Influenza: Challenges In Diagnosis And Management In The Emergency Department

A 20-month-old boy is brought to the emergency department by his mother because he has had a cough and fever for 3 days. He has no known history of medical problems, and routine vaccinations are up to date. He has been eating less than usual, but his urine output is normal, and he has had no vomiting or diarrhea. His temperature is 39.6°C (103.2°F), pulse is 156 beats per min, respiratory rate is 32 breaths per min, and oxygen saturation is 100% on breathing room air. The infant appears well, although his left tympanic membrane is erythematous and bulging, with apparent middle-ear purulence. The oropharynx is clear, with moist mucosal membranes. His neck is supple. The lungs are clear on auscultation, with no signs of respiratory distress. His abdomen is soft and neither tender nor distended. All extremities are warm and well perfused. You make the diagnosis of otitis media in the setting of a presumed upper respiratory viral infection. While preparing the discharge papers, you consider the many patients you’ve seen during the current flu epidemic and wonder whether treatment for influenza would be appropriate in this case. Will treating the otitis media alone be sufficient? You recall that some patients with an influenza infection are at increased risk for a more severe disease course. Can such a young child be given antiviral medications and, if so, which medication would be appropriate? You wonder how such a common presentation can suddenly become so complex.

No sooner did you finish your evaluation of the infant when a 32-year-old male with no significant previous medical problems arrives in the ED with the same chief complaints: cough and fever. His highest temperature over the past 5 days was 40°C (103.9°F). He has been in the ED with the same chief complaints: cough and fever. His highest
taking over-the-counter cold remedies without relief, and today he is markedly short of breath. The patient has no regular primary care provider and has not required any medical care for several years. His initial vital signs are temperature 39.2°C (102.5°F), respirations 28 per min, pulse 118 beats per min, blood pressure 134/78 mm Hg, and oxygen saturation 88% on room air. On examination, the patient appears uncomfortable with notable tachypnea. The oropharynx is clear and the neck supple. Crackles in the right lower lung field are noted, but no wheezes are noted. The abdomen is soft and nontender. The patient is placed on facemask oxygen with an improvement in saturation to 100%. Chest x-ray reveals a right lower lobar pneumonia with a small pleural effusion. Intravenous antibiotics are started, and an inpatient bed is requested because of his pneumonia with hypoxia. You question whether this is a primary bacterial pneumonia or secondary to an underlying primary influenza infection. Is influenza testing appropriate for this patient and, if so, what type of test should be done? How reliable is rapid influenza testing? Should antiviral treatment be initiated at this time and, if so, what medication would be appropriate? You begin to wonder where you put that recent report from the Centers for Disease Control and Prevention, and hope you didn’t file it where most of your other mail gets filed…

A n estimated 50 million people died during the 1918-1919 influenza pandemic, and approximately one-third of the world’s population was infected. Although at the time the responsible organism had not yet been identified, influenza pandemics were not a new occurrence; they had simply not infected and killed with such efficiency and had not been as well documented.

Medical science has advanced considerably over the past 100 years. Yet despite the discovery and manufacture of powerful antibacterial and antiviral medications, influenza remains a significant cause of morbidity and mortality. Each year, over 30,000 deaths result from influenza in the United States — a rate that has risen over the past 2 decades, partly owing to the aging population. The ability to contain regional outbreaks of the disease, and thereby slow the progression of an emerging pandemic, is essentially lost in an era in which an infected person can relocate to any place on the planet within 24 hours. For this reason, today’s emergency clinician must be keenly aware of emerging global infections. The approach to containing a potential epidemic relies on rapid identification, treatment, and in some cases prophylaxis. The ED plays a key role in monitoring and in early recognition of disease outbreaks.

This issue of Emergency Medicine Practice presents a critical appraisal of the most current literature on influenza. Recent studies on clinical presentation, diagnosis, and treatment are reviewed, providing recommendations for the evaluation and management of patients suspected of having influenza. Special attention is focused on the novel H1N1 influenza pandemic of 2009.

Critical Appraisal Of The Literature

A literature search using PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and the ISI Web of Knowledge (http://www.isiwebofknowledge.com) was conducted, and keywords included emergency department, epidemic, pandemic, swine influenza, and novel H1N1. The Cochrane Database of Systematic Reviews yielded several systematic reviews pertaining mainly to the topic of influenza therapies. For the most up-to-date information on the influenza pandemic of 2009, the Centers of Disease Control and Prevention (CDC) and the World Health Organization (WHO) websites were consulted. Reports and clinical practice guidelines from academic specialty societies, including the American College of Emergency Physicians (ACEP), the Infectious Diseases Society of America (IDSA), and the American Academy of Pediatrics (AAP), were also reviewed.

Classification Of Influenza Viruses

The influenza virus is a spherical, RNA-based organism of the Orthomyxoviridae family, which includes 3 classic subgroups: influenza types A, B, and C. The RNA core of the virus particle is associated with a nucleoprotein (NP) antigen. Variations of this nucleoprotein have led to categorization of influenza viruses into these 3 primary subgroups. Influenza A viruses are further identified based on their specific transmembrane or surface proteins: hemagglutinin (H) and neuraminidase (N). (See Figure 1.) There are 16 different hemagglutinin subtypes and 9 different neuraminidase subtypes, of which 3 subtypes of hemagglutinin (H1, H2, and H3) and 2 subtypes of neuraminidase (N1 and N2) have yielded epidemic disease in the human population. Viral strains are classified based on the type of influenza, site of origin for that particular strain, isolate number, year of isolation, and subtype. For example, the influenza pandemic of 1968 has been designated “A/Hong Kong/03/1968(H3N2).” The surface proteins hemagglutinin and neuraminidase play an important role in antigenic variation of the virus over time, which leads to the occurrence of epidemic and pandemic outbreaks of disease. There are 2 types of antigen variation: antigenic drift and antigenic shift. All 3 virus subgroups, influenza A, B, and C, undergo antigenic drift, which consists of small point mutations to the viral genes encoding for hemagglutinin and neuraminidase. This is clinically significant because these mutations are subtle enough that some im-
munity may be maintained within the population infected previously by influenza viruses of a similar subtype. *Antigenic shift* refers to a much more radical change, with reassortment of the viral genes to the extent that the surface proteins less closely resemble those of viral strains that previously caused infection. When cells are infected by 2 or more different influenza strains at once, a new strain can emerge after genetic reassortment.

Evidence suggests that the reassortment of genes that produces new influenza strains involves an animal host. Pigs, horses, and birds are some of the most common intermediate hosts, thus the respective nomenclature of “swine,” “equine,” and “avian” influenza strains. This explanation would account for the influenza epidemics that have affected areas of the world such as China, where close living conditions between animals and humans facilitate coinfection and genetic reassortment. Because animal coinfection with influenza types B and C is less frequent, the phenomenon of antigenic shift is limited to influenza type A, which accounts for the more frequent epidemics and pandemics involving this viral subtype. Historically, these pandemics have emerged at intervals of approximately 15 to 30 years.\(^1\)\(^,\)\(^11\) (See Table 1.)

### Figure 1. Schematic Diagram Of An Influenza Virion

![Influenza Virion Diagram](image)

This influenza virion schematic shows 2 surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA); M2 ion channel (M2); core viral nucleoprotein (NP); 3 polymerase proteins (PA, PB1, PB2); and matrix protein (M1).


Although certain strains of influenza may appear to share similar nomenclature, differences in their amino-acid sequences resulting from evolutionary changes can be significant. For example, the 1918 influenza virus strain, the novel pandemic 2009 strain, and the seasonal influenza virus of 2007 (A/Brissyne/59/2007) are all H1N1 viral strains, yet the amino-acid differences of the hemagglutinins among these viral strains vary by up to 20%. These differences help explain why partial immunity is at work in certain populations even in the setting of a seemingly “novel” influenza strain. The current H1N1 swine influenza strain of 2009, for example, bears a closer genetic resemblance to strains of H1N1 that circulated throughout the 1940s and 1950s than to the strains of H1N1 that have been circulating over the past 2 decades.

Thus, for the current pandemic of 2009, more significant outbreaks of disease have been seen in the younger population, who have no (or weaker) immunity.\(^12\)\(^,\)\(^13\) (See Figure 2, page 4.) Unlike the typical seasonal influenza, in which mortality has been highest among the elderly, the greatest number of deaths for the 2009 novel H1N1 strain has been among young adults.\(^12\)\(^,\)\(^14\) (See Figure 3, page 4.) Such a variation in morbidity and mortality patterns reflects the emergence of a new epidemic strain of influenza virus in the absence of prior immunity among certain hosts.

