Influenza virus strains show increasing drug resistance and ability to spread

December 7 2010

Two new studies raise public health concerns about increasing antiviral resistance among certain influenza viruses, their ability to spread, and a lack of alternative antiviral treatment options. The findings are published in the January 1 issue of The *Journal of Infectious Diseases*.

Influenza viruses are treated with two classes of drugs: M2 blockers (adamantanes) and neuraminidase inhibitors (NAIs), including oseltamivir and zanamivir. While the spread of influenza strains with resistance to one class of drugs has been well documented in recent years, a new report from Larisa Gubareva, MD, PhD and colleagues at the Centers for Disease Control and Prevention (CDC) and at health agencies in West Virginia, Texas, and Canada, confirms that dual resistance can emerge in several ways and has been on the rise during the past three years.

The study analyzed 28 seasonal H1N1 viruses with dual resistance from 2008 to 2010 from five countries, revealing that additional antiviral resistance could rapidly develop in a previously single-resistant strain as a result of mutation, drug response, or gene exchange with another virus.

Although dual resistant viruses are still rare, the investigators noted an increase in the number of tested viruses with this resistance, from 0.06 percent (2007-2008) to 1.5 percent (2008-2009) to 28 percent (2009-2010); however, during the 2009-2010 season the number of circulating seasonal H1N1 viruses was low, and only 25 viruses were tested. "Because only two classes of antiviral agents are approved, the

detection of viruses with resistance to drugs in both classes is concerning," said Dr. Gubareva. "If circulation of viruses with dual resistance becomes more widespread among any of the predominant circulating influenza A viruses, treatment options will be extremely limited. New antiviral agents and strategies for antiviral therapy are likely to be necessary in the future."

A second study, conducted by Catherine Moore and colleagues in the United Kingdom, examined an outbreak of oseltamivir resistant (OR) pandemic H1N1 infection in a hematology unit in the UK. The study is the first to confirm person-to-person transmission of this dually resistant strain through molecular epidemiologic methods. The 2009 pandemic H1N1 virus was inherently resistant to adamantine, but was susceptible to and treated with oseltamivir. However, by October 2009, emergence of OR H1N1 had been documented in rare patients on oseltamivir therapy.

In the hematology unit that Moore and colleagues studied, eight of the 11 pandemic H1N1 virus infections were resistant to oseltamivir, with half of those cases resulting from direct transmission of the resistant virus. Immunocompromised patients were more susceptible to the emergence of OR H1N1 virus on treatment and also transmitted the virus to others, despite often having no influenza symptoms or having completed antiviral therapy. As a result, the screening of patients for OR H1N1 viruses became particularly important, and treatment guidelines were altered to include treatment with zanamivir, to which the viruses remained susceptible.

"These findings suggest that oseltamivir may not be the frontline drug of choice in hematology patients, and zanamivir may prove to be more beneficial," the study authors wrote. "Guidelines may need to be changed to include active screening for the [OR] mutation in hematology patients diagnosed with H1N1 and other patients who are

immunocompromised when oseltamivir is used." If high risk groups are more actively monitored, early diagnosis will help prevent the spread of H1N1 viruses, and proper screening for infection and resistance will aid in making proper therapeutic decisions.

In an accompanying editorial, Frederick G. Hayden, MD, of the University of Virginia School of Medicine, and Menno D. de Jong, MD, of the University of Amsterdam in the Netherlands, agreed that increasingly detailed monitoring and creative preventive and therapeutic choices will be required as unpredictable and antiviral-resistant influenza viruses continue to appear. This is especially true "given our current paucity of therapeutic choices," according to the authors. With only two drug classes approved in the U.S. and most countries for treating influenza virus, future research should focus on the effectiveness of zanamivir and combination antiviral therapy and the need to develop new antivirals with unique mechanisms of action.

"Such information will ensure rapid development and testing of alternative antiviral strategies for use in immunocompromised hosts and seriously ill hospitalized patients to address their unmet medical needs and the associated public health concerns, particularly the continuing threat of antiviral resistance," the authors conclude.

More information: The studies and the accompanying editorial are available online:

"Dual Resistance to Adamantanes and Oseltamivir Among Seasonal Influenza A (H1N1) Viruses: 2008-2010"
www.oxfordjournals.org/our_journals/jid/jiq005.pdf

"Evidence of Person to Person Transmission of Oseltamivir Resistant Pandemic Influenza A (H1N1) 2009 Virus in a Hematology Unit"
www.oxfordjournals.org/our_journals/jid/jiq007.pdf