Evaluation and Management of Seasonal Influenza in the Emergency Department

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Influenza is an acute infectious respiratory disease of viral cause that occurs annually in outbreaks, epidemics, and occasionally pandemics of varying severity and attack rates depending on the influenza virus subtype involved. Although most seasonal flu cases do not produce long-term sequelae, influenza continues to cause substantial morbidity and mortality despite multiple landmark discoveries in infectious diseases during the previous century.[1,2] In the past 2 decades, influenza mortality has even risen, in large part because of an aging population.[3] Worldwide, flu epidemics account for an estimated 3 to 5 million cases leading to approximately 245,000 to 500,000 deaths annually.[4] The Centers for Disease Control and Prevention (CDC) estimates there are about 36,000 influenza-related deaths each year in the United States, and between 1972 and 1992, influenza accounted for an estimated 426,000 deaths.[1,5] In Canada, the Laboratory Center for Disease Control estimates that 70,000 to 75,000 influenza-associated hospitalizations and 6000 to 7000 deaths occur from influenza each year.[6] In Europe, between 40,000 and 220,000 deaths are estimated to be caused by influenza in a moderate flu season and during a severe epidemic respectively.[7]

Influenza also imposes a huge financial burden on health care systems and society overall. Data from the United States reveal that influenza accounts for more than

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226,000 hospitalizations, an estimated 3.1 million hospitalization days, with costs of more than $5 billion annually.[3,8] Costs related to influenza epidemics surpass $12 billion and cause millions of lost work hours each year.[9]

Timely diagnosis of influenza and early recognition of an influenza outbreak or epidemic are key components in preventing influenza-related complications, hospitalizations, and deaths. As the primary gateway to the health care system, emergency departments (EDs) are the most frequent points of entry for patients with influenza who seek medical attention. As a result, emergency physicians are well positioned to play a pivotal role in promptly identifying and adequately managing influenza community outbreaks and epidemics.

This article provides an updated overview of influenza to enhance the clinical judgment of emergency physicians and facilitate accurate decision making and diagnosis of seasonal influenza, thereby minimizing influenza's potential morbidity and mortality.

EPIDEMIOLOGY
Seasonality of Influenza

The epidemiology of influenza differs globally. Influenza outbreaks can occur during a specific season, referred to as seasonal influenza, or influenza activity can be present throughout the year. In northern and southern hemisphere temperate zones, influenza is highly seasonal and attacks predominantly occur during the winter months. For northern hemisphere countries like the United States and Canada, seasonal influenza usually starts in November, peaks from December to March, and abates in May,[10] whereas for southern hemisphere countries like Australia, the flu starts in May, peaks in June to September, and ends in November. Substantial fluctuations in influenza viral transmission patterns may occur with peaks occurring much earlier or later than anticipated.[11] In contrast, tropical regions lacking a distinct winter season exhibit different patterns of activity, in which influenza viruses may be isolated year round[12] with biannual influenza outbreaks.[13]

Onset and Time Course of Influenza Outbreaks

Typical outbreaks usually begin suddenly, spread in the community peaking during a period of 2 to 3 weeks, and continue for an average duration of 3 months.[14] In terms of clinical signs important for the emergency physician, the first indication of onset of a flu outbreak in a community is a surge in pediatric febrile respiratory illnesses, followed by increases in adult influenza-like illnesses (ILI).[15]

As the predominant front line of health care systems, EDs including emergency physicians are well positioned to detect local outbreaks of the flu in their early stages and notify appropriate public health authorities to take proper measures to contain the outbreak. Similarly, emergency physicians can play a pivotal role in containing emerging flu pandemics by keeping abreast of global influenza epidemics.

CLASSIFICATION AND DESCRIPTION OF INFLUENZA VIRUSES

Influenza viruses belong to the Orthomyxoviridae class of viruses and structurally consist of an inner core and outer membrane. The core contains a nucleoprotein antigen that determines the classification of the influenza virus into its 3 basic types: A, B, or C.[16] The outer membrane contains a coat of proteins including glycoproteins. Influenza A viruses are categorized based on 2 immunologically important glycoproteins: hemagglutinin (H) with 16 different subtypes (H1–H16) and neuraminidase (N) with 9 different subtypes (N1–N9).[17] For instance, the influenza A (H1N1) virus responsible for the 2009 flu pandemic expresses hemagglutinin 1 (H1) and neuraminidase 1

(N1) subtypes, whereas influenza A (H2N2) virus, which caused the influenza pandemic of 1957 to 1958, expresses hemagglutinin 2 (H2) and neuraminidase 2 (N2) subtypes. Influenza B and C viruses are not subcategorized.

Influenza A, B, and C viruses have similar structural and biologic characteristics but differ antigenically with varying prevalence and virulence. Influenza A is the most prevalent of the 3, frequently causes seasonal outbreaks and epidemics in humans, and infection with this subtype leads to more severe morbidity than influenza B and C. In addition, influenza A is the only subtype that causes pandemics. Influenza A H1N1 and H3N2 are currently the predominant virus subtypes causing influenza infection in humans. Since 1977, these 2 flu viruses have been circulating, causing seasonal influenza worldwide, whereas influenza A H2N2 subtype has not circulated in humans since 1968.[10]

Influenza B viruses circulate less widely than influenza A, causing fewer seasonal outbreaks and epidemics, whereas influenza C viruses cause only sporadic cases or minor outbreaks but not epidemics. In both cases, humans develop antibodies to these influenza viruses during childhood that provide some protection later against severe disease.[18] However, in children less than 6 years of age who have not yet acquired antibodies to influenza C, this virus can cause serious respiratory infections.[19]

Antigenic Drift and Antigenic Shift

Influenza A viruses, more than influenza B and C viruses, have a natural tendency to periodically undergo hemagglutinin and neuraminidase antigenic changes. Small point mutations in the RNA gene segments that code for these 2 glycoproteins lead to minor hemagglutinin and neuraminidase antigenic changes called **antigenic drifts** that result in localized outbreaks. Large mutations with viral gene reassortment that result in major hemagglutinin and neuraminidase antigenic changes referred to as **antigenic shifts** are associated with more widespread epidemics and pandemics. Influenza A, because of their greater propensity for antigenic variation, is the only influenza virus type able to undergo antigenic shifts, whereas all 3 virus types (influenza A, B, and C) have the ability to undergo antigenic drifts.

PATHOGENESIS AND PATHOPHYSIOLOGY
Cellular Pathogenesis

Influenza viral infection starts with transfer of virus-laden respiratory secretions from an infected person to an immunologically susceptible host. The virus initially attaches to the epithelial cells of the upper respiratory tract and, if not neutralized by the host's immune system, the virus can continue to invade more and more cells as the virus descends the respiratory tract. After adsorption and binding of viral hemagglutinin to host cell sialic acid–conjugated glycoproteins, the virus enters the host cell. This adsorption and binding is deemed necessary for virus cell entry,[20] and is epidemiologically significant because the configuration of sialic acid–conjugated glycoproteins differs from one species to another, which may exert a crucial role in limiting transfer of influenza viruses across species.[21] Once the virus has entered the host cell, it immediately disrupts normal cell function and starts replicating and releasing its viral progeny. Neuraminidase is essential for viral release and propagation.[22] Viral replication leads to host cell degradation and death via several mechanisms that shut off protein synthesis and release potent cytokines.[23,24] Cytokines, such as type I interferons, interleukins, tumor necrosis factor, as well as other inflammatory mediators, are thought to cause coughing and other systemic symptoms of flu.

Virus replication starts within 4 to 6 hours of host cell infection, and continues until about 24 hours before symptom onset.[25] The duration between incubation period, symptom onset, and virus shedding can range from 18 to 72 hours depending, in part, on inoculum dose.[26]

Virus Shedding

The quantities of shed virus measured in specimens exhibit a distinct pattern and temporally correlate with symptom onset and severity of illness. Virus shedding is observed starting within 24 hours before the onset of symptoms, peaks in 1 to 2 days after the onset of symptoms develop, remains high for another 1 to 2 days correlating with when the illness is most severe, and then rapidly declines, coming to an end approximately 7 to 10 days after infection. However, in certain circumstances, virus shedding can continue for weeks. Two key factors that influence the duration of viral shedding are age and severity of illness.[27–29] Young children, because of their relative lack of immunity, can shed virus for 10 days or more.[29,30] Patients with chronic diseases and more severe, complicated influenza shed the virus for an average of 2 days longer than uncomplicated influenza.[27,31,32] In elderly[31] and immunocompromised patients,[33–37] viral shedding and potential infectivity can persist for weeks, even months.

