

## -- BREAKING NEWS --

Below, we reproduce the report that was given in the *International Herald Tribune*, 8 Jan 2009 - "*Flu in U.S. Found Resistant to Main Antiviral Drug*".

### **Flu in U.S. Found Resistant to Main Antiviral Drug**

by

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Virtually all the flu in the United States this season is resistant to the leading antiviral drug Tamiflu, and scientists and health officials are trying to figure out why.

The problem is not yet a public health crisis because this has been a below-average flu season so far and the chief strain circulating is still susceptible to other drugs — but infectious disease specialists are worried nonetheless.

Last winter, about 11 percent of the throat swabs from patients with the most common type of flu that were sent to the Centers for Disease Control and Prevention for genetic typing showed a Tamiflu-resistant strain. This season, 99 percent do.

"It's quite shocking," said Dr. Kent Sepkowitz, director of infection control at Memorial Sloan-Kettering Cancer Center in New York. "We've never lost an antimicrobial this fast. It blew me away."

The single mutation that creates Tamiflu resistance appears to be spontaneous, and not a reaction to overuse of the drug. It may have occurred in Asia, and it was widespread in Europe last year.

In response, the CDC issued new guidelines two weeks ago. They urged doctors to test suspected flu cases as quickly as possible to see if they are influenza A or influenza B, and if they are A, whether they are H1 or H3 viruses.

The only Tamiflu-resistant strain is an H1N1. Its resistance mutation could fade out, a CDC scientist said, or a different flu strain could overtake H1N1 in importance, but right now it causes almost all flu cases in the country, except in a few mountain states, where H3N2 is prevalent.

Complicating the problem, antiviral drugs work only if they are taken within the first 48 hours. A patient with severe flu could be given the wrong drug and die of pneumonia before test results come in. So the new guidelines suggest that doctors check with their state health departments to see which strains are most common locally and treat for them.

"We're a fancy hospital, and we can't even do the A versus B test in a timely fashion," Sepkowitz said. "I have no idea what a doctor in an unfancy office without that lab backup can do."

If a Tamiflu-resistant strain is suspected, the disease control agency suggests using a similar drug, Relenza. But Relenza is harder to take — it is a powder that must be inhaled and can cause lung spasms, and it is not recommended for children under 7.

Relenza, made by GlaxoSmithKline, is known generically as zanamivir. Tamiflu, made by Roche, is known generically as oseltamivir.

Alternatively, patients who have trouble inhaling Relenza can take a mixture of Tamiflu and rimantadine, an older generic drug that the agency stopped recommending two years ago because so many flu strains were resistant to it. By chance, the new Tamiflu-resistant H1N1 strain is not.

"The bottom line is that we should have more antiviral drugs," said Dr. Arnold Monto, a flu expert at the University of Michigan's School of Public Health. "And we should be looking into multidrug combinations."

New York City had tested only two flu samples as of Jan. 6, and both were Tamiflu-resistant, said Dr. Annie Fine, an epidemiologist at the city's health department. Flu cases in the city are only "here and there," she said, and there have been no outbreaks in nursing homes. Elderly patients, and those with the AIDS virus or on cancer therapy are most at risk.

But, she added, because of the resistance problem, the city is speeding up its laboratory procedures so it can do both crucial tests in one day.

"And we strongly suggest that people get a flu shot," she said. "There's plenty of time and plenty of vaccine." Exactly how the Tamiflu-resistant strain emerged is a mystery, several experts said.

Resistance appeared several years ago in Japan, which uses more Tamiflu than any other country, and experts feared it would spread.

But the Japanese strains were found only in patients already treated with Tamiflu, and they were "weak" — that is, they did not transmit to other people.

"This looks like a spontaneous development of resistance in the most unlikely places — possibly in Norway, which doesn't use antivirals at all," Monto said.

Dr. Henry Niman, a biochemist in Pittsburgh who runs recombinomics.com, a Web site that tracks the genetics of flu cases around the world, has been warning for months that Tamiflu resistance in H1N1 was spreading.

He argues that it started in China, where Tamiflu use is rare, was seen last year in Norway, France and Russia, then moved to South Africa (where winter is June to September), and back to the northern hemisphere in November.

The mutation conferring resistance to Tamiflu, known in the shorthand of genetics as H274Y on the N gene, was actually, he said "just a passenger, totally unrelated to Tamiflu usage, but hitchhiking on another change."

The other mutation, he said, known as A193T on the H gene, made the virus better at infecting people.

Furthermore, he blamed mismatched flu vaccines for helping the A193T mutation spread. Flu vaccines typically protect against three flu strains, but none have contained protections against the A193T mutation.

Dr. Joseph Bresee, the CDC's chief of flu prevention, said he thought Niman was "probably right" about the resistance having innocently piggy-backed on a mutation on the H gene — which creates the spike on the outside of the virus that lets it break into human cells. But he doubted that last year's flu vaccine was to blame, since the H1 strain in it protected "not perfectly, but relatively well" against H1N1 infection, he said.

Niman said he was worried about two aspects of the new resistance to Tamiflu. Preliminary data out of Norway, he said, suggested that the new strain was more likely to cause pneumonia.

The flu typically kills about 36,000 Americans a year, the CDC estimates, most of them the elderly or the very young, or people with problems like asthma or heart disease; pneumonia is usually the fatal complication.

And while seasonal flu is relatively mild, the Tamiflu resistance could transfer onto the H5N1 bird flu circulating in Asia and Egypt, which has killed millions of birds and about 250 people since 2003.

Although H5N1 has not turned into a pandemic strain, as many experts recently feared it would, it still could — and Tamiflu resistance in that case would be a disaster.

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