this ability, it could lose some of its virulence in the process. Likewise, if the current swine flu virus turns more deadly, it could end up being less infectious. The worst-case scenario of a virus that is both deadly and highly transmissible, as was seen in 1918, "is a once in a millennium event," says Palese. In any case, the 2009 swine flu virus appears to be evolving very slowly. "It is breeding extraordinarily true," says Gallaher. "It's gone through tens of thousands of people with virtually zero movement genetically."

This could change, but if it does, it is unlikely to catch scientists and health authorities off guard. Influenza experts the world over have come together in an unprecedented effort to study the virus and monitor its progress, aided by recent boosts in research funding in response to bird flu, anthrax, and other threats. As a result, the novel swine flu virus is being tracked virtually in real time, as attested by the hundreds of sequences already uploaded into the GenBank database. "We've never watched any agent of human disease at the molecular level as intensely as this one," says Gallaher. "If it changes at all, we should be able to pick it up quickly and correlate it with changes in virulence."

This intense scrutiny is already paying off. So far, the good news has been that the common flu drugs oseltamivir (Tamiflu) and zanamivir (Relenza) seem effective in fighting the novel virus. However, Gallaher notes that three independent H1N1 isolates from Hong Kong, Japan, and Denmark found during the past few days have a mutation in the neuraminidase protein, a change at position 274 from histidine to tyrosine, that makes the virus resistant to Tamiflu. "If Tamiflu resistance becomes widespread, it will take away one of the weapons we have," says Gallaher.

Another instance relates to the PB2 protein, which plays a key role in viral replication. The current virus has an avian version of this protein and as a result is better adapted to replicate in the warmer bodies of birds (41°C) than in humans. On June 18th, a virus from Shanghai was reported with a mutation in its PB2 protein that would have helped it replicate at the cooler temperature (33°C) of the human upper airway in winter—but fortunately that sequence appears to have been erroneously reported (GenBank: ACS27790.2). "Even though this was a false alarm, it's really important to keep an eye on such mutations," says Princeton University molecular biologist Richard A. Stein, MD, PhD. "During the 1918 pandemic, when the virus returned in the fall after an original mild outbreak in the spring, the increased mortality and morbidity were in part due to this mutation."

Meanwhile, health officials are taking no chances. On April 26th, just 11 days after the first US case was identified, the US government declared a public health emergency of international concern. The same day, WHO announced a phase 3 pandemic alert. On June 11th, the WHO raised the pandemic alert to the highest phase, 6, indicating sustained human-human transmission caused by community-level outbreaks in at least one country in two or more WHO regions. While these measures have placed health systems on alert, their main effect as of now is increased surveillance. The organization does not recommend border closures or travel restrictions and advises that community-level measures such as school closings be considered on a case-by-case basis. A universal vaccination campaign would be the best weapon against the current pandemic, but how feasible is it? Such a campaign would need billions of doses, but there are only about 35 major vaccine manufacturers in the world. "It's a race to see how fast we can make the vaccine," says Robert Belshe, MD, who directs the Center for Vaccine Development at St. Louis University in Missouri. Given the limited manufacturing capacity, Belshe and others recommend giving priority to vaccinating children and young adults, who are falling sick at higher rates, along with caregivers, essential workers, and others with special needs.

Overall, the novel H1N1 virus is a mixed bag—antigenically novel and infectious, but relatively mild, susceptible to antiviral drugs, and genetically stable. Researchers agree that its true nature will emerge this fall when the regular flu season starts. "All eyes are on the southern hemisphere epidemic right now," says Simonsen. "The experience there will provide early clues about whether the novel H1N1 virus will evolve towards greater virulence and whether it will replace or cocirculate with the seasonal influenza viruses."

Chandra Shekhar (chandra@nasw.org) is a science writer based in Princeton, NJ.

 