Pathophysiology

Multiple pathologic changes and pulmonary function abnormalities are observed during active uncomplicated acute influenza infection. Bronchoscopy often shows inflammation and edema of the bronchial mucosa, most notably in the lower respiratory tract, that lead to decreased forced flow rates and increased pulmonary resistance, which may persist for weeks after clinical recovery. In patients with asthma and chronic obstructive pulmonary disease, influenza can cause acute decreases in forced expiratory vital capacity (FVC) and forced expiratory volume in 1 second (FEV1).[38,39] Virus infection can advance into the lung parenchyma either via inhalation or contiguous spread from the upper respiratory tract causing primary viral pneumonia. Tracheitis, bronchitis, and bronchiolitis are seen, characterized by submucosal hyperemia, edema, focal hemorrhage with bloody fluid, and loss of normal ciliated epithelium.[40]

Disruption of the normal epithelial barrier to infection, and abnormalities in ciliary clearance mechanisms, along with increased adherence of bacteria to virus-infected epithelial cells, predispose to bacterial superinfection. The most common pathogens responsible for bacterial infection are *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

CLINICAL PRESENTATION
Clinical Signs and Symptoms

The signs and symptoms of seasonal influenza are variable in severity, and dependent on the age of the patients. In adults, influenza is usually characterized by respiratory symptoms with other constitutional symptoms such as fever, myalgia, malaise, and headache. An abrupt onset is common, such that patients are often able to report the time of onset. Respiratory symptoms and cough may initially be mild, but can progress causing dyspnea and pleuritic chest pain. Degree of fever is variable; fever in the elderly is usually not as severe as in young patients. During the flu season, patients with influenza-like symptoms and proven influenza infection were more likely to have cough (93% vs 80%), fever (68% vs 40%), cough and fever together (64% vs 33%), and/or

nasal congestion (91% vs 81%) compared to those without influenza.[41] For decreasing the likelihood of influenza, the absence of fever (likelihood ratio [LR], 0.40; 95% confidence interval [CI], 0.25–0.66), cough (LR, 0.42; 95% CI, 0.31–0.57), or nasal congestion (LR, 0.49; 95% CI, 0.42–0.59) were the only findings that had summary LRs less than 0.5.[42] Patients may also present with isolated gastrointestinal or central nervous system (CNS) involvement.

Children with influenza often do not present with the classic symptoms. They often cannot describe their symptoms, and tend to have more gastrointestinal symptoms. Symptoms can mimic bacterial sepsis with high fevers, and children with influenza may present with febrile seizures.[43]

In uncomplicated influenza, there are a few physical findings. There may be evidence of hyperemia of the pharynx, even with severe sore throat complaints. Mild cervical lymphadenopathy and otitis media may be present, especially in younger patients. A dry cough is usually noted on chest examination with clear lungs or rhonchi, unless complicated by pneumonia. If there are no complications, fever and body aches can last 3 to 5 days, and the cough and lack of energy may last for 2 or more weeks.[44]

Complications Contributing to Clinical Presentation (Symptomatology)

Pneumonia is the major complication of influenza and occurs especially in high-risk patients:

- Children aged less than 5 years (especially those aged <2 years)
- Adults aged 65 years or more
- Persons with chronic diseases
- Persons with immunosuppression
- Women who are pregnant or postpartum (within 2 weeks after delivery)
- Persons aged 18 years or younger who are receiving long-term aspirin therapy
- First Nations/Alaska Natives
- Persons who are morbidly obese (ie, body mass index [BMI] greater than or equal to 40)
- Residents of nursing homes and other chronic-care facilities.[45]

Pneumonia can either be of viral or secondary bacterial cause. Primary viral pneumonias are uncommon but tend to have increased symptom severity. However, during influenza outbreaks, influenza virus types A and B are responsible for more than half of all community-acquired viral pneumonia cases. Secondary bacterial pneumonia is a significant complication of influenza, accounting for 25% of all influenza deaths.[46] Children hospitalized with influenza-associated pneumonia have a higher risk for intensive care admission, respiratory failure, and death compared to those hospitalized with influenza without pneumonia. Classically, influenza patients complicated with pneumonia have an exacerbation of fever and respiratory symptoms after an initial improvement. The most common bacterium is *S pneumonia*, accounting for approximately 50% of cases. *Staphylococcus aureus* and *Haemophilus influenza* are also important common organisms. During the 2006 to 2007 influenza season, 51 cases of community-acquired *S aureus* pneumonia were reported to the CDC. Almost 50% of these cases had antecedent or concomitant viral illness, and just under 80% of the S aureus cultures were MRSA. The median age was 16 years, 44% had no known pertinent medical history, and approximately half of patients, for whom final disposition was known, died a median of 4 days after symptom onset. Despite the selection bias in the cases reported, *community-associated S aureus* (CA-MRSA)

pneumonia accounts for severe pneumonia with high mortality in young otherwise healthy patients with influenza. Therefore, empiric therapy for severe community-acquired pneumonia should include treatment against *S aureus*, including MRSA.[47]

Neurologic complications include encephalitis, transverse myelitis, and Guillain-Barré syndrome. Reye syndrome has been reported in patients using aspirin after influenza infections. Myositis is rare, but has been reported more commonly in children than adults. It presents in early convalescence with acute onset of pain and tenderness in the lower leg muscles severe enough to limit walking. Serum creatine kinase (CK) levels transiently increase, with complete recovery generally occurring in 3 to 4 days; renal failure is rare.[48]

Cardiovascular involvement occurs by directly affecting the myocardium or exacerbating existing cardiovascular conditions. The frequency of myocardial involvement in influenza infection is variable, with rates of up to 10% having been reported in the literature, although this depends on the methods used to detect myocardial involvement. Although many patients are asymptomatic, a significant proportion of these have electrocardiogram changes. Fulminant myocarditis resulting in cardiogenic shock and death may occur. When a patient's condition deteriorates with hemodynamic compromise, cardiac involvement should be considered. The mainstay of treatment of influenza myocarditis is supportive. Cardiovascular deaths also increase during influenza epidemics by increased deaths from coronary artery disease. These deaths have been shown to be reduced by influenza vaccination, which should be offered to all patients with cardiovascular disease.[49]

Other rare complications encountered include toxic shock syndrome in conjunction with secondary *S aureus* infection and parotitis.[50]

ED EVALUATION

Influenza can be difficult to diagnose based on clinical symptoms alone because the initial symptoms of influenza can be similar to those caused by other infectious agents including *Mycoplasma pneumoniae*, adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza viruses, and *Legionella*.

It is important for the ED to develop clinical pathways to identify ILI so that contagious patients can be segregated and treated effectively. The CDC defines ILI as patients with temperature greater than 37.8°C (100°F) plus either cough or sore throat in the absence of a known cause other than influenza. As described, patients with influenza may have atypical presentations. Fever is not always present, especially in premature infants, young infants, elderly patients, or immunosuppressed patients, and patients may present with only myalgias, headache, fatigue, or other complications.[51] The ED needs to consider the variability of clinical presentations and the prevalence of influenza in the community regarding investigation and treatment, and infection control isolation protocol.

Patients with suspected influenza should have standard laboratory investigations such as a complete blood count and electrolytes; the results are usually nonspecific, but leukopenia is typical and thrombocytopenia may be present. Patients with physical signs that suggest meningitis should undergo a lumbar puncture. In patients with hypoxemia, the elderly, or high-risk patients with pulmonary symptoms, a chest radiograph should be performed to exclude pneumonia. Dyspnea and chest pain are typically used as indicators for obtaining a chest radiograph. Shortness of breath may be a useful indicator of pneumonia-complicating influenza.[52] Radiological findings include bilateral interstitial infiltrates, and focal infiltrates may indicate superimposed bacterial pneumonia.

Diagnostic Workup (Who to Test)

Diagnostic testing does not have to be performed on every patient who presents to the ED with ILI, especially when there is a circulating influenza outbreak or epidemic. Confirmation of influenza virus infection is not required for clinical decisions to prescribe antiviral medication. The decision to administer influenza treatment or chemoprophylaxis should be based on clinical illness and epidemiologic factors, and the start of therapy should not be delayed pending results, especially during an influenza outbreak.[51] Influenza diagnostic testing is not clinically indicated when test results will not alter a patient's clinical care or influence clinical practice for other patients (Fig. 1). A positive influenza test may be used to confirm influenza virus in the community, which may affect clinical practice related to home care guidance, hospital infection control practices, future testing practices, and so forth. Neither the rapid influenza test nor clinical prediction rules were superior to clinical judgment alone in the diagnosis of influenza. In one study of 258 patients with 21% confirmed influenza, the overall clinical judgment had a sensitivity of 29% (95% CI, 18%–43%) and specificity 92% (95% CI, 87%–95%), which improved to a sensitivity of 67% (95% CI, 39%–86%) and specificity of 96% (95% CI, 81%–99%) when patients presented within 48 hours. Rapid influenza tests only had a sensitivity of 33% (95% CI, 22%–47%) and specificity of 98% (95% CI, 96%–99%), and a clinical prediction rule showed a sensitivity of 40% (95% CI, 27%–54%) and specificity of 92% (95% CI, 87%–95%).[53] Thus, in times of high disease prevalence such as during influenza outbreaks or epidemics, most patients exhibiting ILI symptoms can be diagnosed clinically as having influenza, without performing any diagnostic tests. Clinicians should consult the CDC's Global Flu Activity Update (http://www.cdc.gov/flu/international/activity.htm) for the latest updates on the international flu situation, and FluView (http://www.cdc.gov/flu/weekly/) for a summary of flu activity in the United States.

