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In the Clinic® Influenza

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Abstract

Influenza is an acute viral respiratory disease that affects persons of all ages and is associated with millions of medical visits, hundreds of thousands of hospitalizations, and thousands of deaths during annual winter epidemics of variable severity in the United States. Elderly persons have the highest influenza-associated hospitalization and mortality rates. The primary method of prevention is annual vaccination. Early antiviral treatment has the greatest clinical benefit; otherwise, management includes adherence to recommended infection prevention and control measures as well as supportive care of complications.

Annual epidemics caused by infections with seasonal influenza A or B viruses occur during the winter months in temperate climates. Influenza activity may occur year-round in tropical and subtropical climates, peaking during cooler or rainy-season months. Influenza usually involves self-limited symptoms of the upper respiratory tract, fatigue and myalgia, with or without fever. However, young children, elderly persons, pregnant women, and those with certain chronic medical conditions are at higher risk for severe disease.

Influenza A viruses are classified into subtypes based on the 2 main surface glycoprotein components: hemagglutinin (referred to as “HA” or “H”) and neuraminidase (referred to as “NA” or “N”). Influenza viruses bind to receptors on the surface of respiratory epithelial cells (primarily of the upper tract) through the HA protein. Most humoral immunity against the HA protein, acquired through infection or vaccination, is virus strain-specific.

Antigenic “drift” refers to HA gene mutations causing antigenic changes in the HA protein so that antibodies acquired by prior infection or vaccination do not bind to antigenically drifted virus strains. Antigenic drift is the unpredictable evolutionary process that drives seasonal epidemics and is why year-round influenza surveillance and annual updating of vaccine strains are needed. Seasonal influenza viruses currently circulating among humans

CMEObjective: To review current evidence for prevention, diagnosis, treatment, and practice improvement of influenza.

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worldwide include influenza A(H1N1)pdm09 and A(H3N2) viruses and 2main groups (or lineages) of influenza B viruses.

Antigenic “shift” refers to human infection with a novel influenza A virus that is antigenically and genetically distinct from influenza A viruses circulating in humans. Novel influenza A viruses have public health importance because they can cause sporadic human infections resulting from exposure to infected animals (usually poultry or pigs) as well as pandemics in which most of the population lacks immunity to the novel virus strain.

Prevention

Who is at greatest risk for complications and hospitalization?

High-risk persons include young children younger than 5 years and particularly those under 2; adults aged 65 years and older; pregnant women; residents of nursing homes and other long-term care facilities; American Indians and Alaska Natives; persons of any age with certain underlying medical conditions, such as chronic lung disease, cardiac disease (but not isolated hypertension), neurologic and neurodevelopmental conditions, hematologic disorders, kidney or liver disorders, metabolic diseases, or immunosuppression; persons younger than 19 years receiving long-term aspirin therapy; and Extremely obese persons (body mass index ≥40 kg/m^2) (see the Box) (1).

In the United States, persons aged 65 years and older hav the highest rate of influenza associated hospitalization, followed by those aged 50–64 years and then young children. Mortality rates are highest in persons aged 65 years and older.

Who should receive vaccination, and when should it be given?

All persons aged 6 months and older in the United States should be vaccinated annually, ideally before influenza activity begins in the community and by the end of October, if possible (1). Recent studies have reported evidence of waning vaccine effectiveness during the influenza season (2,3), suggesting that summertime vaccination might be too early; however, more studies are needed. Clinicians need to keep abreast of possible changes in recommended timing of influenza vaccination. The Centers for Disease Control and Prevention (CDC) maintains updated recommendations on its Web site (see Tool Kit for links).

Previously unvaccinated children aged 6 months up to 9 years should receive 2 doses at least 4 weeks apart in the first year of vaccination; for all other groups, revaccination is not recommended during influenza season. Although vaccination is not approved for infants younger than 6 months, strategies to prevent influenza in this group include vaccination of pregnant women, household contacts aged 6 months and older, and caregivers. Randomized controlled studies have established that maternal vaccination can prevent influenza in infants (through transplacentally transferred antibodies) up to 6 months after birth (4–6).