### Clinical Presentations

Influenza A is the most common form of the virus, and infection with this subtype causes disease in humans and can lead to pandemics. Influenza B virus infection occurs with less frequency but sometimes results in epidemics. Influenza C virus is the form of the virus least likely to infect humans. When influenza C does infect humans, the illness is typically milder than those caused by types A or B, so diagnosis, prevention, and treatment are not generally pursued.

### Table 1. Influenza Pandemics Over The Past 100 Years

<table>
<thead>
<tr>
<th>Years</th>
<th>Name</th>
<th>Subtype</th>
<th>Extent of Outbreak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918–1919</td>
<td>Spanish flu</td>
<td>H1N1</td>
<td>Estimated deaths: USA: 675,000 Worldwide: 50 million</td>
</tr>
<tr>
<td>1957–1958</td>
<td>Asian flu</td>
<td>H2N2</td>
<td>Estimated deaths: USA: 70,000 Worldwide: 1 to 2 million</td>
</tr>
<tr>
<td>1968–1969</td>
<td>Hong Kong flu</td>
<td>H3N2</td>
<td>Estimated deaths: USA: 34,000 Worldwide: 700,000</td>
</tr>
<tr>
<td>2009–present</td>
<td>Swine flu</td>
<td>H1N1</td>
<td>Ongoing pandemic</td>
</tr>
</tbody>
</table>
Influenza infections are associated with a range of symptoms and presentations that vary by age, making a diagnosis based on clinical presentation alone a challenge. (See Table 2.) The Centers for Disease Control and Prevention (CDC) define “influenza-like illness” (ILI) as a temperature of greater than 37.8˚C (100˚F) plus either cough or sore throat in the absence of a known cause other than influenza.\textsuperscript{15}

Studies have examined patients with laboratory-confirmed influenza in an attempt to distinguish their clinical presentations and symptoms from those of patients with other viral respiratory infections. In 2005, Call et al systematically reviewed the literature to determine the precision and accuracy with which influenza was diagnosed on the basis of signs and symptoms.\textsuperscript{16} Six of the studies met the prespecified inclusion criteria, and the researchers found that no single clinical finding consistently had a positive likelihood ratio high enough to clinically “rule in” influenza, nor did any single finding have a negative likelihood ratio low enough to clinically “rule out” influenza. Another study that focused on more restricted age groups indicated that the strongest predictor of influenza was the acute onset of both fever and cough in patients 60 years of age or older; however, this study quoted an influenza prevalence of 66%, which is much higher than is typical in the average population during seasonal influenza infections.\textsuperscript{17}

The authors of a study of children 13 years of age and younger found that the predominant symptoms among those with influenza were fever (defined as a temperature above 37.5˚C [99.5° F]), cough, and rhinitis, reported in 95%, 77%, and 78% of the study population, respectively.\textsuperscript{8} This study also suggested that the range of fever (> 39˚C [102.2° F]) is significantly higher in children with influenza. Associated gastrointestinal symptoms (vomiting and diarrhea) are also noted more frequently in children than in the adult population.\textsuperscript{19} A prospective study of a pediatric population (age 13 or younger) with symptoms of a respiratory infection and laboratory-confirmed influenza revealed that the diagnosis is being made clinically in only 38.1% of patients, with an even lower degree of accuracy in children under 3 years of age.\textsuperscript{19}

Numerous potential complications can stem from a primary influenza infection and contribute to the initial presentation. An example might be the patient who presents with chest pain in the setting of a viral respiratory illness and is found to have myocarditis as a complication of an influenza infection. Some of the more common complications include acute bronchitis, bacterial pneumonia, and, in children, otitis media.\textsuperscript{20} (See Table 3.)

**Epidemiology**

Up to 20% of the population becomes infected with influenza virus during the winter season in the U.S.\textsuperscript{2} To quantify the precise impact of this disease, epidemiologists face several challenges. Despite the advent of diagnostic testing modalities, accurate estimations of the true morbidity and mortality of the disease is limited.

**Types Of Outbreaks**

Seasonal influenza is the typical outbreak of the infection that occurs at varying times during a given year. When the number of cases of influenza
exceeds what would normally be expected within a circumscribed region, an epidemic is declared. In the past, the term “pandemic” was reserved for outbreaks in which a totally new subtype of the influenza virus was detected, as occurred in 1957 with the discovery of H2N2 and again in 1968 with the discovery of H3N2. Today, however, use of the term pandemic by the WHO is reserved for the occurrence of worldwide events and not for the emergence of a new strain.

Declaration of a pandemic by the WHO raises global awareness of a disease outbreak and allows for aggressive preparedness and response planning. Such a declaration does not necessarily imply a more virulent disease course; it simply indicates the worldwide spread of the disease and its range. In the U.S., the CDC publishes a weekly report, available at http://www.cdc.gov/flu/weekly/, that includes laboratory surveillance data, the frequency of influenza-like illness, and region-based estimates of laboratory-confirmed cases of influenza.

Seasonality And Transmission
Influenza is diagnosed every month of the year somewhere in the world. In the northern hemisphere, the virus is most typically active from November through March. In tropical regions, the virus can often be found year-round. Much of its spread can be attributed to direct person-to-person contact via expelled respiratory secretions, which may explain in part the more rapid transmission during the colder months, when people are often confined to poorly ventilated spaces. While attack rates of the disease from 1 outbreak to another can vary in adult populations based on past resistance and strain patterns, school-age children consistently show higher disease prevalence and rates of transmission across epidemics.

Risk Factors, Morbidity, And Mortality
It is difficult to accurately quantify the yearly morbidity and mortality attributable to influenza or the financial impact this disease has on the health care system. In an attempt to quantify the number of clinic and emergency department visits prompted by this disease process, Poeling et al tested children under 5 years of age who presented to an outpatient setting with influenza-like symptoms over 2 flu seasons. This study also examined the proportion of these illnesses that were recognized based on clinical presentation alone. Of the 2797 children enrolled, 6% were found to have laboratory-confirmed influenza. Of those who tested positive for influenza, the clinician made the diagnosis based on clinical symptoms and presentation alone in only 28% of the cases. This speaks to the lack of specificity of the symptoms, with the great majority of the children being diagnosed with a nonspecific viral illness or upper respiratory infection. In a similar attempt to examine the disease burden of influenza, Ploin et al studied a group of children under 1 year of age who were seen in a pediatric ED during the peak of an influenza epidemic. One in 3 children with an influenza-like illness were found to have laboratory-confirmed influenza and a hospital admission rate of 20%. Follow-up interviews revealed recovery by day 8 in only 63% of the study subjects and parental absenteeism from work in 53% of cases.

Historically, influenza virus infection is associated with the greatest morbidity and mortality in children and in adults with preexisting chronic

Table 2. Most Frequent Clinical Symptoms Of Seasonal Influenza

<table>
<thead>
<tr>
<th>Complication(s)</th>
<th>Incidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Common</td>
<td>Most common in elderly and those with chronic respiratory medical conditions</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Primary viral pneumonia</td>
<td>Common</td>
<td>Typical onset 4-5 days after onset of primary illness</td>
</tr>
<tr>
<td>Secondary bacterial pneumonia</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Myocarditis/pericarditis</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Myositis</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Myoglobinuria and renal failure</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Common</td>
<td>Mostly in children</td>
</tr>
<tr>
<td>Otitis media</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Toxic shock syndrome</td>
<td>Very Rare</td>
<td></td>
</tr>
<tr>
<td>Parotitis</td>
<td>Common</td>
<td></td>
</tr>
</tbody>
</table>

Adapted with permission from Lim et al
medical illnesses such as asthma and chronic obstructive pulmonary disease (COPD). Children under 2 years of age are at increased risk for a more aggressive disease course as well as hospitalization. For infants less than 1 year of age, hospitalization rates are similar to those among elderly populations at high risk. This risk of increased morbidity supports expanded efforts to vaccinate very young children even in the absence of comorbid medical conditions. Mortality studies in the pediatric population show the highest rates of influenza-associated deaths among the very young (age less than 6 months) and among children with underlying comorbid chronic medical conditions. The annual economic impact of seasonal influenza among hospitalized children within the U.S. is estimated to exceed $50 million.