Diagnostic testing is ideally indicated in 2 circumstances: (1) for sporadic cases of ILI, during periods of low disease prevalence, and (2) for severely ill patients. Influenza should be confirmed in sporadic cases of ILI to rule out another viral diagnosis, for example severe acute respiratory syndrome (SARS) or coronavirus. Diagnostic testing is recommended in severely ill patients because there is a greater urgency to make the correct diagnosis to provide appropriate medical management. In these 2 cases, rapid influenza diagnostic tests (RIDTs) and reverse transcriptase polymerase chain reaction (RT-PCR) are appropriate.

The 2009 evidence-based clinical practice guidelines for the diagnosis, management, and chemoprophylaxis of seasonal influenza developed by the Infectious Diseases Society of America recommend that the following patient populations undergo diagnostic testing for influenza if testing results will influence medical management (Box 1).[54]

Types of Specimens and Detection of Influenza Virus

Influenza virus can be isolated from different types of specimens, including nasal, throat, or nasopharyngeal swabs, aspirates or washes, and sputum samples. Nasopharyngeal specimens (swabs and aspirates) are more sensitive for detecting the virus than throat swabs or sputum specimens[54,55]; in one comparison of 3 rapid assays and immunofluorescence for influenza detection, sensitivity for all of these methods increased by approximately 40% when nasopharyngeal swabs instead of throat swabs were used.[56] Acceptable specimens also vary depending on the specific diagnostic test (Table 1). The optimal time frame for collecting diagnostic specimens
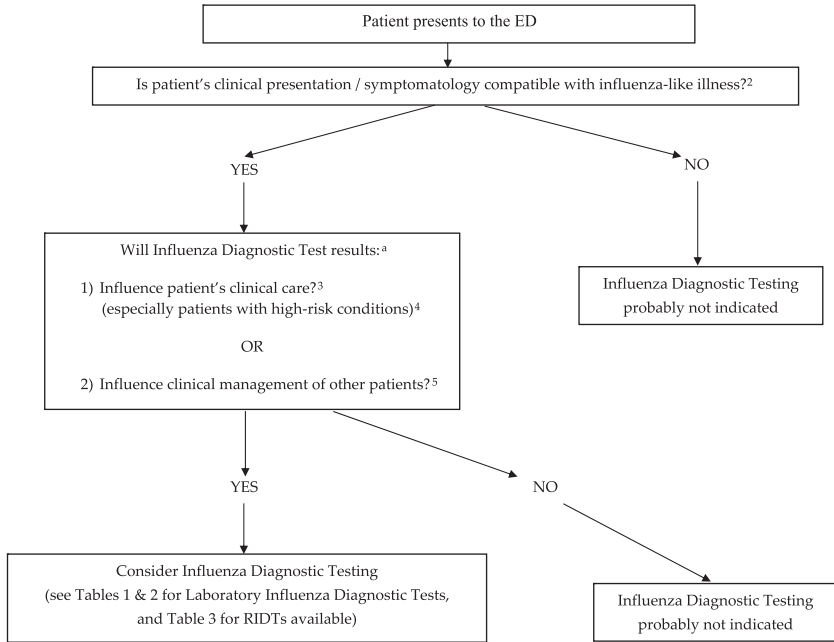
Fig. 1. Guide for considering influenza diagnostic testing (IDT) for patients presenting to the ED with influenza-like illness symptoms when influenza activity is high in the community.[1] [1]Confirmation of influenza virus infection by diagnostic testing is not required for clinical decisions to prescribe antiviral medications. Decisions to administer antiviral medications for influenza treatment or chemoprophylaxis, if indicated, should be based upon clinical illness and epidemiologic factors, and start of therapy should not be delayed pending testing results (http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm). **Respiratory specimens should be collected from an ill patient as early as possible after onset of symptoms (ideally <48–72 hours after onset) to help maximize influenza testing sensitivity.** [2]Influenza like-illness (history of feverishness or documented fever with either cough or sore throat), fever with other respiratory symptoms, etc. Note that some persons may have atypical presentations (eg, elderly, very young infants, immunosuppressed, and patients with certain chronic medical conditions). Fever is not always present (eg, premature infants, young infants, elderly, immunosuppressed). Other symptoms associated with influenza include myalgias, headache, and fatigue. Complications include exacerbation of underlying chronic disease, (eg, congestive cardiac failure, asthma), pneumonia, bacterial co-infection, bronchiolitis, croup, encephalopathy, seizures, myositis, and others. [3]eg, Decisions on use of antibiotics or antiviral medications, on conducting further diagnostic tests, on recommendations for home care, or on recommendations for ill persons living with persons with high-risk conditions. Consult Infectious Disease Society of America, American Thoracic Society, Association of American Physicians, and Advisory Committee on Immunization Practices for antibiotic guidance. [4]Persons ≥65 years or <2 years; pregnant women; persons with chronic lung disease (including asthma), heart disease, renal, metabolic, hematologic and neurologic disease; immunosuppression; and morbid obesity. [5]eg, Decisions on changing infection control practices (such as in hospitalized patients); if a positive influenza test result is used for confirming influenza virus circulation in the community which might inform clinical practices related to home care guidance, hospital infection control practices, future testing practices, etc. RIDT, rapid influenza diagnostic testing. [a]*Initiation of antiviral treatment, if clinically indicated, should not be delayed pending influenza diagnostic test results.* (*Adapted from* the Centers for Disease Control and Prevention (CDC) website: Guidance for Clinicians on the Use of Rapid Influenza Diagnostic Tests for the 2010-2011 Influenza Season. Available at: http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm. Accessed September 30, 2011.)

Box 1
Indications for testing for influenza

During influenza season (testing should be done in the following persons if the result will influence clinical management)

- Outpatient immunocompetent persons of any age at high risk of developing influenza complications (eg, hospitalization or death) presenting with acute febrile respiratory symptoms 5 days or less after illness onset (when virus is usually being shed)

- Outpatient immunocompromised persons of any age presenting with febrile respiratory symptoms, irrespective of time since illness onset (because immunocompromised persons can shed influenza viruses for weeks to months)

- Hospitalized persons of any age (immunocompetent or immunocompromised) with fever and respiratory symptoms, including those with a diagnosis of community-acquired pneumonia, irrespective of time since illness onset

- Elderly persons and infants presenting with suspected sepsis or fever of unknown origin, irrespective of time since illness onset

- Children with fever and respiratory symptoms presenting for medical evaluation, irrespective of time since illness onset

- Persons of any age who develop fever and respiratory symptoms after hospital admission, irrespective of time since illness onset

- Immunocompetent persons with acute febrile respiratory symptoms who are not at high risk of developing complications secondary to influenza infection may be tested for purposes of obtaining local surveillance data

Throughout the year (testing should be done for the following persons)

- Health care personnel, residents, or visitors in an institution experiencing an influenza outbreak who present with febrile respiratory symptoms within 5 days after illness onset

- Persons who are epidemiologically linked to an influenza outbreak (eg, household and close contacts of persons with suspected influenza, returned travelers from countries where influenza viruses may be circulating, participants in international mass gatherings, and cruise ship passengers) who present within 5 days after illness onset

From Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children – diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48(8):1003–32; with permission.