Although influenza activity in the United States usually peaks during December to March, it varies widely and may continue into April or May in some communities. Influenza B viruses

often peak later and circulate longer than influenza A viruses. As long as influenza viruses are circulating in a community, influenza vaccination can be beneficial.

Persons with significant febrile illness generally should not be vaccinated, based on clinical judgment; minor acute illness without significant fever is not a contraindication.

If difficulties in vaccine production or distribution result in shortages or delays, priority should be given to persons at high risk for severe disease or complications and to their close contacts, including health care workers (1). The CDC has provided recommendations on its Web site for prioritizing influenza vaccination under these circumstances.

How effective is the vaccine?

Effectiveness of influenza vaccine varies from season to season and is influenced by such factors as age, baseline health, and immune function as well as the degree of antigenic match between vaccine strains and circulating influenza viruses. If vaccine antigens and virus strains are well-matched, effectiveness is moderate; however, it is lower during seasons when they are mismatched. Effectiveness can also vary by virus type and influenza A virus subtype. In a systematic review and meta-analysis of 10 randomized controlled trials, efficacy of the trivalent inactivated vaccine was found in 8 of 12 seasons, with a pooled efficacy of 59% (95% CI, 51%−67%) in adults aged 18–65 years (7).

> A recent systematic review and meta-analysis of studies of vaccine effectiveness in outpatients reported that the overall pooled effectiveness was 33% for A(H3N2), 54% for influenza B, and 61% for A(H1N1)pdm09. Effectiveness was 33% when the H3N2 vaccine antigen was well-matched to the circulating A(H3N2) viruses but only 23% when antigenic drift was present (8). For adults older than 60 years, pooled effectiveness was 24% for A(H3N2), 62% for A(H1N1)pdm09, and 63% for influenza B.

Vaccination is moderately effective in preventing hospitalization (9–12) and influenza-associated death in children (13) but is generally less effective in elderly than in nonelderly persons. However, few clinical trials have focused on elderly persons, and selection bias may lead to vaccination of healthier persons.

> A meta-analysis of individual-participant data involving case-control studies of nearly 5000 community-dwelling older adults worldwide re- ported that vaccination was moderately effective (adjusted effectiveness was 44.4% during well- matched seasons and 20% during mismatched seasons) in preventing laboratory-confirmed influenza (14). This study also found that vaccination was effective in older adults with cardiovascular disease (adjusted effectiveness, 31%) or respiratory disease (adjusted effectiveness, 31%) and those aged 75 years or younger (adjusted effectiveness, 33%).

Recently, data have become available for vaccines with higher antigen content than standard-dose (SD) vaccine. One randomized controlled trial that included more than 8500 adults aged 50 years or older reported that a recombinant vaccine with 3 times the HA antigen content for each strain provided greater protection against laboratory-confirmed influenza than SD vaccine (15). A cluster randomized trial of high-dose (HD) inactivated influenza

vaccine containing 4 times the antigen content for each strain versus SD inactivated influenza vaccine in elderly nursing home residents reported that HD vaccine significantly reduced respiratory-related hospitalizations compared with SD vaccine (16).

What vaccines are available?

The composition of influenza vaccines is updated annually. A wide variety of vaccines are approved and available in the United States (Table 1), including inactivated trivalent (IIV3) or quadrivalent (IIV4) vaccines; the vaccine given depends on the age of the recipient (1). Vaccines typically become available in the late summer and expire on 30 June after the end of each influenza season.

IIV3 vaccines contain 2 influenza A virus antigens-an A(H3N2) and an A(H1N1)pdm09 virus-and 1 influenza B virus antigen. IIV4 vaccines contain A(H3N2) and A(H1N1)pdm09 virus antigens and 2 influenza B virus antigens-1 each of the 2 main circulating lineages (B/Yamagata and B/Victoria). Most IIV3 and IIV4 vaccines are given by intramuscular injection; however, an intradermal IIV4s vaccine is available for adults aged 18–64 years.

