Mutation identified that might allow H1N1 to spread more easily

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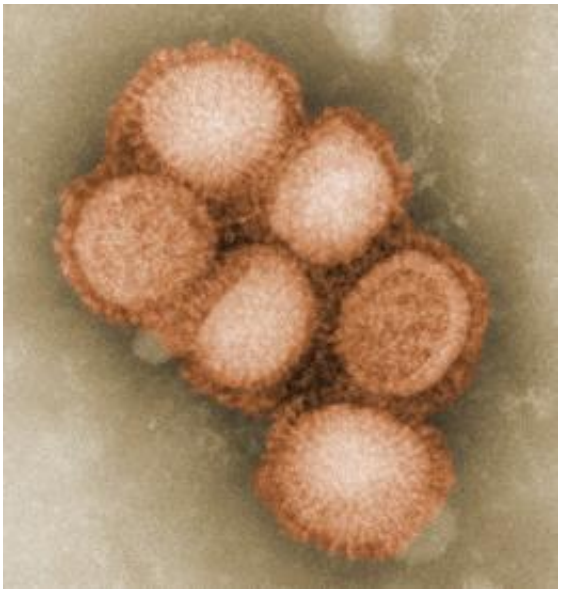

An image of the H1N1 influenza virus taken in the CDC Influenza Laboratory. Image courtesy of the Centers for Disease Control.

In the fall of 1917, a new strain of influenza swirled around the globe. At first, it resembled a typical flu epidemic: Most deaths occurred among the elderly, while younger people recovered quickly. However, in the summer of 1918, a deadlier version of the same virus began spreading, with disastrous consequence. In total, the pandemic killed at least 50 million people — about 3 percent of the world's population at the time.

That two-wave pattern is typical of pandemic flu viruses, which is why

many scientists worry that the 2009 H1N1 ("swine") flu virus might evolve into a deadlier form.

H1N1, first reported in March 2009 in Mexico, contains a mix of human, swine and avian flu genes, which prompted fears that it could prove deadlier than typical seasonal flu viruses. However, the death toll was much lower than initially feared, in large part because the virus turned out to be relatively inefficient at spreading from person to person.

In a new study from MIT, researchers have identified a single mutation in the H1N1 genetic makeup that would allow it to be much more easily transmitted between people. The finding, reported in the March 2 edition of the journal *Public Library of Science* (*PLoS*) *One*, should give the World Health Organization, which tracks influenza evolution, something to watch out for, says Ram Sasisekharan, senior author of the paper.

"There is a constant need to monitor the evolution of these viruses," says Sasisekharan, the Edward Hood Taplin Professor and director of the Harvard-MIT Division of Health Sciences and Technology. Some new H1N1 strains have already emerged, and the key question, Sasisekharan adds, is whether those strains will have greater ability to infect humans.

WHO labs around the world are collecting samples of human and avian flu strains, whose DNA is sequenced and analyzed for potential significant mutations. However, it's difficult, with current technology, to predict how a particular DNA sequence change will alter the structure of influenza proteins, including hemagglutinin (HA), which binds to receptors displayed by cells in the human respiratory tract. Now that this specific HA mutation has been identified as a potentially dangerous one, the WHO should be able to immediately flag any viruses with that mutation, if they appear.

Identifying this mutation is an important step because it is usually very difficult to identify which of the many possible mutations of the HA protein will have any impact on human health, says Qinghua Wang, assistant professor of biochemistry at Baylor College of Medicine. “These are exactly the types of mutations that we need to watch out for in order to safeguard humans from future disastrous flu pandemics,” he says.

Pandemic

On June 11, 2009, about three months after the H1N1 virus first appeared, the World Health Organization declared a level 6 pandemic alert (the highest level). Nearly 5,000 H1N1 deaths were reported to the WHO, and more than 400,000 cases were confirmed, though the true number of cases is significantly higher because many countries stopped counting cases after the first few months of the outbreak, according to the WHO.

In July 2009, a team of researchers from MIT, led by Sasisekharan, and the Centers for Disease Control and Prevention reported in the journal Science that the H1N1 virus was much less easily passed from person to person than seasonal flu viruses and earlier pandemic flu viruses such as the second wave of the 1918 strain.

Sasisekharan and CDC senior microbiologist Terrence Tumpey had previously shown that a major factor in flu-virus transmissibility is the structure of the HA protein, which is found on the viral surface. The tightness of fit between HA and the respiratory cell receptor determines how effectively the virus infects a host.

The 2009 H1N1 strain, like the first wave of 1918 (known as the NY18 strain), does not bind efficiently. However, it took only one mutation of the NY18 virus’ HA protein to become the much more virulent SC18

strain, which caused the second wave.

Viral evolution

In the new *PLoS* study, the MIT researchers focused on a segment of the HA protein that they have shown affects its ability to bind to respiratory cells. They created a virus with a single mutation in that region, which replaced the amino acid isoleucine with another amino acid, lysine. That switch greatly increased the HA protein's binding strength. They also found that the new virus spread more rapidly in ferrets, which are commonly used to model human influenza infection.

If such a mutant virus evolved, it could generate a "second wave" like the ones seen in 1918 and in 1957 (known as the "Asian flu"). "If you look at the history, it takes a very small change to these viruses to have a dramatic effect," Sasisekharan says.

The amino acid in question is located in a part of the viral genome prone to mutate frequently, because it is near the so-called antigenic site — the part of the HA protein that interacts with human antibodies. Antigenic sites tend to evolve rapidly to escape such antibodies, which is why flu vaccine makers have to use new formulas every year. This year's vaccine included a strain of H1N1, which is still circulating around the world.