Among adult age groups, rates of influenza infection vary from season to season, depending on the strains in circulation as well as on local patterns of immunity and vaccination. Historically, mortality associated with seasonal outbreaks disproportionately affects the elderly, with up to 90% of deaths occurring in persons age 65 or older. As the average age of the population within the U.S. increases, this pattern is of growing concern. Nevertheless, morbidity and mortality from influenza can vary depending on a population’s immunity to previous strains, as is evident in the 2009 influenza pandemic. (See Figure 3, page 4.)

**Pathophysiology**

The primary route of transmission in influenza occurs when acutely infected individuals pass on the virus through respiratory secretions emitted during coughing or sneezing. The virus initially infects the epithelial cells of the upper respiratory tract as well as alveolar cells of the lower respiratory tract. Viral replication occurs within 4 to 6 hours, yielding a typical incubation period of 18 to 72 hours, depending on the size of the initial inoculum. Peak viral replication is typically reached by the second or third day, with viral shedding usually complete approximately 7 days after infection. However, in children and immunocompromised hosts, viral shedding can be prolonged, lasting up to 2 weeks according to some studies.

During active infection, pathologic changes can be found throughout the respiratory tract. Most significant are changes in the lower respiratory tract, where bronchoscopy reveals diffuse mucosal inflammation and edema of the bronchi. Subsequent desquamation of the epithelial cells that line the respiratory tract leads to epithelial cell necrosis. Spread of the virus into the lung parenchyma can lead to viral pneumonia and occasionally secondary bacterial pneumonia. The most common bacterial pathogens isolated in this setting are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. These organisms often colonize the respiratory tract but then gain access to the lung parenchyma through the depletion of bronchopulmonary defenses. In fact, *H. influenzae* was found with such frequency in the respiratory secretions of influenza victims during the 1918 epidemic that it was initially thought to be the primary etiologic agent. Only later did further study characterize this organism as the cause of a secondary bacterial infection.

**Differential Diagnosis**

Influenza should be included in the differential diagnosis of any febrile patient who presents with symptoms of an upper respiratory infection. Given the nonspecific symptoms of influenza, the differential diagnosis must include a wide range of bacterial and viral infectious processes. Such organisms include, but are not limited to, *Mycoplasma pneumoniae*, adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza viruses, and *Legionella* species. The emergency clinician must keep in mind the wide range of complications that can constitute the chief complaint in patients with influenza. Acute bronchitis, secondary bacterial pneumonia, otitis media, and, less commonly, myocarditis and pericarditis are just some of the possible presenting medical conditions that can complicate a primary influenza infection. (See Table 3, page 5.)

**Prehospital Care**

The initial evaluation and management of patients with influenza-like illness in the prehospital setting requires an accurate, age-appropriate assessment, stabilization, and management of the patient’s respiratory status. Efforts to stabilize the patient could range from simple oxygen supplementation to more advanced airway management techniques. Strategic plans have been established for the evaluation and management of larger numbers of patients in the prehospital setting in the event of a major influenza outbreak. Local, state, and federal protocols have been set forth to guide management in the event of such an outbreak to facilitate effective triage, stabilization, and transport of patients in the prehospital setting. These protocols, as published by the National Highway Traffic Safety Administration, can be found at [http://www.nhtsa.gov/injury/ems/pandemicinfluenza](http://www.nhtsa.gov/injury/ems/pandemicinfluenza).

**ED Evaluation**

The signs and symptoms of influenza vary in severity and by age of the patient. The CDC defines
influenza-like illness as a temperature greater than 37.8°C (100°F) plus either cough or sore throat. This rather broad definition is needed, since symptoms of the disease are not specific. The Clinical Pathways on pages 8 and 9 summarize the clinical approach to patients who present to the ED with an influenza-like illness. Evaluation and management depend on an understanding of the prevalence, of the availability of diagnostic tests, and on disease risk stratification.

Effective management of patients with influenza includes taking infection control measures within the ED. Important steps include the isolation of patients with suspected influenza virus infection as well as the use of appropriate protective equipment for healthcare staff. All patients with suspected influenza should be managed according to standard isolation and contact precautions. The CDC offers detailed infection-control guidelines.

Given the similarity of influenza symptoms to those of several other viral respiratory illnesses, a knowledge of the current local prevalence of the disease is important to guide further evaluation and management. The initial ED management of the patient with suspected influenza or presenting with an influenza-like illness is guided by the current prevalence of the disease at the time of the evaluation. Making this assessment is an important first step, and numerous resources are available to help the clinician in this process. The weekly report issued by the CDC includes laboratory surveillance data, frequency of influenza-like illness, and region-based estimates of laboratory-confirmed cases of influenza (http://www.cdc.gov/flu/weekly/fluactivity.htm). In times of epidemic disease prevalence, as in the influenza pandemic of 2009, strategic management plans are also released by medical specialty organizations (ACEP, IDSA, and AAP) to help guide clinicians and determine departmental management. (See Table 4, page 10.)

Prevalence
The majority of patients who become infected with the influenza virus will experience a mild to moderate disease course, and supportive therapy alone is the most appropriate management intervention. It is important to identify those who are at high risk for a more severe disease course, such as the very young and the very old or those who have comorbid medical conditions. (See Table 5, page 11.) During seasonal influenza outbreaks in the past, morbidity and mortality have been highest among the elderly; however, this pattern has sometimes varied with the emergence of new epidemic strains, as is evident in the current novel H1N1 pandemic of 2009. Patients with comorbid medical conditions appear to suffer a more severe disease course during seasonal and epidemic disease outbreaks.

Risk Stratification
Extensive literature shows that both adults and children with a history of asthma, COPD, or other chronic respiratory conditions experience a more severe disease course when infected with the influenza virus. Young children (under 24 months of age) are at increased risk for hospitalization when compared with older children, and the risk is even greater (more than 4 times higher) among children with preexisting chronic medical conditions. Studies of adult patients hospitalized with acute respiratory disease during a peak influenza season showed that rates of hospitalization among those with high-risk conditions were more than twice as high as rates among those without such risk factors. Pregnant women are also at risk for a more severe disease course.

Diagnostic Studies
The diagnostic tests for influenza include viral culture, immunofluorescence, reverse transcriptase polymerase chain reaction (RT-PCR) assay, and rapid antigen testing. In the setting of an epidemic, formal testing may not always be indicated, as the initiation of treatment and management based solely on clinical symptoms becomes more accurate. The reliability of laboratory results can vary greatly depending on the type of test performed, the quality of the sample submitted, and the laboratory performing the test.

There are 3 types of tests for influenza: 1 type detects influenza A only, another type detects either A or B but cannot distinguish between the 2, and a third type detects both influenza A and B and is subtype-specific. None of the tests other than viral culture and strain-specific RT-PCR will specify the influenza strain, so this information must be extrapolated based on current local epidemiologic patterns. Table 6 (page 12) shows the currently available diagnostic tests for influenza testing along with the various rapid diagnostic testing kits available. Rapid diagnostic testing currently consists of commercially available kits that detect viral influenza antigen. The majority of the currently available kits will detect influenza A and B, but not all will distinguish between the 2. This can have important clinical implications, since the adamantane class of antiviral medications is not effective against influenza B. Fluorescent antibody testing offers relatively rapid results by direct fluorescent antibody (DFA) staining, yielding results within 2 to 4 hours.

Although viral culture and RT-PCR remain the gold standards for influenza testing, both require significantly more time or expense as well as a specialized laboratory to process the specimens. Testing modalities that allow for more rapid processing and
High Risk: Initiate empiric treatment
- Class I if initiated < 48 hours of onset of illness,
- Class II if > 48 hours
Routine testing not needed
- Discuss isolation instructions

Low Risk: Provide supportive therapy
- Discuss isolation instructions
- Class I

What is the current local disease prevalence?

High: Seasonal influenza
- Epidemic/pandemic

Low: go to “Clinical Pathway For Influenza-Like Illness And Low Regional Prevalence Of Influenza” (page 9)

What is the severity of disease?