Most viruses are grown in embry-onated chicken eggs and then inactivated; however, 2 approved vaccines use antigens that are not grown in eggs, including 1 quadrivalent vaccine comprising viruses that are grown in tissue cell culture (ccIIV4) and then inactivated. One vaccine approved for adults that is not based on cultured viruses is a recombinant HA vaccine (RIV3 or RIV4) produced in insect cells.

For persons aged 65 years and older, SD vaccines have decreased immunogenicity and effectiveness. Two vaccines are now available that may improve protection in this group: an adjuvanted IIV, and an HD IIV with 4 times the antigen concentration of SD vaccines.

Live attenuated influenza virus vaccine is approved by the U.S. Food and Drug Administration for intranasal administration for nonpregnant healthy persons (without underlying medical conditions) aged 2–49 years. However, due to poor effectiveness over multiple seasons, particularly for the influenza A(H1N1)pdm09 virus strain, the Advisory Committee on Immunization Practices and the CDC recommended that this vaccine not be used for the 2016–2017 or 2017–2018 seasons (1).

What adverse effects are associated with vaccination?

The most common adverse effect from injectable inactivated influenza vaccines is soreness at the injection site for about 2 days (1). Pain, low-grade fever, myalgia, headache, and fatigue are less common and may last 1–2 days. Erythema, induration, swelling, and pruritus may be more common with intradermal vaccines. Studies of influenza vaccination in pregnant women have not identified any significant adverse pregnancy or fetal outcomes (17–21).

Whether influenza vaccination increases the risk for Guillain-Barre syndrome (GBS) is unknown. One systematic review and meta-analysis of observational studies reported a slight association between influenza vaccination and GBS (22). In general, persons who previously had GBS within 6 weeks after being vaccinated and are not at risk for severe influenza

complications should not be vaccinated. For persons who are more likely to have influenza complications, the small risk for GBS is probably outweighed by the benefit of vaccination, which can also reduce the small risk for GBS that can be triggered by influenza virus infection (23, 24). For non-pregnant adults, some studies have reported a low risk for GBS (approximately 1 case per 1 million vaccinated persons) (1).

How should clinicians approach vaccination in persons with severe allergies?

Anaphylaxis after influenza vaccination is rare. Although most influenza vaccines are grown in embryonated chicken eggs (except RIV3, RIV4, and ccIIV4 vaccines), severe reactions-even in persons with egg allergies-are uncommon. Influenza vaccine can be given to persons with a history of egg allergy who have had only hives after exposure to eggs. Persons who report other allergic symptoms, such as angioedema, respiratory distress, lightheadedness, or recurrent vomiting, or those who required epinephrine or other emergency medical intervention for anaphylaxis can still be vaccinated, but it should be done in an inpatient or outpatient medical setting supervised by a health care provider who can recognize and manage severe allergic reactions (1). However, anyone who has had a more severe allergic reaction should not be vaccinated.

What is the role of behavioral strategies to prevent transmission?

Immunocompetent persons who are symptomatic from uncomplicated influenza virus infection can shed viruses from the upper respiratory tract for approximately 4–7 days, although shedding and transmissibility generally decrease substantially after 3 days. Influenza viruses are believed to be transmitted primarily by large and small particle droplets that are expelled by coughing or sneezing by an infected person to susceptible close contacts. Contact transmission has been suggested indirectly through hand hygiene studies. The role of asymptomatically infected or presymptomatic persons in transmitting the viruses is unknown, but this is believed to be uncommon.

> A systematic review and meta-analysis examined randomized clinical trials studying the efficacy of hand hygiene (with or with-out facemasks) in reducing influenza virus transmission in community settings (house-holds). It reported that hand hygiene combined with facemasks resulted in a statistically significant reduction in laboratory-confirmed transmission (relative risk, 0.73 [CI, 0.53–0.99]; P = 0.05), but hand hygiene alone did not (25). Another review concluded that evidence of the efficacy of nonpharmaceutical interventions, such as facemasks and hand hygiene, to reduce transmission was lacking, with most studies being significantly flawed (26).

