Pandemic flu, like seasonal H1N1, shows signs of resisting Tamiflu

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If the behavior of the seasonal form of the H1N1 influenza virus is any indication, scientists say that chances are good that most strains of the pandemic H1N1 flu virus will become resistant to Tamiflu, the main drug stockpiled for use against it.

Researchers at Ohio State University have traced the evolutionary history of the seasonal H1N1 influenza virus, which first infected humans during the 1918 pandemic. It is one of three seasonal influenza A viruses that commonly infect humans. The others are H1N2 and H3N2.

Within H1N1, two strains of virus circulate in humans: a seasonal form and the pandemic form of influenza known as swine flu, which has sickened millions and killed thousands of people since it first emerged in North America last spring.

Over time, the H1N1 strain of seasonal influenza surviving around the world has developed mutations that have caused it to become resistant to oseltamivir-based agents. Tamiflu is the brand name for oseltamivir phosphate.

"Something happened in 2008, when drug resistance took hold," said Daniel Janies, associate professor of biomedical informatics at Ohio State and primary author of the study. "The drug-resistant isolates became the ones that survived all over the world. This is just static now. The seasonal H1N1 influenza virus is fixed at resistant."

Janies and colleagues have traced the history of the same mutation in the pandemic H1N1 strain of the virus as well, with data from its emergence last spring until December 2009. And they are starting to see the same kinds of mutation in this virus - changes to an amino acid that allow the virus to resist the effects of oseltamivir - that they saw in the seasonal H1N1 flu.

"It is a pretty good bet that whatever pressure is in the environment, excessive use of Tamiflu or something else, that was driving seasonal influenza to become resistant to Tamiflu is also going to apply to pandemic influenza," Janies said. "We can see it happening already.

"This has potential to indicate that we are going to have to think of something else to use to treat pandemic H1N1 influenza."

The same study showed that resistance to a second antiviral drug - zanamivir, known by the brand name Relenza - is not as prevalent, suggesting this medication might be a good alternative to Tamiflu, he said.

The research appears online in the *International Journal of Health Geographics*.

So far, most pandemic H1N1 strains that have been isolated from humans are susceptible to Tamiflu. As of Feb. 3, 2010, 225 cases of pandemic H1N1 were reported to be resistant to the drug out of the predicted millions of cases of illnesses with swine flu across the United States and elsewhere in the world.

But those resistant cases, as well as the way mutations have led to Tamiflu resistance in seasonal H1N1, offer clues about how the virus changes itself to survive against the popular drug.

The two types of H1N1 virus, seasonal and pandemic, are similar on the surface, where their proteins interact with cells in the human body. But the internal genes of the viruses are configured differently.

The researchers zeroed in on specific points in the neuraminidase protein - this protein is what the "N" refers to in these virus subtype names. Resistance to oseltamivir in H1N1 can evolve as a result of a point mutation at one of several locations on this protein, Janies said.

He and colleagues analyzed mutations in neuraminidase proteins from 1,210 seasonal H1N1 viruses isolated around the world between September 2004 and December 2009. For pandemic H1N1, the researchers examined mutations in specific points on neuraminidase proteins of 1,824 viruses collected between March 2009 and December 2009.

"With the rapid availability of public sequence data on pandemic influenza, we are able to essentially watch evolution in real time," Janies said.

Once they selected the isolates for study, the researchers used powerful supercomputers to analyze the evolution of these proteins and their various mutations. The computational power allows them to match similar regions on the proteins and put the mutation data into context in time and geography.

One result of these computations is called a phylogenetic tree, which documents the history of mutations - including those that cause drug resistance. Phylogenetics is the study of the evolutionary relationships and features among various biological species, genes or proteins that share a common ancestor.

In tracing the history of neuraminidase in pandemic and seasonal H1N1,

the group found that mutations in the same amino acid position in both seasonal and pandemic H1N1 drove the viruses toward resistance to antivirals.

"Basically a change in the amino acid changes how the neuraminidase protein folds, and the molecule in Tamiflu no longer has the ability to interfere with the virus," Janies said.

The researchers also used a technique in which they compared different types of mutations - those that do cause antiviral resistance and others that don't have that effect - to see which type of mutation is more common.

"We look at the ratio of mutations that do confer resistance vs. those that don't, and if the ratio is higher than 1, it means that change is being promoted by natural selection rather than chance. Something is driving the evolution of drug resistance," Janies said. "We could see that happening in seasonal influenza and in the data we have so far for pandemic influenza, as well.

"A Darwinian would say that something changed that made the Tamiflu-resistant strain more fit than the wild type," he said.

The group also examined mutations that alter these two strains of H1N1 viruses' responses to Relenza. Resistance to that drug is relatively rare, Janies said, which could be attributed to less frequent use of the drug or to the possibility that mutations leading to resistance to Relenza aren't tolerated by the virus itself, so those strains die off.

Janies noted that there is another phenomenon with flu that could further make the pandemic strains difficult to treat. In at least 50 geographic regions identified by the analysis, both seasonal and pandemic H1N1 viruses are co-circulating, including Tamiflu-resistant strains. Because

the flu virus in general is not precise when it makes copies of itself, this means that a drug-susceptible pandemic strain might exchange a gene with a drug-resistant viral strain and add it to the new genome.

"And then we would have drug-resistant pandemic influenza without any mutation. It's a random swap of the whole gene," Janies said of this phenomenon, which is called reassortment.

"That's how we got into this situation with pandemic influenza. We have something that's called pandemic H1N1, but all of its internal genes are different. It underwent a few rounds of reassortment and it's a virus we've never seen before because its genome is highly reshuffled compared to seasonal H1N1. This same process could confer resistance to a drug," he said.

The researchers have plotted areas where pandemic influenza and drug-resistant seasonal influenza circulate together into Google Earth using software called Pointmap. Regions in the United States and Japan are among those in which pandemic flu isolates carry the Tamiflu-resistant mutation. The regions of co-circulation can be seen at http://pointmap.osu.edu.

Provided by The Ohio State University

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