MMWR
Morbidity and Mortality Weekly Report

MMWR Dispatch
Vol. 55 / January 17, 2006

High Levels of Adamantane Resistance Among Influenza A (H3N2) Viruses and Interim Guidelines for Use of Antiviral Agents — United States, 2005–06 Influenza Season

An estimated 200,000 persons are hospitalized each year and 36,000 persons die from complications of influenza in the United States (*1,2*). The cornerstone of influenza prevention is annual vaccination. However, antiviral drugs are an important adjunct to vaccination for influenza prevention and control. Two classes of antiviral medications are available currently: adamantanes or M2 ion channel inhibitors (i.e., amantadine and rimantadine) and neuraminidase inhibitors (i.e., oseltamivir and zanamivir). The adamantanes are active against only influenza A viruses and are used for both treatment and chemoprophylaxis of influenza A, whereas the neuraminidase inhibitors are active against both influenza A and B viruses. Zanamivir is not approved for chemoprophylaxis of influenza in the United States. This report describes new findings regarding the resistance to adamantanes of influenza A viruses currently circulating in the United States and provides interim recommendations that these drugs not be used during the remainder of the 2005–06 influenza season. Amantadine also is used to treat symptoms of Parkinson disease and may continue to be used for this indication.

Resistance of influenza A viruses to adamantanes can occur spontaneously or emerge rapidly during treatment (*3*). A single point mutation in the codons for amino acids at positions 26, 27, 30, 31, or 34 of the M2 protein can confer cross-resistance to both amantadine and rimantadine (*4*). Neither replication, transmission, nor virulence of adamantane-resistant influenza A viruses are impaired by the point mutations conferring resistance (*5*). A recent report on the global prevalence of adamantane-resistant influenza A viruses indicated a significant increase of drug resistance, from 1.8% during the 2001–02 influenza season to 12.3% during the 2003–04 season (*4*). In the United States, the frequency of adamantane resistance increased from 1.9% during the 2003–04 influenza season to 11% during the 2004–05 season (CDC, unpublished data, 2005). In contrast to adamantane resistance, neuraminidase inhibitor resistance remains rare worldwide (*6*).

The World Health Organization (WHO) Collaborating Laboratories and National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories in the United States submit influenza isolates to CDC as part of routine virologic surveillance. A subset of these isolates is further characterized at CDC, which includes testing for antiviral susceptibility. Although isolates are submitted by all U.S. states and territories, they are not necessarily a representative sample of all influenza viruses circulating in the United States.

Since the beginning of the 2005–06 influenza surveillance season, WHO and NREVSS laboratories have tested a total of 38,932 specimens for influenza viruses; 1,557 (4.0%) tested positive. Among the 1,557 influenza viruses, 1,499 (96.3%) were influenza A viruses, and 58 (3.7%) were influenza B viruses. A total of 765 (51.0%) of the 1,499 influenza A viruses have been subtyped; 760 (99.3%) were influenza A (H3N2) viruses, and five (0.7%) were influenza A (H1N1) viruses. During October 1, 2005–January 14, 2006, a total of 123 influenza A viruses collected from 23 states were tested at CDC for adamantane resistance. Among the 120 influenza A (H3N2) viruses tested, 109 (91%) demonstrated the S31N substitution in the M2 protein that confers resistance to amantadine and rimantadine. Conventional sequencing on a subset of 20 viruses confirmed this substitution. Among the three influenza A (H1N1) viruses tested, none contained any mutations associated with resistance. As of January 14, all U.S. influenza viruses screened for antiviral resistance at CDC had demonstrated susceptibility to neuraminidase inhibitors. Procedures for virus propagation, RNA extraction, and pyrosequencing for adamantane resistance have been described previously (*4*).

Reported by: *WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza; RA Bright, PhD, D Shay, MD, J Bresee, MD, A Klimov, PhD, N Cox, PhD, Div of Viral and Rickettsial Diseases, National Center for Infectious Diseases; J Ortiz, MD, EIS Officer, CDC.*

Editorial Note: The high levels of resistance to amantadine and rimantadine detected among influenza A viruses tested during this season necessitate an interim change in recommendations for the use of these drugs. On the basis of available antiviral testing results, CDC recommends that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza A infections in the United States for the remainder of the 2005–06 influenza season. During this period, oseltamivir or zanamivir should be prescribed if an antiviral medication is indicated for the treatment of influenza, or oseltamivir should be prescribed for chemoprophylaxis of influenza. On January 14, 2005, a CDC Health Alert* with these recommendations was sent via the Health Alert Network (HAN) to state and local health officers, public information officers, epidemiologists, HAN coordinators, and clinician organizations.

Testing of influenza isolates for resistance to antivirals will continue throughout the 2005–06 influenza season, and recommendations will be updated as needed. These findings of adamantane resistance pertain to human influenza A (H3N2) viruses and not to avian influenza A (H5N1) viruses isolated from birds or humans in Asia or Europe.

Recommendations for the use of the oseltamivir and zanamivir have not changed. The Food and Drug Administration (FDA) recently extended chemoprophylaxis approval of oseltamivir to include children aged 1–12 years; previously, chemoprophylaxis approval had been limited to children aged ≥13 years (*7*).

When administered for treatment within 48 hours of illness onset, neuraminidase inhibitors can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day when compared with placebo (*8*). Persons at high risk for serious complications from influenza can benefit most from neuraminidase inhibitors (*8*). CDC recommends that neuraminidase inhibitors be used as treatment for any person experiencing a potentially life-threatening influenza-related illness and for persons at high risk for serious complications from influenza. CDC recommends that oseltamivir be used as chemoprophylaxis for 1) persons who live or work in institutions caring for persons at high risk for serious complications from influenza infection in the event of an institutional outbreak and 2) persons at high risk for serious influenza complications if they are likely to be exposed to others infected with influenza. The FDA-approved indications for the use of neuraminidase inhibitors are available at http://www.cdc.gov/flu/professionals/treatment.

Annual influenza vaccination remains the primary means of preventing morbidity and mortality associated with influenza. Because the influenza season has only recently begun in many areas of the United States, persons for whom influenza vaccination is recommended should still be vaccinated (*9*).

Additional information regarding the prevention and control of influenza is available at http://www.cdc.gov/flu. New information will be provided at this website as it becomes available.

* Available at http://www.cdc.gov/flu/han011406.htm.

References

1. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333–40.
2. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179–86.
3. Belshe RB, Smith MH, Hall CB, Betts R, Hay AJ. Genetic basis of resistance to rimantadine emerging during treatment of influenza virus infection. J Virol 1988;62:1508–12.
4. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet 2005;366:1175–81.
5. Sweet C, Hayden FG, Jakeman KJ, Grambas S, Hay AJ. Virulence of rimantadine-resistant human influenza A (H3N2) viruses in ferrets. J Infect Dis 1991;164:969–72.
6. Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med 2005;353:1363–73.
7. Food and Drug Administration. FDA news: FDA approves Tamiflu for prevention of influenza in children under age 12. Rockville, MD: Food and Drug Administration; 2005. Available at http://www.fda.gov/bbs/topics/news/2005/new01285.html.
8. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2005;54(No. RR-8).
9. CDC. Update: influenza activity—United States, December 25–31, 2005. MMWR 2006;55:11–3.