Community nonpharmaceutical interventions, such as school closures, have been implemented to control seasonal and pandemic influenza; effectiveness has varied (27).

What is the role of antiviral agents in prevention?

The neuraminidase inhibitors oral oseltamivir and inhaled zanamivir are approved for antiviral treatment and chemoprophylaxis of influenza. Antiviral chemoprophylaxis (before or after exposure) of individuals or in households has moderate to high effectiveness for influenza prevention (28) but is not routinely recommended. Antiviral chemoprophylaxis

can be considered for persons in whom vaccination is contraindicated or who are not expected to benefit, such as severely immunosuppressed patients.

Antiviral chemoprophylaxis is an important component of a bundle of interventions to control institutional influenza outbreaks, and oseltamivir chemoprophylaxis has been shown to be effective in controlling established outbreaks in nursing homes (29–31). When an institutional outbreak is recognized, some exposed residents or patients may already be incubating influenza virus when antiviral chemoprophylaxis is implemented. Therefore, consideration can be given to twice-daily (i.e., treatment dosing) versus once-daily chemoprophylaxis dosing in long-term care facilities or health care facilities, including in immunosuppressed persons (32, 33).

A cluster randomized trial compared oseltamivir treatment of symptomatic persons with oseltamivir chemoprophylaxis for elderly long-term care residents over 3 seasons. It found that postexposure chemoprophylaxis reduced the influenza attack rate among residents compared with treating symptomatic persons (34). One multicountry randomized controlled trial of oseltamivir chemoprophylaxis versus placebo for 6 weeks in vaccinated nursing home residents reported high efficacy in preventing outbreaks (35).

During an institutional outbreak, unvaccinated staff members and residents should receive influenza vaccine if it is available. In nursing homes, the potential for high-intensity virus exposure and possible suboptimal immune response to vaccine by debilitated residents suggests that all residents, regardless of previous vaccination, should receive chemoprophylaxis in an outbreak. Antiviral medications should be continued for at least 2 weeks, and then for 1 week longer than the duration of the outbreak.

Antiviral chemoprophylaxis may also be considered for high-risk persons and close contacts (including health care workers) when vaccine is unavailable or contraindicated, when a major difference exists between the predominant virus antigens and the vaccine strains such that effectiveness is expected to be very low, or when severe immunosuppression makes response to the vaccine unlikely.

What measures should clinicians take to prevent influenza among patients and staff in health care institutions?

All health care personnel should be vaccinated annually unless it is contraindicated or the vaccine is unavailable. In outpatient settings, persons with suspected or confirmed influenza should be encouraged to adhere to respiratory hygiene, cough etiquette (use facemasks or tissues to cover the nose and mouth when coughing, and dispose of contaminated materials), and hand hygiene recommendations. For inpatient settings, patients with suspected or confirmed influenza should be isolated or cohorted (co-located) if isolation is not possible. Standard and droplet precautions are recommended, and for aerosol-generating procedures a fit-tested N95 respirator or respirator equivalent is recommended (36).

The use of standing orders, which allow trained health care professionals other than physicians to identify and vaccinate high-risk patients, improves influenza vaccine coverage of hospitalized patients at discharge and nursing home residents, especially if structured in

an “opt-out” format. Likewise, providing free vaccination at convenient times and places may increase coverage among hospital and nursing home staff.

During outbreaks, infection prevention and control measures, such as limiting visitors, using droplet precautions, isolating or cohorting symptomatic patients, and performing active daily surveillance for new cases, should also be implemented.

Diagnosis

What signs and symptoms should prompt clinicians to suspect influenza?