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largely depends on the amount of viral shedding at the time of testing. In immunocompetent children and adults, in whom viral shedding is brief, specimen samples yield the best results during the first 1 to 5 days of illness.[54,57] Low viral titers in the first 12 to 24 hours following onset of clinical illness have been suggested as a cause of false-negative results in patients tested early[58]; similarly, specimens obtained after 5 days of illness have an increased likelihood of false-negative results because of decreased virus shedding. Immunocompetent infants and young children spread virus for longer ($\geq$1 week), which ideally permits the collection of specimens after 5 days of illness.[54] Irrespective of age, specimen collection in immunocompromised persons can also exceed 5 days of illness because virus shedding in this patient population can last for weeks, even months.[54]

In the ED, collection of serum specimens is not recommended for diagnostic purposes because results are not readily available and therefore cannot guide clinical decision making and management.[54]

Table 1
Laboratory diagnostic testing methods for influenza currently available in the United States

Diagnostic Testing Method(s)	Acceptable Specimens	Influenza Virus Types Detected	Time to Final Result
Immunofluorescence microscopy Direct fluorescent antibody staining Indirect fluorescent antibody staining	1. NP swab/aspirate 2. Nasal swab/aspirate/wash 3. Throat swab	A and B	≈1–4 h
Viral culture Conventional culture Rapid shell vial culture	1. NP swab/aspirate 2. Nasal swab/aspirate/wash 3. Throat swab 4. Bronchioalveolar lavage	A and B	Conventional culture ≈3–10 d Rapid shell vial culture ≈1–3 d
RT-PCR	1. NP swab/aspirate 2. Nasal swab/aspirate/wash 3. Throat swab 4. Bronchioalveolar lavage 5. Sputum	A and B	≈1–6 h
RIDTs	Depends on specific RIDT (see **Table 3**)	A and B[a]	≈10–15 min
Serologic testing[b]	Paired acute and convalescent serum samples[c]	A and B	≥2 wk

Abbreviation: NP, nasopharyngeal.
[a] Most RIDTs detect A and B, some detect A or B, others only A (see **Table 3**).
[b] Serologic testing is not recommended for routine patient diagnosis.
[c] A fourfold or greater increase in antibody titer from the acute (collected within the first week of illness) to the convalescent phase (collected 2–4 weeks after the acute sample) indicates recent infection.
Data from Refs.[55,59,64]

Table 2
Laboratory diagnostic testing methods for influenza currently available in Canada

Test	Method	Influenza Virus Types Detected	Turnaround Time[a]
RT-PCR (nucleic acid testing)	RNA detection	A and B	24–96 h (6–8 h to perform test)
Viral culture	Virus isolation	A and B	2–10 d
Direct immunofluorescence tests Indirect immunofluorescence tests	Antigen detection	A and B	2–4 h
Point-of-care tests	Antigen detection	A and B	0.5 h

[a] Length of time needed from specimen collection until results are available.
From Canadian Public Health Laboratory Network. Guidance for laboratory testing for detection and characterization of human influenza virus for the 2010-2011 respiratory virus season. Available at: http://www.cphln.ca/documents/EN_Influenza_Seasonal_Best_Practices_2010-2011.pdf. Accessed September 30, 2011; with permission.

Influenza Laboratory Testing Methods

Several different laboratory testing methods for detecting influenza virus are available in the United States (**Table 1**) and Canada (**Table 2**). These methods include immuno-fluorescence microscopy (direct or indirect antibody staining), viral culture (conventional and rapid), RT-PCR, RIDTs, and serologic testing. Among these testing methods, RIDTs with rapid processing yielding timely results that can influence clinical decision making and patient management are most pertinent for the needs of the ED.

Based on which type(s) of influenza virus (A and/or B) can be detected, diagnostic tests can be categorized into 3 types: (1) those that detect only influenza A; (2) those that detect either influenza A or B, but cannot discriminate between the two; and (3) tests that both detect and distinguish between influenza A or B viruses. Only RT-PCR and viral culture can identify influenza strains.

RIDTs

RIDTs are rapid antigen point-of-care tests capable of identifying influenza A and B viral types in respiratory specimens in approximately 10 to 15 minutes.[59] RIDTs are immunoassays that come in user-friendly, diagnostic kits with varying complexity that either: (1) only detect influenza A virus, (2) detect but cannot distinguish between influenza A and B viruses, or (3) both detect and distinguish between influenza A and B viruses. Commercial RIDTs currently available in the United States and Canada are listed in **Table 3**, and general RIDT characteristics, including advantages and disadvantages, are described in **Box 2**. RIDTs are valuable in the ED because they produce results in a timely and clinically relevant manner that facilitate on-site point-of-care diagnosis of influenza that, according to limited research, has led to a decrease in demand for further diagnostic tests (eg, chest radiography, blood cultures) and the use of antibiotics, thus resulting in decreased patient costs.[61]

Recommendations for the use of RIDTs were developed and promulgated by the World Health Organization (WHO) (**Box 3**). The CDC has recently issued guidelines for clinicians on the use of RIDTs for the 2010 to 2011 influenza season.[59]

A major drawback of RIDTs is their limited reliability in accurately detecting influenza virus, which depends on a wide variety of factors, including RIDT sensitivity, specificity, positive and negative predictive values, type of specimen collected, and time of collection with respect to onset of symptoms. Although RIDTs exhibit high specificities ranging between 90% and 95%, RIDTs have substantially lower sensitivities, ranging from about 70% to 90% in children, decreasing even further to approximately 40% to 60% or lower in adults, compared with viral culture and RT-PCR.[54,62,63] Thus, if RIDTs are the only diagnostic assay used in a center, positive results can be trusted but a negative result cannot reliably exclude disease. **Table 4** displays specifically selected commercially available RIDTs and corresponding test sensitivities, specificities, and positive and negative predictive values, which also vary according to the study.

Time of specimen collection also influences the accuracy of RIDT results: the closer within the period of viral shedding and illness the specimen sample is obtained, the more accurate the result.[60,64] In an effort to minimize false interpretation of RIDTs, the CDC has published the following guidance statements that emergency physicians and other health care professionals must keep in mind when performing and interpreting RIDTs[59,65]:

1. The reliability of a positive RIDT result increases in patients with clinical signs and symptoms consistent with influenza.
2. Collection of specimens within 48 to 72 hours of illness onset increases the likelihood of producing a positive RIDT result.

Table 3
Examples of commercial rapid influenza diagnostic tests (RIDTs) currently available in the United States and Canada

Rapid Influenza Diagnostic Test (RIDT) Name	Manufacturer	Influenza Virus Type Detected	Distinguishes Between A and B?	Acceptable Specimens	Time to Final Results	Approved in the United States	Approved in Canada
BinaxNOW® Flu A and Flu B	Binax Inc., www.binax.com	A and B	Yes	NP swab nasal wash/aspirate	15 min	Yes	Yes
BinaxNOW® Influenza A and B	Binax Inc., www.binax.com	A and B	Yes	NP swab nasal wash/aspirate/swab	15 min	Yes	Yes
BioSign® Flu A + B	Princeton BioMeditech Corp. www.pbmc.com	A and B	Yes	NP swab/wash/aspirate	15 min	Yes	No
Clearview Exact® Influenza A and B	Alere www.alere.com	A and B	Yes	Nasal swab	15 min	Yes	No
Clearview Exact® II Influenza A and B	Alere www.alere.com	A and B	Yes	Nasal swab	15 min	Yes	No
Directigen™ EZ Flu A + B	Becton-Dickinson, www.bd.com	A and B	Yes	NP swab/wash/aspirate throat swab	15 min	Yes	No
Directigen™ Flu A	Becton-Dickinson, www.bd.com	A	Detects A only	NP swab/wash/aspirate pharyngeal swab	15 min	Yes	Yes
Directigen™ Flu A + B	Becton-Dickinson, www.bd.com	A and B	Yes	NP swab/wash/aspirate lower nasal swab, throat swab, bronchioalveolar lavage	15 min	Yes	Yes
Flu OIA	Thermo Biostar, Inc., www.biostar.com	A and B	No	NP swab, throat swab nasal aspirate, sputum	20 min	Yes	Yes
ImmunoCard STAT! Flu A and B	Meridian Bioscience, Inc., www.meridianbioscience.com	A and B	Yes	NP swab/aspirate nasal swab/wash	15–20 min	Yes	Yes
Influ-A Respi-Strip	Coris BioConcept, www.corisbio.com	A	No	NP swab	5–15 min	No	Yes
Influ-A and B Respi-Strip	Coris BioConcept, www.corisbio.com	A and B	Yes	NP swab/wash/aspirate	5–15 min	No	Yes

3M™ Rapid Detection Flu A + B Test	3M www.3m.com	A and B	Yes	NP swab/aspirate nasal wash/aspirate	15 min	Yes	No
OSOM® Influenza A and B	Genzyme www.genzyme.com	A and B	Yes	Nasal swab	10 min	Yes	No
SAS™ FluAlert A	SA Scientific Inc., www.sascientific.com	A only	No	Nasal wash/aspirate	15 min	Yes	No
SAS™ FluAlert B	SA Scientific Inc., www.sascientific.com	B only	No	Nasal wash/aspirate	15 min	Yes	No
SAS™ FluAlert A and B	SA Scientific Inc., www.sascientific.com	A and B	Yes	Nasal wash/aspirate	15 min	Yes	No
QuickVue® Influenza Test	Quidel Corporation www.quidel.com	A or B	No	Nasal swab/wash/aspirate	10 min	Yes	No
QuickVue® Influenza A + B Test	Quidel Corporation www.quidel.com	A and B	Yes	NP swab nasal swab/wash/aspirate	10 min	Yes	Yes
Quick S-INFLU A/B Seiken	Denka Seiken Co., Ltd. www.denkaseiken.co.jp	A and B	Yes	Nasal swab/aspirate	25 min	Yes	Yes
TRU FLU®	Meridian Bioscience Inc., www.meridianbioscience.com	A and B	Yes	NP swab/aspirate nasal wash	15 min	Yes	No
XPECT™ Flu A and B	Remel Inc., www.remelinc.com Thermofisher	A and B	Yes	Nasal swab/wash throat swab, (sputum, NP Swab, tracheal aspirates, bronchoalveolar wash)	15 min	Yes	Yes
ZstatFlu-II test	Zyme Tx, Inc., www.zymetx.com	A and B	No	Throat swab	30 min	Yes	No

Abbreviation: NP, nasopharyngeal.

