Flu virus reported to resist drug envisioned for pandemic

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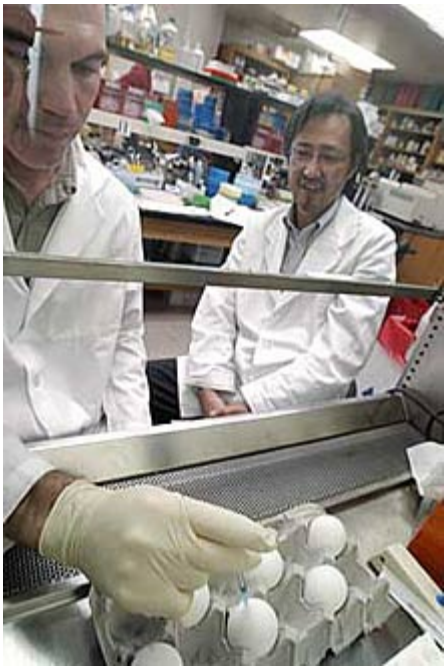

Professor of virology Yoshihiro Kawaoka, right, and lab technician Barry McClernon conduct research on the constant mutation of the influenza virus. The researchers injected 10-day-old chicken eggs with two strains of a flu virus, each with different portions of its genetic code deleted. Although neither strain was viable on its own, together the viruses survived by mutating to recombine their genetic codes. Photo: Michael Forster Rothbart

by Terry Devitt

An avian influenza virus isolated from an infected Vietnamese girl has been determined to be resistant to the drug oseltamivir, the compound better known by its trade name Tamiflu, and the drug officials hope will serve as the front line of defense for a feared influenza pandemic.

Scientists from the University of Wisconsin-Madison, working with colleagues in Vietnam and Japan, report in a brief communication in next week's edition (Oct. 20, 2005) of the journal Nature that a young girl, provided with a prophylactic dose of the drug after experiencing mild influenza symptoms, developed a strain of the virus that was highly resistant to the drug.

The finding suggests that health officials - now stockpiling millions of doses of the drug to forestall a global outbreak of influenza and buy time to develop and mass produce a vaccine - should also consider other options, according to Yoshihiro Kawaoka, an international authority on influenza and the senior author of the Nature paper.

Recent reports indicate the federal government may spend billions of dollars to stockpile as much as 81 million courses of Tamiflu to forestall a possible influenza pandemic. The government has already stockpiled an estimated 12 to 13 million courses.

"This is the first line of defense," says Kawaoka, a professor in the UW-Madison School of Veterinary Medicine who holds a joint appointment at the University of Tokyo. "It is the drug many countries are stockpiling, and the plan is to rely heavily on it."

The drug would be used to slow the spread of influenza until a vaccine is developed, which may take up to six months.

Tamiflu is delivered orally and works to impede the spread of the virus by binding to and inhibiting one of the surface enzymes the virus uses to exit infected cells of a host. Once inside a host cell, the virus commandeers the cell's reproductive machinery to make new infectious particles that go on to take over other cells. When the drug is at work, Kawaoka explains, "the virus is still able to replicate inside a cell, but is unable to get out and infect other cells."

Oseltamivir, which Kawaoka describes as an "amazing drug," is one of three compounds proven to be effective against influenza. One class, derivatives of the compound adamantine, would be less effective, as some flu viruses have already evolved resistance to it. The other drug, zanamivir, which was developed prior to oseltamivir, is effective, but is formulated as a powder and requires that a clinician provide instructions for use. Thus, it is more cumbersome to administer than the orally delivered Tamiflu.

These flu-fighting drugs, says Kawaoka, are by no means a replacement or alternative to a vaccine. Effective vaccines can confer immunity, preventing the virus from gaining a toehold in the body. But it is unlikely sufficient quantities of a vaccine can be produced and stockpiled prior to the emergence of a new virus in human populations.

If avian influenza does emerge and becomes infectious from human to human - and nearly all experts agree that will happen at some point in the future - an outbreak similar to the 1918 influenza pandemic could occur. That pandemic killed as many as 50 million people, more than died on all the battlefields of World War I. Scientists and vaccine manufacturers would be in a race against time to produce enough doses to forestall disaster. Drugs like Tamiflu, used in combination with quarantine, would be intended to slow the spread of the disease until a vaccine is produced.

Kawaoka says there may not be enough Tamiflu to go around even though countries are stockpiling it. The Wisconsin scientist says that will create a risk of patients sharing the drug and using smaller doses, which could accelerate the emergence of virus resistant to the drug and hamper efforts to contain the spread of the disease.

He says health officials should consider stockpiling zanamivir and recommending that only the therapeutic dosages of Tamiflu be administered to patients.

"We've been watching for this change (in the virus)," Kawaoka says. "This is the first, but we will see others. There's no question about it."