Mild/moderate disease symptoms

Severe disease symptoms:
- Respiratory distress
- Acute respiratory distress syndrome
- Pneumonia
- Requires hospitalization

Rapid test for influenza:
- Rapid antigen test, or
- Direct fluorescent antibody (DFA) test (Class II)

Positive:
- Initiate antiviral treatment based on local strain and susceptibility patterns
  - Class I if initiated < 48 hours of onset of illness, Class II if > 48 hours
  - Perform confirmatory strain-specific testing

Negative:
- Perform confirmatory testing (viral culture, PCR) (Class I)
- Initiate and continue empiric therapy in the severely ill
  - Class I if initiated < 48 hours of onset of illness, Class II if > 48 hours

Is the patient at high risk for complications of a more severe disease course? (See Table 5, page 11.)

High Risk:
- Initiate empiric treatment (Class I if initiated < 48 hours of onset of illness, Class II if > 48 hours)
- Routine testing not needed
- Discuss isolation instructions

Low Risk:
- Provide supportive therapy
- Discuss isolation instructions (Class I)

Class Of Evidence Definitions

Each action in the clinical pathways section of Emergency Medicine Practice receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful
- Level of Evidence: Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Clinical Pathway For Patient Who Presents To The ED With An Influenza-like Illness And Low Regional Prevalence of Disease

Influenza-like illness and low regional prevalence of influenza

Is the patient at high risk for complications of a more severe disease course? (See Table 5, page 11.) (Class I)

YES

Rapid test for influenza:
• Rapid antigen test, or
• Direct fluorescent antibody (DFA) test (Class II)

Positive:
• Initiate antiviral treatment based on local susceptibility patterns (Class I if initiated < 48 hours of onset of illness, Class II if > 48 hours)
• Perform confirmatory testing (viral culture, PCR) due to high false positive-rate when disease prevalence is low (Class I)

NO

• Supportive therapy
• Discuss isolation instructions (Class I)

Negative:
• Perform confirmatory testing (viral culture, PCR) (Class I)

(Adapted from Clinical Practice Guidelines of the Infectious Diseases Society of America.)

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• Results consistently positive

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• May be acceptable
• Possibly useful
• Considered optional or alternative treatments
Level of Evidence:
• Generally lower or intermediate levels of evidence
• Case series, animal studies, consensus panels
• Occasionally positive results

Indeterminate
• Continuing area of research
• No recommendations until further research
Level of Evidence:
• Evidence not available
• Higher studies in progress
• Results inconsistent, contradictory
• Results not compelling

identification of influenza-positive patients have become the mainstay of diagnostic testing, since they provide more immediate results and thus obviate delays in treatment and management decisions. Numerous studies support the usefulness of obtaining a positive result on rapid influenza testing in deciding whether to perform additional tests, prescribe an antibiotic or an antiviral medication, and consider additional medical management for both pediatric and adult populations.49-55

The sensitivity and specificity of a given diagnostic test remain stable, but its positive and negative predictive values (PPV and NPV, respectively) are affected by disease prevalence. This is an important factor to keep in mind when one must decide whether a particular patient with an influenza-like illness warrants rapid diagnostic testing. In periods of low influenza activity (typically during the summer months), a rapid test will have its lowest PPV and its highest NPV and is more likely to yield false-positive results — up to 50% in 1 study — when the disease prevalence drops to below 5%.56 Conversely, in times of peak influenza activity (eg, during an epidemic or pandemic), a rapid test will have a higher PPV and lower NPV and is more likely to produce a false-negative result.57, 58 (See Table 8, page 14.) In times of epidemic infection, the high prevalence of the disease combined with the greater likelihood of false-negative test results may make empiric treatment based on clinical presentation alone a reasonable consideration in certain patient populations and can greatly reduce the resources, time, and money required for clinical decision making. In 1 prospective study of adults who presented with influenza-like illness when the prevalence of seasonal influenza was high, rapid testing was found to be no better than clinical judgment alone in making the diagnosis of influenza.59 It may be better to reserve testing for more seriously ill patients in whom a confirmed diagnosis of influenza is more critical. In this patient population, rapid testing should always be confirmed by either viral culture or RT-PCR. Even these “gold standard” tests will not reliably exclude influenza virus infection 100% of the time, since the quality of the specimen and the experience of the technician can greatly affect these assay results. Thus, empiric treatment of the critically ill patient must be considered until a clear alternative etiologic explanation can be found.

### Treatment

For patients with evidence of mild-to-moderate disease severity and no underlying high-risk conditions, treatment with supportive therapy alone is reasonable at all times, even with variations in disease prevalence. Antiviral therapy is best reserved for those with a more severe disease course or in whom a high-risk condition predicts increased morbidity and mortality resulting from an influenza virus infection. Early treatment of patients with high-risk chronic medical conditions has been shown to reduce the rate of influenza-related complications.45

Treatment of the patient with an influenza infection involves addressing the primary infection as well as any secondary bacterial infections or complications. Many previously healthy patients with uncomplicated mild to moderate disease can be treated with symptom-based supportive therapy. For those patients with a more severe disease course or underlying high-risk conditions, antiviral therapy is indicated. Owing to the increased prevalence of drug-resistant isolates in some influenza strains, the continual shifting of sensitivity patterns, and the rate at which drug resistance is emerging during therapy, emergency clinicians must be familiar with local patterns of influenza infection as well as susceptibility patterns within their community.

### Table 4. Internet Resources For Evaluation/Management Of Influenza

<table>
<thead>
<tr>
<th>Organization</th>
<th>Topic</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC</td>
<td>Up-to-date information on novel H1N1 outbreak</td>
<td><a href="http://www.cdc.gov/h1n1flu/">http://www.cdc.gov/h1n1flu/</a></td>
</tr>
<tr>
<td>CDC</td>
<td>Weekly flu activity and surveillance</td>
<td><a href="http://www.cdc.gov/flu/weekly/fluactivity.htm">http://www.cdc.gov/flu/weekly/fluactivity.htm</a></td>
</tr>
<tr>
<td>CDC</td>
<td>Influenza infection in pregnancy</td>
<td><a href="http://www.cdc.gov/h1n1flu/clinician_pregnant.htm">http://www.cdc.gov/h1n1flu/clinician_pregnant.htm</a></td>
</tr>
<tr>
<td>CDC</td>
<td>Antiviral susceptibility information and treatment recommendations</td>
<td><a href="http://www.cdc.gov/flu/professionals/antivirals/index.htm">http://www.cdc.gov/flu/professionals/antivirals/index.htm</a></td>
</tr>
</tbody>
</table>

*CDC = Centers for Disease Control and Prevention.
**Antiviral Medications**

There are 2 classes of antiviral medications for influenza. *(See Table 7, page 13.)* The first class to be discovered was the adamantane derivatives, amantadine and rimantadine. A more recent class of antiviral drugs is the neuraminidase inhibitors, which include zanamivir and oseltamivir. All these drugs are taken orally except for zanamivir, which is orally inhaled, and all 4 can be used for disease prophylaxis in certain clinical situations.

**The Adamantane Derivatives**

Amantadine and rimantadine inhibit activity of the M2 protein within the influenza A virus. This protein is a transmembrane polypeptide involved in the viral replication process through its actions as an ion channel. Because the genetic sequence of this protein channel within the influenza B virus is significantly different, this class of medications is effective only for the treatment and prevention of influenza A.

Although these 2 medications have similar clinical antiviral activities, their side effect profiles and pharmacokinetics differ significantly. Amantadine clearance depends on adequate renal function, so careful dose adjustment is required for patients with renal insufficiency. This agent has also been associated with more significant central nervous system and psychiatric side effects, such as hallucinations, insomnia, headaches, dizziness, and depression — symptoms that have proved to be especially problematic in the elderly.

Rimantadine, in contrast, is metabolized in the liver and therefore does not require dose adjustment in the presence of renal insufficiency. In addition, it does not have the same degree of central nervous system activity and associated side effect profile as amantadine.

Studies have shown that starting these medications early (i.e., within 2 days of the onset of symptoms) will reduce the severity and duration of influenza symptoms in drug-sensitive viral strains. Nevertheless, reductions in the duration of viral shedding found in isolated studies of amantadine and rimantadine has not been confirmed in more systematic reviews. Another systematic review of these medications among children and the elderly found that rimantadine was effective in abating fever in children by the third day of treatment, as opposed to 4 to 8 days without this drug. There were too few studies to reach a significant conclusion regarding the use of amantadine in children or the use of either of these medications in the elderly.