Adapted from World Health Organization: WHO recommendations on the use of rapid testing for influenza diagnosis. July 2005. Available at: http://www.who.int/influenza/resources/documents/rapid_testing/en/index.html. Accessed September 30, 2011; with permission, and Centers for Disease Control and Prevention (CDC) website: Guidance for Clinicians on the Use of Rapid Influenza Diagnostic Tests for the 2010-2011 Influenza Season. Available at: http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm. Accessed September 30, 2011.

Box 2
Advantages and disadvantages of RIDTs

Advantages

1. Simple to perform

2. Results available within 15 minutes

3. Produce results in a timely and clinically pertinent manner

4. Selective RIDTs are waived from CLIA requirements in the United States, permitting their use in any medical facility (including doctor's office)

Disadvantages

1. No uniformity in distinguishing between influenza A or B virus

2. Do not identify virus strains

3. Do not identity influenza A virus subtypes

4. Frequently yield false-negative results because of reduced test sensitivity (40%–70%), particularly during increased influenza activity

5. False-positive results can be produced, particularly during months of low influenza activity

Abbreviation: CLIA, Clinical Laboratory Improvement Amendment of 1988.

   Data from Centers for Disease Control and Prevention. Guidance for clinicians on the use of rapid influenza diagnostic tests for the 2010-2011 influenza season. Available at: http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm. Accessed September 30, 2011.

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3. Different RIDTs have different acceptable specimens and test specifications. Accuracy of RIDT results depends on collecting a good quality, acceptable specimen; following test procedures according to RIDT package instructions; and using appropriate viral transport media, consistent with specifications (if testing is to be performed at another location than the specimen collection).

Box 3
WHO recommendations on the use of RIDTs for influenza diagnosis in countries with influenza surveillance

WHO RIDT recommendations

1. Influenza surveillance should be used to guide the optimal use of rapid tests.

2. At the beginning of the influenza season or an influenza outbreak, rapid tests may influence clinical decisions and contribute to clinical awareness.

3. During periods of high influenza activity, it is impractical to test every individual meeting an influenza case definition. Clinical judgment and local influenza surveillance data should be used for case management in the first instance. Rapid tests are recommended to be used only when they can influence timely patient management.

4. During periods of low influenza activity, if rapid tests are used, positive results must be interpreted with caution and confirmed by immunofluorescence assay, viral culture, or RT-PCR.

5. Because of the differing complexity of rapid tests, education of laboratory personnel about methods and limitations before their use is essential.

Data from World Health Organization. WHO recommendations on the use of rapid testing for influenza diagnosis. July 2005. Available at: http://www.who.int/influenza/resources/documents/rapid_testing/en/index.html. Accessed September 30, 2011; with permission.

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4. Use RIDTs with high sensitivity and specificity (see **Table 4**):
   a. RIDT sensitivities are generally low to moderate, ranging between 10% and 70% (most are approximately 50%–70%) compared with the gold standard viral culture or RT-PCR. An RIDT with low sensitivity yields false-negative results.
   b. RIDT specificities are generally high, approximately 90% to 95%, compared with the gold standard viral culture or RT-PCR. An RIDT with high specificity yields few false-positives.
5. Disease prevalence (level of influenza activity) in the community affects the accuracy of RIDT results:
   a. During periods of high disease prevalence (high influenza activity) at the height of the influenza season:
      i. Likelihood of true-positive RIDT results increases (positive predictive value [PPV] is high)
      ii. Likelihood of false-negative RIDT results increases (negative predictive value [NPV] is low)
   b. During periods of low disease prevalence (low influenza activity) usually at the start and end of the influenza season:
      i. Likelihood of false-positive RIDT results increases (PPV is low)
      ii. Likelihood of true-negative RIDT results increases (NPV is high).

RT-PCR

RT-PCR is replacing viral culture as a reference standard because it is currently the most sensitive, specific, and versatile diagnostic test available for diagnosing influenza.[66] Based on nucleic acid amplification, RT-PCR can detect the influenza virus but also differentiate between virus types, subtypes, and even determine viral strain, all in approximately 4 to 6 hours. As a result, RT-PCR has become the recommended test of choice for accurately diagnosing influenza in a timely fashion.[54] During the recent pandemic, the CDC released a method through the WHO for RT-PCR detection of influenza A that allowed clinical and reference laboratories to standardize methodology and thus produce data that could be compared between laboratories.[67] However, the major advantage of RT-PCR lies in its ability to more readily detect influenza viruses in people with chronic lung diseases and immunosuppressed persons, who may exhibit lower levels of the virus.[68] In these susceptible patients, RT-PCR can efficiently and accurately confirm the diagnosis of influenza to support therapeutic and infection control decisions.

Immunofluorescence

Immunofluorescence yields timely results within 2 to 4 hours, and this can be used as a screening test. However, immunofluorescence has several disadvantages, including lower sensitivity (47%–93%)[69,70] and specificity compared with viral culture, and is labor intensive, requiring specially trained laboratory personnel who may not be available 24/7, even in large hospitals. In addition, test performance depends on an adequate specimen sample that must include respiratory epithelium cells.[54]

Viral Culture

Influenza virus can be cultured either by isolation of virus in cell culture (conventional tube culture), which provides results in 3 to 10 days, or by shell vial culture, which offers the advantage of a faster turnaround time of 48 to 72 hours.[54] Because of the lengthy turnaround times of either method, viral culture is not a useful diagnostic test in the ED for aiding initial clinical decision making and management. However,

Table 4
Ease of use, sensitivity, specificity, and positive and negative predictive values of selective RIDTs

RIDT Name	General Ease of Use	Ease of Interpretation	Sensitivity[a]	Specificity[a]	Positive Predictive Value[a]	Negative Predictive Value[a]
BinaxNOW Flu A and Flu B	Easy	Easy	(1) A, 78%–82%; B, 58%–71% (2) A, 52%; B, 54% (3) A, 73%; B, 100%	(1) A, 92%–94%; B, 58%–71% (2) 93% combined (3) A, 95%; B, 100%	(3) 93% combined	(3) 89% combined
BinaxNOW Influenza A and B	Easy	Easy	(1) A, 100%; B, 92%–100%	(1) A, 92%–93%; B, 94%–99%	—	—
Directigen Flu A	Moderate	Easy	(1) 67%–96% (4–8) 75%–100%	(1) 88%–100% (4–8) 92%–100%	(4–8) 92%–100%	(4–8) 89%–100%
Directigen Flu A+B	Moderate	Easy	(1) A, 96%; B, 88% (3,11,14,16) A, 55%–100%; B, 62%–88% (3) 29% (11–15) 55%–88%	(1) A, 99.6%; B, 96.8% (3,11,14,15) A, 99%; B, 93%–100% (3,11–15) 93–100%	(1) A, 96%; B, 80% (11–14) 74%–89% (14,15) A, 81%; B, 90%–100% (3) 93% combined	(1) Flu A, 99.6%; Flu B, 98% (11–14) 93%–98% (14,15) A, 99%; B, 97% (3) 85% combined
Flu OIA	Moderate	Moderate	(1,17) 62%–88% (18,20,22) 46%–64% (21) 48%–100%	(1,17) 52%–80% (18–20,22) 74%–97% (22) 93%–97%	(18–19) 73%–91%	(18–19) 56%–77%
QuickVue Influenza Test	Easy	Easy	(1) AB, 73%–81% (13–14,24–28) AB, 55%–91%	(1) AB, 96%–99% (13–14,24–28) AB, 83%–99%	(1) AB, 92%–96% (13–14,24–25,28) AB, 55%–93%	(1) AB, 85%–93% (13–14,25–25,28) AB, 77%–99%
QuickVue Influenza A+B Test	Easy	Easy	(1) A,72%–77%; B, 73%–82%	(1) A, 96%–99%; B, 96%–99%	(1) A, 87%–91%; B, 80%–90%	(1) A, 90%–96%; B, 94%–97%
Influ AB Quick	Easy	Easy	(1) A, 90%–93%; B, 92%–93% (15) A, 55%–58%; B, 63%–67%	(1) A, 98%–99%; B, 98%–99% (15) A, 100%; B, 99.6%	(15) 91%	(15) 98%