Signs and symptoms of uncomplicated influenza frequently overlap with those of other respiratory viral infections, but abrupt onset of fever, especially high fever or feverishness, and cough can help in differentiation, especially if influenza activity is present in the community (37–39). Although weakness, myalgia, sore throat, nausea, rhinorrhea, and headache are common in patients with influenza, they occur with similar frequency in other viral illnesses. Not all persons with influenza manifest fever, including immunosuppressed and elderly persons (40). Young children with respiratory symptoms may have diarrhea, and adults with respiratory symptoms may have vomiting. The presence of crackles or decreased breath sounds on chest examination may suggest such pulmonary complications as viral pneumonia, secondary bacterial pneumonia, or heart failure.

When should clinicians suspect novel influenza A virus infection?

The key to diagnosing novel influenza A virus infection is to elicit a history of recent exposure to poultry or pigs where novel influenza A viruses are circulating among animal hosts, or exposure to an ill person with novel influenza A virus infection. Disease severity in infected animals does not necessarily correlate with severity in infected humans.

Similar to seasonal influenza, a wide clinical spectrum of human infection with novel influenza A viruses has been reported, including asymptomatic infection, conjunctivitis only, upper respiratory tract illness, pneumonia, encephalopathy and encephalitis, and multi organ failure with fatal outcomes (41, 42). Therefore, novel influenza A virus infection cannot be distinguished from seasonal influenza A virus infection by clinical findings or by commercially available tests and must be diagnosed by specific influenza molecular assays at public health laboratories (43, 44).

When should clinicians test to confirm a clinical diagnosis?

Influenza testing (Table 2) is not needed to confirm the clinical diagnosis or to decide whether to prescribe antiviral medications to a patient when influenza viruses are circulating in the community (45). Testing should be considered when the results will influence individual clinical management decisions. In an institutional (long-term care facility or hospital ward) outbreak of respiratory illness, diagnostic testing can help establish influenza as the cause, supporting prompt implementation of prevention and control measures.

Respiratory specimens should be collected as close to illness onset as possible. In critically ill patients, the diagnosis may be missed if only upper respiratory tract specimens are tested, even with molecular assays. Viral replication may be prolonged in the lower respiratory

tract, and testing endotracheal aspirate or bronchoalveolar fluid specimens may thus yield a diagnosis of influenza (46, 47).

Clinicians must understand the limitations of influenza tests and interpretation of their results (48, 49). Sensitivity of virus detection is generally higher in children than in adults, higher with nasopharyngeal or nasal specimens than with throat samples, and higher during the first few days of illness. The positive predictive value of the tests is highest during high influenza activity, and the negative predictive value is highest during low influenza activity or outside the season. Clinicians who are evaluating travelers returning from overseas should understand that during periods of low influenza activity in the United States, activity may be high in temperate climates in the Southern Hemisphere and that influenza activity occurs year-round in countries with tropical and subtropical climates.

Different influenza tests (Table 2) are available for respiratory specimens (50). The most accurate tests with the highest sensitivity and specificity are molecular assays, including reverse transcription polymerase chain reaction (RT-PcR) assays (51). Most molecular assays take about 60–80 minutes to produce results, but some require only 20 minutes, with moderately high sensitivity compared with other molecular assays. Antigen detection assays, including rapid influenza tests that yield results in approximately 10 minutes, and immunofluorescence assays have low to moderate sensitivity in detecting influenza viruses in respiratory specimens; therefore, false-negative results with these tests are common during peak influenza activity. For hospitalized patients with suspected influenza, molecular assays are recommended (51). Isolation and implementation of infection prevention and control measures and initiation of empirical antiviral treatment should not be delayed pending test results.

Viral culture is important for influenza virus surveillance and public health but does not yield timely results to inform clinical management. Serologic testing should not be routinely done to diagnose influenza because of the need for collection of acute and convalescent serum specimens. Serologic testing of a single serum specimen is not interpretable and has no role in diagnosis or clinical management of seasonal influenza.