The recent discovery of increasing mutations in the M2 protein gene among avian influenza viral isolates has suggested the potential for human pandemics with drug-resistant strains. This was a concern during the influenza season of 2005–2006, during which up to 92% of viral isolates were found to have point mutations within the M2 gene, conferring resistance to the adamantane class of medications. The restriction of these medications to the treatment of influenza A, the rapid emergence of drug resistance, and their side effect profiles have limited the usefulness of this class of medications in clinical practice. The most recent systematic reviews discourage the primary use of these medications in the treatment and prophylaxis of influenza except in select situations when other medication approaches have failed and regional viral isolate susceptibility has been documented.

**The Neuraminidase Inhibitors**

The newer generation of antiviral medications, oseltamivir and zanamivir, inhibit the spread of newly formed virus particles within the host cell by blocking the function of neuraminidase, a viral cell surface protein. This enzyme is necessary to cleave newly formed viral particles that are bound by their hemagglutinin surface proteins to the sialic acid receptors of the host cell. Since these medications inhibit neuraminidase, they are effective in patients infected with either type A or B influenza virus. Both drugs tend to be well tolerated; the most frequently noted side effects are oseltamivir-induced nausea and vomiting and zanamivir-induced diarrhea.

Oseltamivir is taken orally and is currently approved for the treatment of influenza in patients 1 year of age and older and for prophylaxis in patients 13 years of age and older. However, in the setting of an influenza epidemic, emergency use of the drug has been authorized by the FDA for both treatment and chemoprophylaxis in children under age 1.

**Table 5. Populations At High Risk For A More Severe Course Of Influenza Infection**

<table>
<thead>
<tr>
<th>Age &gt; 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 2 years</td>
</tr>
<tr>
<td>Chronic pulmonary disease, such as asthma or chronic obstructive lung disease</td>
</tr>
<tr>
<td>Chronic cardiovascular, renal, and/or hepatic disease</td>
</tr>
<tr>
<td>Hematologic disease, such as sickle cell anemia</td>
</tr>
<tr>
<td>Metabolic disorders, such as diabetes mellitus</td>
</tr>
<tr>
<td>Immunosuppression secondary to either disease, as in HIV, or a medication</td>
</tr>
<tr>
<td>Compromised respiratory function or other conditions that increase risk of aspiration</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Patients on long-term aspirin therapy for chronic medical conditions</td>
</tr>
<tr>
<td>Neuromuscular disorders, seizure disorders, or other cognitive dysfunction that may compromise handling of respiratory secretions</td>
</tr>
</tbody>
</table>

*(Adapted from Clinical Practice Guidelines of the Infectious Diseases Society of America.)*
Zanamivir is administered via inhalation because of its poor bioavailability. It is approved for the treatment of influenza in patients 7 years of age and older and for prevention of the disease in patients 5 years of age and older. Because of its possible association with bronchospasm, zanamivir is not recommended for patients with underlying reactive airway disease, although studies have not shown direct causality.\(^67\)

The literature on the use of neuraminidase inhibitors for the treatment and prevention of influenza has been systematically reviewed. In previously healthy adults, oral oseltamivir resulted in an efficacy rate of approximately 73% against symptomatic influenza when given in a dose of 150 mg/day, and the duration of clinical symptoms was shortened by approximately 1 day.\(^68\) Inhaled zanamivir at a dose of 10 mg/day was 62% efficacious.

### Table 6. Currently Available Diagnostic Tests For Influenza In The United States\(^1\)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Influenza Types Detected</th>
<th>Acceptable Specimens</th>
<th>Time For Results</th>
<th>Rapid Result Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral culture</td>
<td>A and B</td>
<td>NP(^2) swab, throat swab, nasal wash, bronchial wash, nasal aspirate, sputum</td>
<td>3-10 days(^3)</td>
<td>No</td>
</tr>
<tr>
<td>Immunofluorescence; Direct Fluorescent Antibody (DFA) Staining</td>
<td>A and B</td>
<td>NP(^2) swab, nasal wash, bronchial wash, nasal aspirate, sputum</td>
<td>2-4 hours</td>
<td>No</td>
</tr>
<tr>
<td>RT-PCR(^5)</td>
<td>A and B</td>
<td>NP(^2) swab, throat swab, nasal wash, bronchial wash, nasal aspirate, sputum</td>
<td>2-4 hours</td>
<td>No</td>
</tr>
<tr>
<td>Serology</td>
<td>A and B</td>
<td>Paired acute and convalescent serum samples(^6)</td>
<td>2 weeks or more</td>
<td>No</td>
</tr>
<tr>
<td>Enzyme Immuno Assay (EIA)</td>
<td>A and B</td>
<td>NP(^2) swab, throat swab, nasal wash, bronchial wash</td>
<td>2 hours</td>
<td>No</td>
</tr>
<tr>
<td><strong>Rapid Diagnostic Tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3M(^TM) Rapid Detection Flu A+B Test(^7,9) (3M)</td>
<td>A and B</td>
<td>NP(^2) swab/aspirate, nasal wash/aspirate</td>
<td>15 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>Directigen EZ Flu A+B(^7,9)          (Becton-Dickinson)</td>
<td>A and B</td>
<td>NP(^2) wash/aspirate/swab, lower nasal swab, throat swab; bronchioalveolar lavage</td>
<td>less than 15 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>BinaxNOW Influenza A&amp;B(^7,9)         (Inverness)</td>
<td>A and B</td>
<td>Nasal wash/aspirate, NP(^2) swab</td>
<td>less than 15 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>OSOM® Influenza A&amp;B(^9) (Genzyme)</td>
<td>A and B</td>
<td>Nasal swab</td>
<td>less than 15 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>QuickVue Influenza Test(^4,8) (Quidel)</td>
<td>A and B</td>
<td>NP(^2) swab, nasal wash, nasal aspirate</td>
<td>less than 15 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>QuickVue Influenza A+B Test(^4,8) (Quidel)</td>
<td>A and B</td>
<td>NP(^2) swab, nasal wash, nasal aspirate</td>
<td>less than 15 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>SAS FluAlert(^7,9) (SA Scientific)</td>
<td>A and B</td>
<td>Nasal wash/aspirate</td>
<td>less than 15 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>TRU FLU(^7,9) (Meridian Bioscience)</td>
<td>A and B</td>
<td>Nasal wash/swab, NP aspirate/swab</td>
<td>15 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td>XPECT Flu A&amp;B(^7,9) (Remel)</td>
<td>A and B</td>
<td>Nasal wash, NP(^2) swab, throat swab</td>
<td>less than 15 minutes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

1. List may not include all test kits approved by the U.S. Food and Drug Administration.
2. NP = nasopharyngeal.
3. Shell vial culture, if available, may reduce time for results to 2 days.
4. Does not distinguish between influenza A and B virus infections.
5. RT-PCR = reverse transcriptase polymerase chain reaction.
6. A fourfold or greater rise in antibody titer from the acute- (collected within the 1st week of illness) to the convalescent-phase (collected 2-4 weeks after the acute sample) sample is indicative of recent infection.
7. Moderately complex test – requires specific laboratory certification.
8. CLIA-waived test. Can be used in any office setting. Requires a certificate of waiver or higher laboratory certification.

Disclaimer: Use of trade names or commercial sources is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention or the Department of Health and Human Services.

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The use of oseltamivir as postexposure prophylaxis among household contacts had an efficacy rate of 58.5%, with a range of efficacy of 68% to 89% among direct contacts of index cases.51 Both medications also led to a statistically significant decrease in viral nasal titers as well as a reduction in secondary lower respiratory tract complications, particularly bronchitis and pneumonia.51

A similar review of neuraminidase inhibitor therapy in children under 12 years of age found that the duration of clinical symptoms was reduced by 36 hours among previously healthy children taking oseltamivir and by 30 hours among those taking zanamivir.70 In addition, a significant reduction in complications from influenza, particularly otitis media, was also noted among children taking oseltamivir. A 51.7% reduction in future diagnoses of pneumonia was reported in another study of pediatric patients.59

