

## The Diagnosis and Treatment of Influenza: A Managed Care Perspective

**T**his Special Report supplement to *The American Journal of Managed Care* includes 2 articles that were based on presentations given at a meeting held on April 21, 1999, in New Orleans, Louisiana, on influenza epidemiology and the treatment of influenza. The supplement also includes 2 review articles on influenza diagnosis and management.

One article, based on a presentation by Frederick G. Hayden, MD, Professor of Internal Medicine and Pathology at the University of Virginia School of Medicine in Charlottesville, provides insights into the advances made in the prophylaxis and treatment of influenza. The other, based on a presentation by Arnold S. Monto, MD, Professor of Epidemiology, University of Michigan, School of Public Health, Ann Arbor, Michigan, focuses on the epidemiology and virology of influenza illness. This meeting, supported by Roche Pharmaceuticals, gave attendees an overview of the treatment and diagnostic tools that will soon be available and provided clinicians with updated information for managing influenza illness in the clinical setting.

One of the 2 review articles, one from researchers at the University of Rochester Medical Center and Clinical Microbiology Laboratories, focuses on the clinical and laboratory diagnosis of influenza. The other, from researchers at Roche Pharmaceuticals, provides a basic overview of influenza management.

### Prevention and Treatment

Each year's formulation of influenza vaccine provides the primary means of preventing influenza illness, although only about half the individuals who could benefit most from the vaccine receive it. Although current vaccines afford a high rate of protection, they do not provide complete protection in frail elderly or immunocompromised patients. Researchers have developed new formulations that use live attenuated, cold-adapted vaccine. In children, this vaccine behaves differently from standard inactivated vaccine and offers protection against an antigenic variant, reducing influenza-related complications such as otitis media and lower respiratory tract illness as well as the use of antibiotics for these complications. This vaccine has been well tolerated and represents an exciting step forward.

Two drugs—amantadine and rimantadine—have been available for several years for the prophylaxis and treatment of influenza A virus infection. However, their use is limited by a high risk of side effects in elderly persons (an activity limited to influenza A) and the emergence of viral resistance to the drugs. A new class of anti-influenza agents, the neuraminidase inhibitors, offers potent inhibition of both influenza A and B viruses. After demonstrating clinical efficacy in both treating and preventing influenza illness, 2 such drugs—inhaled zanamivir and oral oseltamivir—have now received Food

and Drug Administration approval for clinical use.

### Epidemiology and Virology

A variety of ways to prevent and treat influenza illness are now available. However, an understanding of how the virus reaches and spreads through human populations is critical to controlling future epidemics and pandemics, as well as in limiting associated costs.

From approximately November to April each year, Americans suffer the morbidity, mortality, and financial losses due to interpandemic influenza. Although the elderly and those with respiratory problems or who are immunocompromised are at highest risk of hospitalization and death from influenza, the illness' greatest clinical and financial impact falls on adults 19 to 65 years of age, who account for some 60% of diagnosed cases of influenza. In the United States, influenza annually results in 20,000 to 40,000 deaths, more than 300,000 hospitalizations, and substantial direct and indirect costs.

Moreover, the social and financial implications of annual influenza epidemics result in significant workplace disruptions, with tens of millions of workdays lost. Parents may have to stay at home to care for sick school children, and worker performance and safety can be seriously compromised. In addition, influenza sufferers incur the costs of physician visits, prescription and over-the-counter drugs, and hospitalizations. Together, the direct and indirect costs of influenza exact a toll on the US economy of as much as \$14 billion annually. Fortunately, improved surveillance, vaccines, medications, and diagnostic tests provide clinicians with the tools to limit morbidity, mortality, and financial costs.

The virology of influenza offers the key to understanding annual epidemics and how to treat and control them. The recurrent threat presented

by influenza arises from the virus' changing antigenicity (ie, its ability to regularly reinvent itself). Antigenic *drift*, caused by subtle changes in surface proteins, leads to viral escape from host immunity and results in the annual epidemics known as interpandemic influenza. The pandemic forms of influenza arise from antigenic *shift*, (ie, major changes in the viral hemagglutinin or the surface protein neuraminidase).

Type A influenza, which accounts for most cases, infects not only humans but also several animal species. Birds, specifically waterfowl, serve as the virus' primary hosts, harboring nearly all of the influenza viruses that have so far been recognized. In these avian hosts, the viruses constantly replicate in the birds' intestines, which serve as great reservoirs of influenza genes that are shed in the feces. These viruses then enter the environment by various animal routes, through which they can eventually reach and infect humans.

Because of the influenza virus' ever-changing antigenicity, researchers face challenges annually to develop vaccine and control interpandemic influenza outbreaks. Epidemiologists at the Centers for Disease Control and Prevention track these interpandemic influenza outbreaks around the United States by observing the severity of influenza attacks in 122 cities. Such tracking provides information about the mixture of influenza types and the appropriate use of drugs and vaccines.

### Diagnosis

In many cases, clinicians can diagnose influenza illness on the basis of clinical features alone. Studies have demonstrated that during influenza season such a diagnosis can be as much as 85% accurate in individuals with fever, cough, and myalgia. Although culturing for virus offers the most sensitive way to detect the influenza virus, in the clinical setting

it generally does not yield results quickly enough. A fast, accurate diagnosis of influenza infection calls for a combination of clinical presentation, epidemiological context, and the availability of diagnostic tools. The exact tools to use will depend on the patient population, the skill of the laboratory staff, and how sensitive and rapid the results must be. Current

diagnostic tests may be too complex for most clinic settings; however, practices that have easy access to a laboratory can perform a test and then delay any treatment until the results are known, assuming they are available within 4 to 6 hours.

These tests can detect viral antigens in clinical specimens using commercial enzyme immunoassay devices. Such devices vary as to the length of time needed to perform the test (15 to 45 minutes), the virus types detected (influenza A only, or both influenza A and B), the test format, and the type of specimens required for testing.

Such rapid diagnostic tests may be more useful in hospital or institutional settings, where early diagnosis of influenza can differentiate it from other causes of fever in patients with a complex medical history, such as in those who are immunocompromised or have respiratory problems. Such data would enable clinicians to avoid antibacterial drugs and make decisions about whether to isolate infected patients or discharge them sooner. In addition, use of rapid tests could permit early detection of influenza outbreaks in institutions, resulting in more effective utilization of prevention strategies.

Not only do human populations worldwide suffer the annual costs of influenza epidemics, but experts also generally agree that another pandemic of the illness is virtually inevitable. As a result, clinicians must make every effort to use currently available preventive and treatment tools, and researchers must continue to strive for better means of diagnosis, prevention, and treatment.

#### ACRONYM LIST

The following acronyms appear in the pages of this Special Report supplement:

<b>CDC</b>	Centers for Disease Control and Prevention
<b>cDNA</b>	Complementary DNA
<b>CPE</b>	Cytopathic effect
<b>ED</b>	Emergency department
<b>FDA</b>	Food and Drug Administration
<b>HA</b>	Hemagglutinin
<b>NA</b>	Nucleic acid
<b>NI</b>	Neuraminidase inhibitor
<b>NP-RNA</b>	Nucleoprotein ribonucleic acid
<b>NS</b>	Nucleoside
<b>OTC</b>	Over-the-counter
<b>P&amp;I</b>	Pneumonia and influenza
<b>PCP</b>	Primary care physician
<b>PCR</b>	Polymerase chain reaction
<b>POL</b>	Physician's office laboratory
<b>RT-PCR</b>	Reverse transcriptase-polymerase chain reaction