Test	Technical Complexity	Ease of Use	Sensitivity	Specificity	PPV	NPV
Quick S-Influ A/B Seiken	Easy	Easy	(1) A, 90%–93%; B, 92%–93% (29) A, 81%; B, 88%	(1) A, 98%–99%; B, 98%–99% (29) A, 96%; B, 99%	—	—
XPECT Flu A and B	Moderate	Easy	(1) A, 89%–100%; B, 93%–100% (30) A, 92%–94%; B, 98%	(1) A, 100%; B, 100% (30) A, 100%; B, 100%	(28) A, 100%; B, 100%	(30) A, 98%–99%; B, 99.7%
Wampole Clearview Flu A/B	—	Easy	(1) A, 92% B, 98%	(1) A, 100%; B, 100%	—	—
ZstatFlu-II test	Easy	Easy	(4–7,12,23,31–32) 65%–96% A, 76%; B, 41%	(4–5,31–32) 77%–98%	(4–5,31) 59%–76%	(4–5,31) 90%–98%
Influ A Respi-Strip	Easy	Easy	(1) A, 91%	(1) A, 86%	(1) A, 94%	(1) A, 80%
Influ A and B Respi-Strip	Easy	Easy	(1) A, 99% B, 72.2%	(1) A, 88%; B, 100%	(1) A, 78%; B, 100%	(1) A, 99%; B, 98%
Espline Influenza A and B-N	—	—	(33–34) A, 85%–100%; B, 72%–91%	(33–34) A/B, 98%–100%	—	—
Capila FluA,B	Easy	—	(1) A,69%–94%; B, 81%–96% (35) A/B, 75%–82%	(1) A, 93%–95%; B, 96%–99% (35) A/B, 94%–100%	—	—
RapidTesta FLU AB	—	—	(36) A, 82%–83%; B, 80%–83%	(36) A, 98%–99%; B, 98%	—	—
ImmunoCard STAT! Flu A and B	Easy	Easy	(1) A, 83%; B, 100%	(1) A, 98%; B, 100%	—	—

[a] See Appendix 1 for sensitivity, specificity, positive predictive value, and negative predictive value references.
Data from World Health Organization. WHO recommendations on the use of rapid testing for influenza diagnosis. July 2005. Available at: http://www.who.int/influenza/resources/documents/rapid_testing/en/index.html. Accessed September 30, 2011; with permission.

viral culture allows for subsequent analyses, including sensitivity testing and subtyping performed by reference laboratories.

During the influenza season, viral culture is indicated primarily for confirming negative RIDT and immunofluorescence results, as well as for influenza virus surveillance because it provides key information regarding influenza virus strains and subtypes.[54] During the off-season, viral culture is indicated in patients who present to the ED within 5 days of symptom onset with suspected ILI, especially if the person is epidemiologically linked to an influenza outbreak.[54]

Serologic Testing

Serologic testing is not useful or recommended in the ED because results are not readily available and therefore cannot facilitate clinical judgment, diagnosis, or management of influenza.[57] Serologic tests that include hemagglutinin inhibition, neutralization, complement-fixation, and enzyme-linked immunosorbent assay (ELISA) are mainly used to establish a diagnosis retrospectively and for research purposes.[57] Because most individuals have previously been infected with influenza viruses, to reliably determine antibody titers, a single serum sample collected in the ED is inadequate, but paired specimen samples (acute and convalescent sera) are needed.

Interpretation of Laboratory Test Results

Whenever interpreting any influenza diagnostic test, the emergency physician or other health care professional must keep in mind the limitations of these tests, especially for RIDTs. In addition, the clinician should be aware of the disease prevalence in the community at any given time, because the level of influenza activity is known to affect the accuracy and reliability of test results. With respect to patient management, a positive influenza test result does not necessarily rule out any overlying coinfection by additional pathogens, and in the case of initial negative influenza test results from less sensitive diagnostic methods like RIDTs, the clinician should contemplate additional diagnostic testing (such as RT-PCR or culture) and decide whether antiviral treatment should be initiated empirically.

ED MANAGEMENT
Antiviral Medications

Currently, 4 antiviral medications from 2 drug classes have been approved and are available for the treatment and prevention of influenza in the United States, Canada, and most other countries. These medications include amantadine and rimantadine, which belong to the drug class adamantanes, and oseltamivir (Tamiflu; Roche) and zanamivir (Relenza; GlaxoSmithKline), which belong to the class neuraminidase (NA) inhibitors. Adamantanes are active only against influenza A virus, whereas NA inhibitors are active against both influenza A and B viruses. Other antiviral pharmacologic properties are compared in **Table 5**. In the last several years, adamantines have become less clinically useful because of their widespread resistance to influenza A (H3N2) and 2009 (H1N1) virus strains.[71] As a result, amantadine and rimantadine are currently not recommended for the treatment or chemoprophylaxis of influenza A virus.[45]

Guideline Indications for Antiviral Treatment

The goals of influenza pharmacotherapy are to decrease symptoms, prevent associated complications, and reduce functional disability, hospitalizations, and mortality. Treatment decisions on administering antiviral therapy should take into account factors such as time since symptom onset, underlying conditions, and severity of disease.

Table 5
Comparison of antiviral medication pharmacologic properties

	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Protein target	M2	M2	Neuraminidase	Neuraminidase
Activity	A only	A only	A and B	A and B
Side effects	CNS (13%) GI (3%)	GI (6%) GI (3%)	? Bronchospasm	GI (9%)
Metabolism	None	Multiple (hepatic)	None	Hepatic
Excretion	Renal	Renal and other	Renal	Renal (tubular secretion)
Drug interactions	Antihistamines Anticholinergics	None	None	Probenecid (increased levels of oseltamivir)
Dose adjustments needed	≥65 y old CCl <50 mL/min	≥65 y old CrCl <10 mL/min	None	CrCl <30 mL/min Severe liver dysfunction
Contraindications	Acute-angle glaucoma	Severe liver dysfunction	Underlying airway disease	None
FDA-approved Indications				
Therapy	Adults and children ≥1 y of age	Adults only	Adults and children ≥7 y of age	Adults and children ≥1 y of age[a]
Prophylaxis	Yes	Yes	No	Adults and children ≥13 y of age[b]

Abbreviations: CrCl, creatinine clearance; FDA, US Food and Drug Administration; GI, gastrointestinal.
[a] FDA has authorized treatment of S-OIV with oseltamivir in children greater than or equal to 3 months of age.
[b] FDA has authorized prophylaxis for S-OIV with oseltamivir in children greater than or equal to 1 year of age.
Data from Treanor J. Influenza viruses, including avian influenza and swine influenza. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th edition. Philadelphia: Churchill Livingston Elsevier; 2010. p. 2265–88.

According to the CDC[45] and other published guidelines,[54] antiviral treatment is recommended for patients infected by the influenza virus who meet the following criteria:

1. Patients with laboratory-confirmed or highly suspected influenza virus infection considered high risk for developing influenza complications (**Box 4**). Treatment is recommended irrespective of illness severity or vaccination status;

Box 4
Persons at high risk for influenza complications recommended for antiviral therapy

1. Infants aged less than 2 years[a]

2. Adults aged 65 years or more

3. Women who are pregnant or postpartum (within 2 weeks after delivery)

4. Persons with asthma or other chronic pulmonary diseases, such as cystic fibrosis in children or chronic obstructive pulmonary disease in adults

5. Persons with hemodynamically significant cardiovascular disease (except hypertension alone)

6. Persons with chronic renal dysfunction

7. Persons with hepatic disorders

8. Persons with hematological conditions (including sickle cell anemia and other hemoglobinopathies)

9. Persons with chronic metabolic disease (including diabetes mellitus)

10. Persons with neurologic and neuromuscular disorders (including cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], muscular dystrophy, and spinal cord injury)

11. Persons with immunosuppressive disorders (including those caused by immunosuppressive therapy)

12. Persons with cancer

13. Persons with human immunodeficiency virus infection

14. Persons aged less than 19 years receiving long-term aspirin therapy (eg, for conditions such as rheumatoid arthritis or Kawasaki disease)

15. American Indians/Alaska Natives

16. Persons morbidly obese (ie, BMI$\geq$40)

17. Residents of any age of nursing homes or other long-term care institutions

[a] Although all children aged less than 5 years are considered at higher risk for complications from influenza, the highest risk is for those aged less than 2 years, with the highest hospitalization and death rates among infants aged less than 6 months. Because many children with mild febrile respiratory illness might have other viral infections (eg, respiratory syncytial virus, rhinovirus, parainfluenza virus, or human metapneumovirus), knowledge about other respiratory viruses as well as influenza virus strains circulating in the community is important for treatment decisions.

Data from Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza - Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60(No. RR-1):1–28; and Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children – diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48(8):1003–32.