Table 7. Antiviral Medications For Treatment And Prophylaxis Of Influenza

<table>
<thead>
<tr>
<th>Antiviral Agent</th>
<th>Treatment</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuraminidase Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir™ (Tamiflu™)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults or Child &gt; 40 kg</td>
<td>75 mg twice daily for 5 days</td>
<td>75 mg once daily for 10 days</td>
</tr>
<tr>
<td>Children (&gt; 12 mo of age)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 15 kg</td>
<td>30 mg twice daily for 5 days</td>
<td>30 mg once daily for 10 days</td>
</tr>
<tr>
<td>16-23 kg</td>
<td>45 mg twice daily for 5 days</td>
<td>45 mg once daily for 10 days</td>
</tr>
<tr>
<td>24-40 kg</td>
<td>60 mg twice daily for 5 days</td>
<td>60 mg once daily for 10 days</td>
</tr>
<tr>
<td>Children (&lt; 12 mo of age)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-11 mo</td>
<td>25 mg twice daily for 5 days</td>
<td>25 mg once daily for 10 days</td>
</tr>
<tr>
<td>3-5 mo</td>
<td>20 mg twice daily for 5 days</td>
<td>20 mg once daily for 10 days</td>
</tr>
<tr>
<td>&lt; 3 mo</td>
<td>12 mg twice daily for 5 days</td>
<td>Not Recommended Routinely</td>
</tr>
<tr>
<td>Zanamivir (Relenza™)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>10 mg inhaled twice daily for 5 days</td>
<td>10 mg Inh. once daily for 10 days</td>
</tr>
<tr>
<td>Children</td>
<td>10 mg inhaled twice daily for 5 days (age ≥ 7 years)</td>
<td>10 mg Inh. once daily for 10 days (age ≥ 5 years)</td>
</tr>
<tr>
<td>Adantamaines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults/Adolescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-64 yr of age</td>
<td>100 mg twice daily</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td>&gt; 64 yr of age</td>
<td>100 mg once daily</td>
<td>100 mg once daily</td>
</tr>
<tr>
<td>Children (&gt;12 mo of age)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 yr of age and ≥ 40 kg</td>
<td>100 mg twice daily</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td>≥10 yr of age and &lt; 40 kg or 1-9 yr of age</td>
<td>5 mg/kg/day divided twice daily (max daily dose 150 mg)</td>
<td>5 mg/kg/day divided twice daily (max daily dose 150 mg)</td>
</tr>
<tr>
<td>Rimantadine¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults/Adolescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-64 yr of age</td>
<td>100 mg twice daily</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td>&gt; 64 yr of age</td>
<td>100 mg once daily</td>
<td>100 mg once daily</td>
</tr>
<tr>
<td>Children (&gt;12 mo of age)#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 yr of age and ≥ 40 kg</td>
<td>100 mg twice daily#</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td>≥10 yr of age and &lt; 40 kg or 1-9 yr of age</td>
<td>5 mg/kg/day divided twice daily (max daily dose 150 mg)#</td>
<td>5 mg/kg/day divided twice daily (max daily dose 150 mg)#</td>
</tr>
</tbody>
</table>

* FDA approved under emergency use authorization during 2009 influenza pandemic.
** Dose reduction for oseltamivir recommended for creatinine clearance < 30 mL/min.
** Dose reduction for amantadine recommended for creatinine clearance ≤ 50 mL/min.
¶ Reduction in dose of rimantadine to 100 mg/day recommended for severe hepatic dysfunction or creatinine clearance < 10 mL/min.
# FDA approved for treatment and prophylaxis in adults and prophylaxis in children, but published data exist suggesting safety and efficacy for the treatment of influenza in the pediatric population.

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More modest reductions in the duration of clinical symptoms in children with high-risk conditions were also noted, but these values did not reach statistical significance, probably owing to the limited number of studies in this patient population.70 When the neuraminidase inhibitors were first developed and used in clinical practice, the emergence of resistant viral isolates was rare. However, continual changes in gene sequences within the influenza viral genome have led to an increase in the number of drug-resistant viral strains. During the 2007–2008 influenza season, oseltamivir-resistant H1N1 seasonal influenza emerged globally at rates of up to 68% in some regional populations.71 This led to a resurgence of the adamantane derivatives as the recommended primary agent in regions of the world where the rates of oseltamivir-resistant H1N1 seasonal virus isolates were high.

### Table 8. Test Characteristics And Accuracy Of Rapid Antigen Test Results As Influenced By Disease Prevalence

<table>
<thead>
<tr>
<th>Test Characteristic</th>
<th>Description</th>
<th>Affected By Disease Prevalence?</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Proportion of positive tests in patients who actually have the disease</td>
<td>No</td>
<td>True-positive rate</td>
</tr>
<tr>
<td>Specificity</td>
<td>Proportion of negative tests in patients who do not have the disease</td>
<td>No</td>
<td>True-negative rate</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>Proportion of people with a positive test result who actually have the disease</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>Proportion of those with a negative result who do not have the disease</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Influenza Prevalence</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low (summer)</td>
<td>Low</td>
<td>Very high</td>
</tr>
<tr>
<td>High (seasonal outbreak)</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Very high (epidemic/pandemic)</td>
<td>Very high</td>
<td>Moderate/low</td>
</tr>
</tbody>
</table>

Adapted from Centers for Disease Control and Prevention.57

### Special Circumstances: The Influenza Pandemic Of 2009: “Novel” H1N1 Influenza A

#### Genetics And Epidemiology

Strains of H1N1 influenza have been implicated in past seasonal and epidemic outbreaks of disease. The current pandemic strain appears to be novel and to have genetic elements of past swine, avian, and human influenza strains.72 Genetically, the H1N1 novel influenza A virus is most similar to the strain of H1N1 that circulated in the 1950s and is thought to have evolved via a genetic pathway different from that of the H1N1 strain that has circulated over the past 3 decades.12,13 This explains the pattern of infection seen when this virus first emerged in the spring of 2009, with children and young adults representing a large majority of the new infections. Some evidence of partial immunity has been seen in the older population even though this group has historically been hit hardest by seasonal influenza infections and their numerous complications.12 (See Figures 2 and 3, page 4.) In some cases, the greatest number of new infections have occurred among people between 5 and 24 years of age, as evidenced by the large number of school closings in some US cities during the initial wave of infection.

Several pandemics over the past century, including the infamous pandemic of 1918–1919, were characterized by several waves of infection — a pattern that is of great concern to health care professionals and public health officials. Although the H1N1 novel influenza A infection retained its pandemic status throughout the summer of 2009, its rate of transmission within the US decreased significantly during this time, owing perhaps to the warmer weather, less crowding indoors, and less cohorting of children within schools. Initially, transmission rates for this virus were significant, but its level of virulence in terms of morbidity and mortality does not appear to match that of past pandemics.3,73 Early in the pandemic, the majority of deaths were among people who were at high risk for a more aggressive disease course.3 (See Table 5, page 11.) Within this group, pregnant women in particular have been shown to have significantly higher morbidity and mortality, making aggressive diagnosis and treatment critical in this population.74,75

Initial genetic evaluation of the novel H1N1 strain has provided some reassurance, since this virus appears to lack the PB1-F2 gene, a known molecular marker of pathogenicity that has been consistently present in more virulent influenza strains in the past. This gene was present within the influenza viral genome have led to an increase in the number of drug-resistant viral strains. During the 2007–2008 influenza season, oseltamivir-resistant H1N1 seasonal influenza emerged globally at rates of up to 68% in some regional populations. This led to a resurgence of the adamantane derivatives as the recommended primary agent in regions of the world where the rates of oseltamivir-resistant H1N1 seasonal virus isolates were high.

Influenza Prevalence

- **Very low (summer)**: Low
- **High (seasonal outbreak)**: Moderate
- **Very high (epidemic/pandemic)**: Very high

Adapted from Centers for Disease Control and Prevention.57
who are susceptible to infection may remain low. However, reassortment of genes has been known to occur even within a single epidemic, so close monitoring of morbidity and mortality rates throughout the pandemic will be important to detect any changes in the transmission and virulence patterns of this newly emerged strain of virus.

Clinical Presentation
The clinical presentation of patients infected with the novel H1N1 strain is similar to that of seasonal influenza, with fever, cough, sore throat, and shortness of breath being among the most common complaints. Complaints of gastrointestinal symptoms are higher than one would expect in typical cases of influenza, with vomiting and diarrhea reported in up to 25% of patients.39,77,78

Diagnosis
Several tests are available to facilitate diagnosis of the novel H1N1 influenza, such as rapid antigen testing kits for influenza A. (See Table 6, page 12.) However, given the heightened prevalence of the disease during this epidemic outbreak as well as the resulting increase in the false-negative rate with rapid antigen testing, a diagnosis based on clinical presentation alone may be warranted in some patient populations. Early studies on the use of rapid antigen tests for this influenza strain revealed a sensitivity of 51% using the QuickVue Influenza A+B test® (Quidel).79 This finding emphasizes the importance of not relying on rapid testing alone for this diagnosis and the need for empiric therapy in patients who are severely ill or at high risk for a more severe disease course. Further testing using the RT-PCR assay or viral culture should be performed in patients with a negative result on rapid antigen testing for whom a confirmed diagnosis is important. Even the historical “gold standards” of PCR and viral culture cannot be relied on to exclude an influenza infection 100% of the time, since variations in the quality of the specimen obtained and the experience of the technician can affect the results of these assays. Thus, empiric treatment of the critically ill patient must be considered until a clear alternative diagnostic explanation can be found.

