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Compound found to safely counter deadly bird flu

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The specter of a drug-resistant form of the deadly H5N1 avian influenza is a nightmare to keep public health officials awake at night.

Now, however, a study published this week (Dec. 21) in the *Proceedings of the National Academy of Sciences* (*PNAS*) suggests that a new compound, one on the threshold of final testing in humans, may be more potent and safer for treating "bird flu" than the antiviral drug best known by the trade name Tamiflu.

Known as T-705, the compound even works several days after infection, according to Yoshihiro Kawaoka, a University of Wisconsin-Madison virologist and the senior author of the new *PNAS* study.

"H5N1 virus is so pathogenic even Tamiflu doesn't protect all the infected animals," explains Kawaoka, a professor of pathobiological sciences at the UW-Madison School of Veterinary Medicine and a world authority on influenza. "This compound works much better, even three days after infection."

The Wisconsin research was conducted in mice and demonstrated that the compound was effective and safe against H5N1 virus, the highly pathogenic bird flu virus, which some scientists fear could spark a global epidemic of deadly influenza. The compound is also effective against seasonal flu and more worrisome varieties such as the H1N1 virus, and has already been tested against circulating seasonal influenza in humans in Japan where it is on the brink of Phase III clinical trials in people.

The prospect of a new front-line drug for influenza, in particular highly pathogenic strains such as H5N1 virus, is important as there are few drugs capable of checking the shifty influenza virus. The new study showing the efficacy and safety of T-705 assumes more importance as instances of Tamiflu-resistant strains of H5N1 virus have recently been reported, raising concerns about the ability of current antiviral drugs to blunt a pandemic of deadly avian flu.

Antiviral drugs are viewed as a readily available first line of defense against pandemic flu and are especially important for protecting health workers and others during an outbreak of disease. Vaccines, which utilize inactivated or weakened viruses to confer immunity, are the primary line of defense for influenza, but require months to formulate and mass-produce.

Aside from its safety and basic efficacy, another key trait of the T-705 compound is the fact that it is effective even after an infection is acquired. Bird flu, notes Kawaoka, is almost always diagnosed in the hospital after symptoms of the disease manifest themselves: "This compound has a chance to save people who have gone into the disease course," he says.

T-705 targets a critical viral molecule, polymerase, an enzyme that enables the virus to copy its genetic material, RNA. By disabling polymerase, the virus is unable to make new virus particles and maintain the chain of infection. Tamiflu, which remains an effective drug for blocking influenza virus, targets and regulates the enzyme neuraminidase, a protein found on the surface of the flu virus particle and that is essential for spreading the virus throughout the respiratory system.

"The activity of this agent is considerably higher than Tamiflu," says Kawaoka, adding, "the compound is very specific to viral polymerase. It

doesn't affect host polymerase, which is important for safety and reducing side effects."

Provided by University of Wisconsin-Madison