2. Patients with laboratory-confirmed or highly suspected influenza virus infection requiring hospitalization, irrespective of underlying illness or vaccination status;
3. Patients with laboratory-confirmed or highly suspected influenza virus infection who have severe, complicated, or progressive illness;

Antiviral treatment should be considered for adults and children with influenza virus infection who meet the following criteria:

1. Outpatients at high risk of complications (see **Box 4**) with illness that is not improving and who have a positive influenza test result from a specimen obtained more than 48 hours after onset of symptoms;
2. Outpatients with laboratory-confirmed or highly suspected influenza virus infection who are not at increased risk of complications, whose onset of symptoms is less than 48 hours before ED presentation, and who would like to shorten the duration of illness and further reduce their risk of complications;
3. Outpatients with laboratory-confirmed or highly suspected influenza virus infection who are in close contact with persons at high risk of complications secondary to influenza infection;
4. Patients whose onset of symptoms occurred more than 48 hours before ED presentation with persisting moderate to severe illness may also benefit from treatment.

Benefits of Early Initiation Antiviral Treatment (≤48 Hours After Symptom Onset)

Because viral titers rapidly decrease by day 3 to 4 of illness in untreated, previously healthy persons, efficacy of antiviral therapy is directly related to time of treatment initiation.[72] Studies have found that early treatment, especially initiated within the first 6 hours of symptom onset, provides the greatest benefit in reducing symptoms.[72] Antiviral treatment initiated within 48 hours of onset of influenza illness can lead to shorter duration of symptoms and decreased illness severity. Studies administering NA inhibitor antiviral medications in previously healthy patients with uncomplicated influenza resulted in a shorter duration of illness by 1 to 2 days.[28,29,73–79] In addition, research has shown that early initiation of treatment with antivirals can also decrease the rate of serious influenza-related complications (eg, pneumonia, respiratory failure, and death) in high risk patients.[80] In contrast, slight or no benefit has been observed in healthy people when antiviral treatment is started more than 48 hours after the onset of uncomplicated influenza.[45] As a result, influenza antiviral treatment, when clinically indicated, should be initiated in a timely fashion, preferably within 48 hours of symptom onset, and not after laboratory confirmation of influenza.

Benefits of Antiviral Treatment Administered More Than 48 Hours After Symptom Onset

In certain patient populations, antiviral treatment may still be beneficial even if given more than 48 hours after symptom onset. These patients include pregnant women, patients with severe or progressive illness requiring hospitalization, and patients at high risk for suffering influenza complications. A study by Siston and colleagues[81] found that, in pregnant women, treatment with antiviral medications decreased respiratory complications and death even when initiated 3 to 4 days after symptom onset compared with 5 days or more. Based on observational studies, oseltamivir decreases severe clinical outcomes in hospitalized patients with influenza. In a multivariate

analysis, treatment with oseltamivir led to a significantly decreased risk of death within 15 days of hospitalization (odds ratio [OR], 0.2; 95% CI, 0.1–0.8).[82] Benefits were detected even in patients whose treatment was initiated more than 48 hours after the onset of symptoms. A study by Lee and colleagues[83] found that among 99 hospitalized patients (median age, 70 years) with laboratory-confirmed influenza who received oseltamivir, benefits were observed even when oseltamivir was started up to 96 hours after illness onset.

Choice of Antiviral Medication

Influenza virus vulnerability to antiviral drugs is continuously evolving. As a result, emergency physicians need to be familiar with the most recently updated information available on antiviral resistance and recommendations on antiviral use. As of January 2011, the CDC recommends the following antiviral drugs for treatment and chemoprophylaxis of seasonal influenza (**Table 6**).[45]

ISOLATION AND PREVENTION OF NOSOCOMIAL SPREAD OF INFLUENZA

The most effective way to prevent and control seasonal influenza is through immunization of both health care workers and patients.[84] Procedures should be institutionalized, which ensures that patients and visitors with respiratory infection symptoms follow triage procedures in the ED that effectively isolate them as rapidly as possible.

In hospital entrances and the ED triage, there should be clear signage with instructions regarding respiratory hygiene and cough etiquette. Face masks should be available to cover the nose and mouth when coughing or sneezing, and waste receptacles are needed to dispose of contaminated tissues. There should also be instructions on how and when to perform hand hygiene. Passive signage asks patients to self-identify; the triage health care team should actively ask patients about possible symptoms while maintaining a distance of at least 1 m from them. Waiting times should be minimized and closely monitored, with staffing adjustments made accordingly. During periods of increased influenza activity, facilities should consider setting up pretriage stations that facilitate rapid screening of patients for symptoms of influenza to separate those patients from others. Registration can identify the charts of patients with potential influenza to expedite care. Waiting rooms should be segregated into 2 areas; patients with and without respiratory symptoms. When possible, physical barriers should separate the patients.

In the ED, patients should be evaluated in single treatment areas.[85] The health care worker should use personal protection equipment (PPE), including a surgical mask, and a face-shield or mask with visor attachment, if there is a high chance of splash or spray of respiratory secretions. Gloves and a long-sleeved gown should be worn when entering the room of a patient with suspected or confirmed influenza.[85] The health care worker should remove all PPE just before leaving the patient's room and discard it in the hands-free waste and linen receptacle within the room. Hand hygiene should be performed after removing gloves and gown, before removing mask and protection, and again after leaving the room.[86]

If a patient with droplet precautions in the ED needs to be moved for investigation, the patient should wear a face mask and continue to follow cough etiquette and hand hygiene. There should be appropriate communication to other personnel about patients with suspected or confirmed influenza before transferring them to other departments (eg, radiology) and admitting units in the facility.

Some procedures performed on patients with suspected or confirmed influenza infection may be more likely to generate higher concentrations of infectious respiratory aerosols. These procedures include intubation and related procedures (eg, manual ventilation, open endotracheal suctioning, cardiopulmonary resuscitation, sputum induction, nebulized therapy, and noninvasive positive pressure ventilation such as continuous positive airway pressure [CPAP] or biphasic positive airway pressure [BiPAP]). Although there are limited data available on influenza transmission related to such aerosols, many authorities recommend the additional precautions to be used when such procedures are performed.[87] The number of health care workers present should be limited to only those essential for patient care and support. Those present should have received influenza vaccine. There should be a low threshold for intubation rather than using prolonged aerosol-generating procedures such as BiPAP and CPAP. The health care worker should wear respiratory protection including a fitted N95 respirator during aerosol–generating procedures. N95 respirators should be used in the context of a comprehensive respiratory protection program that includes fit testing and training as required under the respiratory protection standard (29 CFR 1910.134) of the Occupational Safety and Health Administration (OHSA).[88] The procedures should be conducted in an airborne infection isolation room (AIIR), when feasible. AIIRs reduce the concentration of infectious aerosols and prevent spread into adjacent areas using controlled air exchanges and directional airflow. AIIR are negative-pressure rooms relative to the surrounding areas, with a minimum of 6 air exchanges per hour. The air should be exhausted directly to the outside or filtered through a high-efficiency particulate air (HEPA) filter before recirculation. There should be environmental surface cleaning following the procedure.

Visitors should not be present during aerosol-generating procedures. Visits to patients with suspected or confirmed influenza should be controlled such that visitors should be instructed to limit their movement within the facility. Facilities should provide instruction before visitors enter a patient's room on hand hygiene, limiting surfaces touch, and use of PPE.[89] Visitors should be advised to contact their health care provider for information on influenza vaccination, if this has not been received; if they are high-risk patients (as described earlier),[45] chemoprophylaxis may be offered if they are in close contact with the patient.

Health care workers in the ED presumably receive education and training programs on preventing transmission of all infectious agents, including influenza. These programs should be updated periodically and competency should be documented. Health care workers who develop fever and respiratory symptoms should be instructed not to report to work, or, if working, they should put on a face mask and promptly notify their supervisor and/or infection control personnel. Health care workers should be excluded from work for at least 24 hours after they no longer have fever. Those with ongoing respiratory symptoms should be evaluated to determine appropriateness of contact with patients. Health care workers caring for immunocompromised patients should be considered for temporary assignment or exclusion from work for 7 days from symptom onset or until the resolution of symptoms, whichever is longer.[85] Administration of antiviral treatment and chemoprophylaxis of health care workers should be considered when appropriate. Early treatment with antiviral agents and vaccination are especially important for health care workers at higher risk for influenza complications, including pregnant women and women up to 2 weeks after giving birth; persons 65 years and older; and persons with chronic diseases such as asthma, heart disease, diabetes, diseases that suppress the immune system, and morbid obesity.[45] Work reassignment should be considered

Table 6
Recommended dosage and schedule of influenza antiviral medications[a] for treatment[b] and chemoprophylaxis[c]

