



Resistance to oseltamivir changes management of influenza in children

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Antimicrobial resistance is in the news again. The latest reported resistance will influence the management of serious influenza virus infections in children the rest of this influenza season.

The Centers for Disease Control and Prevention (CDC) recently documented that, so far, all of the tested H1N1 influenza A virus strains circulating this winter in the United States are uniformly resistant to oseltamivir (Tamiflu).

These resistant H1N1 strains first were isolated in Europe last winter. One of the many mutations that characterize this ever-changing virus now prevents the binding of oseltamivir to its target, the neuraminidase enzyme that allows new virus particles to be released from infected cells. Remarkably, this conformational change does not significantly alter the binding of zanamivir (Relenza), another antiviral in the same neuraminidase inhibitor class; thus, these strains remain susceptible to zanamivir.

These oseltamivir-resistant H1N1 strains are susceptible to amantadine (Symmetrel) and rimantadine (Flumadine), antivirals that had been uniformly ineffective for influenza A for the past three to four years.

The H3N2 influenza A strains tested so far remain susceptible to both oseltamivir and zanamivir, but are resistant to amantadine and rimantadine. Influenza B strains also remain susceptible to both oseltamivir and zanamivir, but are intrinsically resistant to amantadine and rimantadine.

Two classes of antiviral medications currently are available in the United States for treatment or prophylaxis of influenza infections:

1. neuraminidase inhibitors — oseltamivir (Tamiflu; Roche Laboratories) and zanamivir (Relenza; GlaxoSmithKline)
2. adamantanes — amantadine (Symmetrel; Endo Pharmaceuticals) and rimantadine (Flumadine; Forest Pharmaceuticals)

Guidelines for the use of these four antiviral agents are available in the AAP clinical report, "Antiviral Therapy and Prophylaxis for

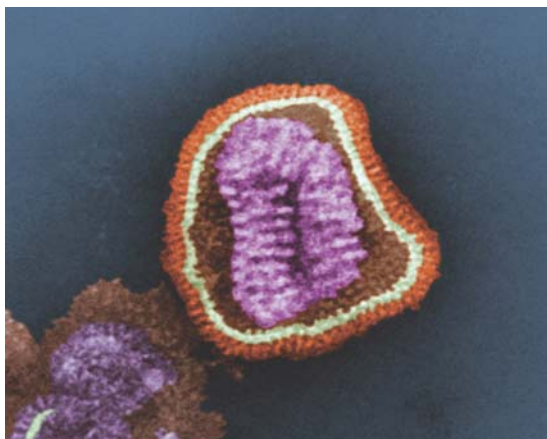


Photo courtesy of Cynthia Goldsmith

Negative-strained transmission electron micrograph depicts the ultrastructural details of an influenza virus particle, or "virion."

Influenza in Children" (<http://aap.policy.aappublications.org/cgi/reprint/pediatrics;119/4/852.pdf>).

No antiviral medicine is approved for infants younger than 12 months of age.

For the practitioner, the diagnosis of influenza infection often is a clinical one, backed by a rapid diagnostic test that identifies either 1) influenza A or B or 2) just positivity for influenza, but does not differentiate between A and B. Unfortunately, the proportion of influenza A (H1N1) viruses among all influenza A and B viruses that will circulate during any influenza season cannot be predicted and likely will vary

geographically among communities throughout the season.

None of the currently approved rapid tests can differentiate between the H1N1 or H3N2 strains of influenza A. Hence, this year, the practitioner is faced with the challenge of choosing the most effective therapy when the child is suspected to be infected with influenza A and requires antiviral therapy.

For children who are 7 years of age or older, inhaled zanamivir should provide effective treatment for those with serious infections caused by either influenza A or B. For children younger than 7 years (but not younger than 1 year of age), a combination of oseltamivir (in case the strain is H3N2) and amantadine/rimantadine (in case the strain is H1N1) may be most appropriate.

Although local and state health departments and the CDC will attempt to track which strains are causing outbreaks in various regions throughout the United States, it is unlikely that strain-specific information will be available quickly enough to guide therapy for community outbreaks.

More background and treatment guidance are provided by the CDC at www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279.

The influenza strains circulating so far this flu season appear well-matched to this year's influenza vaccines. This highlights the value in continuing to give influenza vaccine throughout the entire influenza season to all children 6 months through 18 years of age, and to everyone who lives with, provides care for or comes in contact with children.

Drs. Bradley and Bernstein are members of AAP Committee on Infectious Diseases.



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