Treatment
Early studies have shown the novel H1N1 influenza strain to be sensitive to the neuraminidase inhibitors (oseltamivir and zanamivir) but resistant to amantadine and rimantadine.78 The seasonal influenza H1N1 strain that circulated during the season of 2008–2009 demonstrated resistance to oseltamivir. The addition of this novel H1N1 influenza strain to those likely to circulate during the upcoming 2009–2010 influenza season presents several challenges in terms of diagnosis and treatment decisions.

Table 9 shows the 4 viral strains of influenza that are currently expected to circulate during the 2009–2010 influenza season, along with their antiviral drug sensitivities.7

For testing purposes, influenza B remains a concern, since some rapid testing kits detect influenza A exclusively. This is an important consideration when one is choosing antiviral therapy because the adamantane derivatives provide no coverage for influenza B. With regard to the influenza A strains, seasonal influenza virus A/Brisbane/59/2007/H1N1 has shown increasing resistance to oseltamivir, the medication which has become the first-line drug of choice for patients with suspected 2009 pandemic influenza A (H1N1). Thus, close, consistent monitoring of local influenza strain prevalence and susceptibility patterns is paramount. In the majority of clinical settings, empiric therapy is based on clinical presentation as well as information obtained on rapid antigen testing. Since rapid testing does not provide strain-specific information, an awareness of local influenza strain patterns will be necessary when one is choosing an antiviral agent. In settings in which more than 1 influenza strain is circulating, empiric therapy with more than 1 agent may be indicated until strain-specific information can be obtained by means of viral culture or RT-PCR assay.7

Disposition
Final disposition of the patient with a suspected or confirmed influenza infection will depend on many clinical factors, including (but not limited to)
respiratory status and work of breathing, oxygen saturation, age, comorbid medical conditions, and reliability in obtaining follow-up care. Admission to the hospital may be needed at any point for a patient with influenza to manage not only the primary viral infection but also the many complications that may arise. The patient’s age is also an important consideration, since the very young and very old are at higher risk for a more severe and complicated disease course. For patients who can be safely discharged from the ED, the emergency clinician must arrange for close follow-up with the patient’s primary care provider and discuss specific reasons why a return to the emergency department might be necessary.

**Summary**

Because influenza infections can present with a wide range of nonspecific clinical signs and symptoms and can be responsible for numerous complications, emergency clinicians must be keenly alert for this possible diagnosis. A knowledge of the local seasonal prevalence of influenza as well as the

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**Risk Management Pitfalls For Influenza**

1. **“The fever was low grade; I thought the baby just had a cold.”**
   The presenting signs and symptoms of influenza infection are nonspecific, and a diagnosis based on clinical presentation alone becomes less accurate in children under 3 years of age. Although many children will experience a mild disease course and can be managed with supportive therapy, patients under age 2 years are at high risk for a more severe clinical course. Therefore, emergency clinicians need to be vigilant and have a high index of suspicion for possible influenza infection in high-risk populations, especially when disease prevalence is high.

2. **“The patient had an infiltrate on chest x-ray, so bacterial pneumonia appeared to be the clear diagnosis.”**
   Numerous secondary complications can stem from an initial primary influenza infection. When addressing and treating these complications, the emergency clinician must not overlook the possibility of a primary influenza infection and the need for medical management. Some of the most common influenza-related complications include acute bronchitis, bacterial pneumonia, and otitis media. In certain clinical situations, treatment with antiviral medications as well as antibacterial medications may be indicated.

3. **“I thought I would just let it run its course.”**
   Many previously healthy people can be treated with supportive therapy alone. However, it is crucial for the emergency clinician to be aware of the numerous risk factors that are likely to result in a more severe disease course. For those patients deemed well enough to be safely discharged from the ED, the clinician must ensure that the patient’s primary care provider will maintain close follow-up and that possible reasons for needing to return to the ED are discussed.

4. **“It is the summer. Influenza occurs in the winter, so I do not need to be concerned about it at this time of the year.”**
   Although influenza certainly exhibits seasonal fluctuations and regional outbreaks, the disease can occur year round. Testing and possible empirical treatment of patients with an influenza-like illness are influenced by the regional prevalence of the disease, so emergency clinicians should be aware of medical agencies that track the prevalence of influenza on a regional and national level, such as the Centers for Disease Control and Prevention.

5. **“Swine flu appears to be everywhere. I don’t have the time to consult the CDC website. I will just give oseltamivir to my patient and be done with it.”**
   Even in times of epidemic influenza infection, numerous strains can be circulating at a given time within a particular region. During the 2008–2009 influenza season, a strain of influenza circulated that was resistant to oseltamivir. In April 2009, a novel H1N1 influenza strain emerged that showed antiviral susceptibilities different from those of the seasonal influenza strain. Thus, without knowing the prevalence of local strains, the emergency clinician might mistakenly choose an antiviral agent that will prove less effective on those strains. Treatment with more than 1 agent may even be indicated in some regions until more formal strain-specific diagnostic testing can be undertaken. Since certain medications are effective only against influenza type A, the local prevalence of any type B influenza should be determined in order to select the appropriate drug therapy.
specific strains circulating within a particular region are crucial for appropriate diagnostic and treatment decisions and will help to limit useless testing when empiric therapy would be more appropriate. Such considerations will improve efficiency in the ED while still ensuring that patients who are at increased risk for a more severe disease course will receive timely and appropriate therapy. With the evolution of new influenza strains through genetic reassortment combined with the globalization of disease, the world is at greater risk than ever before for pandemics. Today’s emergency clinician must be both an epidemiologist and a clinician in order to recognize emerging pathogens and make the complex decisions required for individual and community health.

**Case Conclusions**

A colleague reminds you that the Centers for Disease Control and Prevention have published guidelines for the evaluation and treatment of patients who present with an influenza-like illness. A visit to the CDC website confirms your impression that your area is experiencing an epidemiologic reassortment of strains circulating locally, which requires careful consideration of diagnostic and treatment strategies.

**Risk Management Pitfalls For Influenza** (Continued from page 16)

6. “The World Health Organization has declared a pandemic. I feel better giving all my suspected influenza patients antiviral therapy, since I don’t want anyone to have a poor outcome.” Such a declaration does not necessarily mean that the particular infectious organism is more virulent. It merely recognizes that the disease is spreading worldwide. Pandemics thus can occur during both mild and more severe disease courses.

7. “I see so many patients in the ED every hour. I can’t possibly wear a mask and wash my hands for every patient. Plus, I must have been exposed to influenza 100 times already.” Maintaining effective infection control is crucial to protect not only other patients in the ED but also the health care staff. Patients suspected of having influenza require appropriate isolation, and strict hand washing as well as personal protective equipment (e.g., masks) are necessary to protect health care staff who are in direct contact with patients. Absenteeism due to influenza infection can be a significant drain on health care personnel and staffing. The Strategic Plan for Management of an Influenza Outbreak, published by the American College of Emergency Physicians, is a great resource to ensure the highest level of preparedness on the part of the ED staff as well as their ability to handle a surge in patient volume that can be expected during a disease pandemic.

8. “I performed a rapid influenza test and it was negative, so I am safe sending home my patient on supportive therapy alone.” Numerous forms of testing are available to detect influenza infection. Rapid diagnostic tests help guide clinicians in their immediate management decisions, but the quality of the specimen and skill of the technician performing the assay can significantly influence results. Certain rapid assays are specific for influenza type A, so knowing what strains are circulating locally is important. In times of high disease prevalence, the chance that a given patient with an influenza-like illness actually has the disease is increased, as are the number of false-positive results obtained from rapid diagnostic testing. At such times, empiric therapy based on clinical presentation alone is advised for patients at high risk. In more severely ill patients, viral culture and PCR testing is indicated when the initial rapid test yields a negative result.