Antiviral Agent	Treatment/ Chemoprophylaxis	Age Groups (y)				
		1–6	7–9	10–12	13–64	≥65
Zanamivir	Treatment					
	Influenza A	Not approved	10 mg twice a day	10 mg twice a day	10 mg twice a day	10 mg twice a day
	Influenza B	Not approved	10 mg twice a day	10 mg twice a day	10 mg twice a day	10 mg twice a day
	Chemoprophylaxis					
	Influenza A	Not approved for ages 1–4 y	Children aged 5–9 y			
	—	—	10 mg every day	10 mg every day	10 mg every day	10 mg every day
	Influenza B	Not approved for ages 1–4 y	Children aged 5–9 y	—	—	—
	—	—	10 mg every day	10 mg every day	10 mg every day	10 mg every day
Oseltamivir[d]	Treatment					
	Influenza A					
	Weight of Child (kg)	≤15 / >15–23 / >23–40 / >40	≤15 / >15–23 / >23–40 / >40	≤40 / >40	75 mg	75 mg
	Dose	30 mg twice a day / 45 mg twice a day / 60 mg twice a day / 75 mg twice a day	30 mg twice a day / 45 mg twice a day / 60 mg twice a day / 75 mg twice a day	Dose varies[e] / 75 mg twice a day	twice a day	twice a day
	Influenza B					
	Weight of Child (kg)	≤15 / 15–23 / 23–40 / >40	≤ 15 / 15–23 / 23–40 / >40	≤40 / >40	75 mg	75 mg
	Dose	30 mg twice a day / 45 mg twice a day / 60 mg twice a day / 75 mg twice a day	30 mg twice a day / 45 mg twice a day / 60 mg twice a day / 75 mg twice a day	dose varies[e] / 75 mg	twice a day	twice a day

Chemoprophylaxis

Influenza A

Weight of Child (kg)	≤15	>15–23	>23–40	>40	≤15	>15–23	>23–40	>40	≤40	>40	75 mg every day	75 mg every day
Dose	30 mg every day	45 mg every day	60 mg every day	75 mg every day	30 mg every day	45 mg every day	60 mg every day	75 mg every day	dose varies[e]	75 mg every day		

Influenza B

Weight of Child (kg)	≤15	>15–23	>23–40	>40	≤15	>15–23	>23–40	>40	≤40	>40	75 mg every day	75 mg every day
Dose	30 mg every day	45 mg every day	60 mg every day	75 mg every day	30 mg every day	45 mg every day	60 mg every day	75 mg every day	dose varies[e]	75 mg every day		

[a] Zanamivir is manufactured by GlaxoSmithKline (Relenza, an inhaled powder). Zanamivir is approved for treatment of persons aged greater than or equal to 7 years and approved for chemoprophylaxis of persons aged greater than or equal to 5 years. Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Patients benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease. Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu, a tablet). Oseltamivir is approved for treatment or chemoprophylaxis of persons aged greater than or equal to 1 year. Oseltamivir is available for oral administration in 30 mg, 45 mg, and 75 mg capsules and liquid suspension. No antiviral medications are approved for treatment or chemoprophylaxis of influenza among children less than 1 year old. This information is based on data published by the FDA (Available at: http://www.fda.gov/Drugs/DrugSafety/informationbyDrugClass/ucm100228.htm).

[b] Recommended duration for antiviral treatment is 5 days. Longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.

[c] Recommended duration is 10 days when administered after a household exposure and 7 days after the most recent known exposure in other situations. For control of outbreaks in long-term care facilities and hospitals, CDC recommends antiviral chemoprophylaxis for a minimum of 2 weeks and up to 1 week after the most recent case was identified.

[d] A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance less than 30 mL/min.

[e] For the recommended treatment dose for oseltamivir for children aged 10 to 12 years who weigh 40 kg or less, please see weight of child and dose for age groups 7 to 9 years.

Data from Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011;60(No. RR-1):1–28.

for those at higher risk to avoid potentially high-risk exposure such as performing or assisting aerosol-generating procedures in patients with suspected or confirmed influenza.

The ED should have adequate isolation facilities and clear protocols of rapid admission to the wards to prevent boarding. Lastly, discharge instructions should be developed and given to every patient with influenza discharged home from the ED.

Discharge instructions for adult patients with suspected or confirmed influenza

The Emergency Department team feels that you have the seasonal flu or influenza and your symptoms are mild enough to send you home for observation and recovery of your illness.

Influenza is contagious, and you should use proper precautions so that you do not pass your infection on to others.

When you leave the Emergency Department, please wear a mask and keep it on until you arrive home if you cannot keep a distance of 2 m from others. You may also wear it at home, as necessary.

Do not use public transportation (bus, subway) to go home. Go straight home; do not make any stops on the way (eg, drug store, grocery store). If you were given a prescription, make arrangements for a family member or friend to pick it up.

You should isolate yourself in your home until 7 days after the onset of illness or at least 24 hours after symptoms have resolved, whichever is longer. Do not go to work, school, or public places. Do not share personal items, such as towels, drinking cups, cutlery, thermometers, and toothbrushes.

Always use hygiene and prevention measures to avoid contamination:

- Wash your hands frequently.
- Cough or sneeze into the crook of your elbow rather than into your hands.
- Use tissues and dispose in waste basket.
- Keep your surroundings clean.

While at home, it is important that you monitor your own health to be sure that your illness does not worsen. You should consult your doctor or return to the Emergency Department if you develop one of these symptoms: shortness of breath, difficulty breathing, chest pain, recurrent vomiting, or high fever 38.5°C (101.3°F).

Household contacts should:

- Pay attention to the onset of any illness
- Stay home if mild flulike symptoms occur
- Go to a doctor with a fever more than 38°C (100.4°F) and belong to a group at risk of developing influenza complications (children less than 2 years of age, pregnant women, person 65 years old and older, and persons with chronic diseases such as asthma, heart disease, diabetes, and diseases that suppress the immune system)
- Go to a doctor with a fever more than 38°C (100.4°F) and one of these symptoms:
  - Shortness of breath
  - Difficulty breathing
  - Chest pain
  - Recurrent vomiting
  - Child who is too quiet and less active than normal, or refuses to play, or is agitated

SEASONAL VERSUS PANDEMIC INFLUENZA

The symptoms of an influenza pandemic can be similar to those of seasonal flu (ie, fever, headache, myalgia, coryza, gastrointestinal symptoms, sore throat, or cough). In the last century, 4 influenza pandemics were caused by novel influenza viruses. The most significant was in 1918, when the so-called Spanish flu killed 40 to 50 million people worldwide.[90] In 2009, there was the emergence of a novel H1N1 virus, a genetic combination of human and swine influenza viruses. Because many persons have little or no immunity to a new pandemic virus, the disease can spread quickly. With the H1N1 pandemic, the rate of infection was highest among young individuals; infections were less common in persons older than 65 years, perhaps secondary to preexisting immunity against antigenically similar viruses.[91–93] There are several differences between seasonal and pandemic influenza[94]:

Seasonal and pandemic influenza	
Seasonal Influenza	**Pandemic Influenza**
Seasonal flu happens every year	An influenza pandemic happens only 2 or 3 times a century
Seasonal flu is usually around from November to April, and then stops	An influenza pandemic usually comes in 2 or even 3 waves several months apart. Each wave lasts about 2 months
About 10% of the population gets ordinary seasonal flu each year	About 35% of the population may get the influenza during the course of the full outbreak
Seasonal flu is hardest on people who do not have a strong immune system: the very young and old, and those with certain chronic illnesses	People of any age may become seriously ill with influenza during a pandemic. Often it affects a younger population
In a normal flu season, a minority die of complications from the flu, such as pneumonia	During an influenza pandemic, many more persons are infected and there may be many more deaths (see FluAid 2.0 regarding estimates based on attack rates)
Annual flu shots are protective from seasonal flu	There is no existing vaccine for an influenza pandemic. It takes 4 to 6 months after the pandemic starts to develop a vaccine
Antivirals should help the seasonal flu	Antivirals may help but the effectiveness is unknown until the virus is identified

Adapted from Ontario Ministry of Health and Long-Term Care. What you should know about a flu pandemic. http://www.healthgov.on.ca/en/public/programs/emu/pan_flu/#4. Accessed May 2011.

The WHO is responsible for monitoring the spread of influenza worldwide, declaring a pandemic, and coordinating the global response. However, the local health care systems need to develop surveillance to detect and monitor for a pandemic strain. It is important for the emergency physician to be cognizant that patients presenting with severe ILI, with epidemiologic links to southeast Asia, in particular China, with no diagnosis within the first 72 hours of hospitalization may represent the patient with an emerging respiratory infection.[95] Patients with severe respiratory infections are those with fever and new onset of cough or shortness of breath with radiographic evidence of acute respiratory distress syndrome or other life-threatening complications such as encephalitis. The emergency physician should enquire about the patient's travel history or any close contact with persons who have traveled (especially from southeast Asia) or contact with any health care provider.[95] Such patients require isolation and

consultation with the infection control team. During a pandemic, a comprehensive screening process is needed at triage to limit the exposure to other patients and health care workers. Further elaboration of pandemics is beyond the scope of this article.

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APPENDIX 1: REFERENCES FOR TABLE 4 (SENSITIVITY, SPECIFICITY, PPV, AND NPV OF SELECTIVE RIDTS)

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