H7N9 influenza strain resistant to antivirals, but tests fail to identify resistance

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Some strains of the avian H7N9 influenza that emerged in China this year have developed resistance to the only antiviral drugs available to treat the infection, but testing for antiviral resistance can give misleading results, helping hasten the spread of resistant strains.

The authors of a study published in *mBio*, the online open-access journal of the American Society for Microbiology, characterized viruses taken from the first person known to be stricken with H7N9 influenza and found that 35% of those viruses are resistant to oseltamivir (commercially known as Tamiflu) and zanamivir (Relenza), front line drugs used for treating H7N9 infections. However, lab testing of the viruses, which detects the activity of a viral enzyme, fails to detect that these strains are resistant, so monitoring for the development of resistance using this technique would prove futile.

"If H7N9 does acquire human-to-human transmissibility, what do we have to treat it with until we have a vaccine? Oseltamivir. We would be in big trouble," says corresponding author Robert Webster of St. Jude Children's Research Hospital in Memphis, Tennessee. Resistant strains of H7N9 can flourish in patients treated with oseltamivir or zanamivir, he says, inadvertently leading to the spread of resistant infections.

In the mBio study, the authors tested antiviral susceptibility of an H7N9 strain isolated from the first confirmed human case of avian H7N9 influenza using a method that tests the activity of the neuraminidase enzyme. The reassuring results were, unfortunately, misleading: the

enzyme-based test indicated that the flu strain was susceptible to NA inhibiting antiviral drugs, but it is not.

A closer look at the viral isolate revealed it is actually made up of two distinct types of H7N9 viruses. Roughly 35% of the viruses carry the R292K mutation, making them resistant to NA inhibitors, and 65% are sensitive to these same drugs. The enzyme-based testing gave misleading results, says Webster, because the functioning wild-type enzymes masked the presence of the non-functioning mutant enzymes.

Using NA inhibitors to treat a patient infected with a resistant strain of H7N9 only encourages the virus to proliferate and can lead to enhanced spread of the resistant strain. The authors write that these results prove that it is crucial to use a gene-based surveillance technique that can detect these resistant influenza strains in a mixed infection.

H7N9 first emerged in China in early 2013, in some cases infecting individuals who had been in contact with poultry or with places where poultry are housed. The virus has since been detected in poultry at live markets near where human infections have been reported. After the closure of many live poultry markets in China and with the start of the warm season, which is not conducive to influenza spread, the infection rate appears to have slowed. As of July 12, the number of infections stands at 132 and the number of deaths at 43.

A recent study found that antiviral treatment failed in two patients infected with a strain of H7N9 influenza that carries a mutation called R292K, and that these patients had a poor clinical outcome. The mutation causes a change in the neuraminidase gene and makes the virus resistant to neuraminidase (NA) inhibitors, including Tamiflu and Relenza. NA inhibitors have been the front line therapeutic option for treating H7N9 influenza because the virus is already resistant to M2 ion channel blockers Amantadine (Symmetrel) and its methyl derivative

Rimantadine (Flumadine). Considering the severity of H7N9 flu infection and the fact that so few options exist for treatment, it is important to continue to evaluate the sensitivity of clinical isolates to NA inhibitors and to monitor for the emergence of resistant variants.

If the recent history of H5N1 influenza is a guide, says Webster, then H7N9 could rapidly evolve the ability to spread from person to person. If it does, and if the virus reemerges in the fall, the situation with H7N9 could become quite serious. In the event of a widespread outbreak, Tamiflu and Relenza will work alright as treatments, but the development of the R292K mutation puts those options in jeopardy, says Webster.

But the news isn't all bad. Webster also points out that antiviral resistance is something of a burden for influenza viruses, and that fitter wild-type H7N9 strains may eventually win out over resistant strains. In the absence of a drug like Tamiflu, Webster says, it seems unlikely that these resistant viruses would acquire epidemic characteristics.

Regardless of the specific evolutionary steps H7N9 will take, influenza is an ongoing threat - and the lack of suitable drugs is a grave cause for concern.

"The great need at the moment are additional drugs aimed at additional sites in the influenza genome. There are some [drugs] in the pipeline, but they are still under testing at the moment," says Webster. "We'd better get some vaccine seed stocks up and ready. The antiviral option for controlling H7N9 isn't too good."

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