9. “My patient is pregnant and has influenza. The side effect profile of antiviral medications concerns me, so I feel better treating her with supportive care.” Pregnancy is a risk factor for a more severe disease course during an influenza infection. Initial epidemiologic data from the influenza pandemic of 2009 indicate that some of the highest rates of morbidity and mortality are among pregnant women. Although any medication taken during pregnancy can have a deleterious effect on the fetus, the potential for complications and significant morbidity is too great to forgo antiviral therapy in this population.

10. “Medical knowledge has advanced considerably over the past few decades, and now we have great antiviral medications. I simply do not need to worry about a devastating influenza infection today.” While it is true that medical science has advanced considerably since the pandemic of 1918, influenza remains a significant threat. The ability of the virus to undergo genetic reassortment allows for the rapid development of new influenza strains to which the population has little or no previous immunity. Resistance to antiviral medications has been known to develop quickly for certain influenza strains and appears to be a rapidly increasing concern over time.
Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.


**Cost- and Time-Saving Strategies**

1. **Reserve formal diagnostic testing for patients who are more severely ill or during times of low disease prevalence.**
   
   *Risk Management Caveat:* The clinical presentation of influenza is nonspecific, and not every patient requires formal testing. Patients with more severe illness who require hospitalization should be tested to help guide treatment and management decisions. In times of high disease prevalence, many patients who are at high risk of complications and a more severe disease course can be treated empirically without formal diagnostic testing. Many patients who are otherwise healthy and at low risk for disease complications can be treated with supportive therapy. Testing is appropriate in times of low disease prevalence, since the signs and symptoms of influenza can closely mimic many other upper respiratory infections. For patients with an influenza-like illness in which influenza testing and antiviral treatment are not warranted, close follow-up with the patient’s primary care provider is important as is a discussion of reasons to return to the ED.

2. **Be familiar with the available Internet-based public health resources that can inform the clinician about local influenza strain prevalence as well as strain-specific medication susceptibilities.**

3. **Prescribe antiviral medications only for patients who are more severely ill or at high risk for a more severe disease course.**
   
   *Risk Management Caveat:* The vast majority of previously healthy patients without underlying comorbid medical conditions can be treated with supportive therapy alone. Antiviral medication should be reserved for patients who are more severely ill or who are at higher risk for a more severe disease course. For patients in whom antiviral treatment is not warranted, follow-up with the patient’s primary care provider is important as well as a discussion of important reasons to return to the emergency room.

4. **A careful review and clear understanding of published strategies for ED management during influenza epidemics will result in greater skill and proficiency in the rapid processing of a large number of patients.**

5. **Careful ED infection control is important for the protection of both patients and health care personnel and will reduce absenteeism among staff.**
null


CME Questions

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1. Lack of which of the following symptoms allows you to clinically rule out an influenza infection?
   a. Sore throat
   b. Cough
   c. Nasal congestion
   d. None of the above

2. Regarding a particular influenza strain, declaration of an influenza pandemic implies that
   a. It has been isolated on every major continent
   b. It is more virulent than the typical strain of influenza
   c. There are more cases of the disease occurring over a worldwide distribution than would typically be expected
   d. There is no vaccine available for that particular strain of influenza

3. Which of the following is not a common complication of an influenza infection?
   a. Otitis media
   b. Guillain-Barré syndrome
   c. Bacterial pneumonia
   d. Acute bronchitis

4. Which of the following is not included in the CDC clinical presentation definition for an influenza-like illness?
   a. Muscle aches
   b. Cough
   c. Sore throat
   d. Fever > 37.8°C (100°F)

5. Which of the following is not a risk factor for a more severe disease course during an influenza infection?
   a. A history of asthma
   b. Age > 65 years
   c. Previous influenza infection
   d. Pregnancy

6. Which of the following test characteristic(s) is/are affected by the prevalence of a disease?
   a. Sensitivity
   b. Positive predictive value
   c. Negative predictive value
   d. Specificity
   e. All of the above
   f. Only a + d
   g. Only b + c

7. During an influenza epidemic, which of the following influenza-positive patients does not warrant empiric antiviral therapy and can be safely discharged home on supportive therapy?
   a. Well-appearing, previously healthy 12-year-old boy with a temperature of 39.4°C (103°F), cough, upper respiratory infection (URI), clear lungs, and no respiratory distress on exam
   b. Well-appearing, previously healthy 12-year-old boy with a temperature of 39.4°C (103°F), cough, URI, hypoxia, tachypnea, and a right lower lobar pneumonia on chest x-ray
   c. Well-appearing 12-year-old boy with a history of moderate persistent asthma, a temperature of 39.4°C (103°F), cough, URI, clear lungs, and no respiratory distress on exam
   d. Well-appearing, previously healthy 18-month-old infant male with a temperature of 39.4°C (103°F), cough, URI, clear lungs, and no respiratory distress on exam

8. If you are treating a severely ill patient with suspected influenza infection, which of the following diagnostic tests is most definitive, requires no further confirmatory testing, and rules out influenza infection?
   a. Direct fluorescent antibody testing
   b. Viral culture
   c. Rapid antigen immunoassay
   d. Enzyme immunoassay
9. Which of the following factors is most important to consider when choosing an antiviral medication for treatment of an influenza infection?
   a. The strains of influenza circulating in your region and their susceptibility patterns
   b. The renal function of your patient
   c. The age of your patient
   d. The hepatic function of your patient
   e. All of the above

10. Which of the following is appropriate empiric antiviral therapy in a severely ill hospitalized patient with confirmed influenza in which local strain-specific epidemiologic and culture data are not yet available?
   a. A neuraminidase inhibitor (oseltamivir or zanamivir)
   b. An adamantane (amantadine or rimantadine)
   c. One from each of the categories above
   d. Ribavirin

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**Date of Original Release:** November 1, 2009. Date of most recent review: September 20, 2009. Termination date: November 1, 2012.

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**Target Audience:** This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

**Goals & Objectives:** Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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**Key Points**

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<th>Clinical Presentation of Influenza</th>
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<td>The clinical presentation of influenza is non-specific and can mimic many other acute respiratory infections.</td>
<td><strong>Influenza-like illness</strong> is defined by the CDC as temperature &gt; 37.8°C (100°F) plus either cough or sore throat.15 This is a broad definition that includes the presenting symptoms of many other viral respiratory infections. No one symptom can fully rule in or rule out an influenza infection.16</td>
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<th>Rapid Testing for Influenza</th>
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<td>Rapid testing for influenza allows faster results to help facilitate immediate management decisions, but the sensitivity and specificity of these tests varies.</td>
<td>Rapid antigen testing for influenza can have significant false negative rates, especially when disease prevalence is at its highest.57,58 The accuracy of these tests is an important factor for the clinician to consider when making treatment decisions, as empiric treatment of certain patient populations may be warranted at times of heightened disease prevalence.</td>
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<th>Viral Culture and RT-PCR</th>
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<td>Viral culture and RT-PCR are the gold standards for influenza testing but they are more costly, time-consuming, and require specialized laboratories.</td>
<td>Numerous forms of diagnostic testing exist for influenza, with varying degrees of accuracy. While viral culture and RT-PCR remain the gold standards for diagnosis, they require more time, expense and specialized laboratory facilities to perform.</td>
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<th>Empiric Treatment and Management Decisions</th>
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<td>Empiric treatment and management decisions based on clinical presentation alone may be reasonable at times of high disease prevalence.</td>
<td>Although rapid diagnostic testing for influenza has higher false negative rates in times of high disease prevalence, diagnosis based on clinical presentation gains increased accuracy.17,57,58</td>
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<td>Treatment decisions should be guided not only based on the clinical severity of the patient’s symptoms but also by the patient’s risk factors for having a more severe disease course.</td>
<td>Many patients with influenza who have been previously healthy can be treated with supportive therapy alone. Antiviral therapy should be reserved for those patients who are more severely ill or whose age or chronic medical condition puts them at high risk for a more severe disease course.6,45</td>
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<td>The choice of antiviral medication must be guided by regional strain prevalence information as well as known strain susceptibilities.</td>
<td>Because several different strains of influenza can circulate within a particular season, antiviral strain sensitivities can vary within a particular region depending on the influenza strains that are most prevalent within that region. The CDC website provides resources to help track the prevalence rate of particular influenza strains within various regions throughout the United States.3</td>
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*See reverse side for reference citations.*
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