Diagnosing influenza through testing can preclude unnecessary antibiotic use and additional laboratory tests and facilitate antiviral use and patient isolation (52, 53).

What complications are associated with influenza?

Complications vary by age, immune function, and underlying medical conditions. Influenza may exacerbate underlying chronic disease (e.g., chronic obstructive pulmonary disease or heart failure). Persons with chronic obstructive pulmonary disease or severe immunosuppression and elderly persons may be at greater risk for pneumonia with influenza.

Other complications include otitis media, bronchiolitis, and croup in young children and sinusitis in older children and adults. Bronchospasm, bronchitis, and pneumonia can occur at any age. Pneumonia can be directly due to influenza virus or bacterial co-infection; can occur with or without pleural effusion; and can progress rapidly to respiratory failure, acute

respiratory distress syndrome, and refractory hypoxemia. Cardiac complications include myocarditis, pericarditis, heart failure, and myocardial infarction. A wide range of neurologic complications includes seizures, transient encephalopathy to acute necrotizing encephalopathy and encephalitis, cerebrovascular accident, acute disseminated encephalomyelitis, and GBS. Musculoskeletal complications include severe myositis and rhabdomyolysis. Levels of hepatic aminotransferases can be elevated, but liver failure is rare. Bacterial co-infection can result in pneumonia, bacteremia, and meningitis. Acute kidney injury and renal failure can occur in some patients. Critically ill patients may manifest with multi organ failure (respiratory and renal), shock, and sepsis.

When should clinicians suspect bacterial co-infection in patients believed to have influenza?

Clinicians should consider bacterial co-infection in patients with suspected or confirmed influenza who present with severe disease, remain ill, worsen, or have acute onset of high fever or respiratory distress after initial improvement. Adults with uncomplicated influenza typically have fever and symptoms for about 3 days, by which time most show signs of improvement. Although it may take 10–14 days for complete recovery, and longer in older adults, lack of improvement or worsening symptoms suggest either a complication or an alternative diagnosis.

The bacteria most commonly implicated in community-acquired pneumonia with influenza are *Streptococcus pneumoniae, Staphylococcus aureus* (both methicillin-sensitive and methicillin-resistant), and group A *Streptococcus* (54). An association between bacterial meningitis due to *Neisseria meningitides* and influenza has been reported (55).

Patients who remain febrile for more than 3–5 days or who develop fever, worsening symptoms, or progressive disease require evaluation. Symptoms and clinical findings should guide blood tests, cultures, and imaging studies. Consultation with an infectious disease specialist should be considered, especially if the patient is severely ill or immunosuppressed. The differential diagnosis should be expanded to include bacterial infection in patients whose condition deteriorates rapidly, and work-up and treatment should be adjusted accordingly.

Treatment

What is the role of hydration and antipyretics?

Hydration is important to replace insensible water loss that occurs with fever. Antipyretics, such as acetaminophen or ibuprofen, can help reduce fever and prevent further insensible water loss. Reduction of fever can prevent other consequences of increased metabolic rate, such as tachycardia, and relieve such symptoms as chills and myalgia. There is no convincing evidence that antipyretic therapy prolongs or shortens the disease course. Aspirin and aspirin-containing medication must be avoided in patients with suspected or confirmed influenza, particularly in adolescents and children, because of the association between salicylates and Reye syndrome in persons with influenza (56, 57).

What is the role of antiviral medications?

Neuraminidase inhibitors (oral oseltamivir, inhaled zanamivir, and intravenous peramivir) are recommended antiviral treatments for influenza. Treatment duration in outpatients is typically 5 days. These drugs have activity against influenza A and B viruses but differ by approved age groups, routes of administration, and adverse effects (Table 3). Dual neuraminidase inhibitor treatment is not recommended because of reports of antagonism with this therapy compared with monotherapy (58). Inhaled zanamivir is generally not recommended for hospitalized patients. In critically ill patients, oseltamivir can be given enterally by orogastric or nasogastric administration. The adamantane drugs (amantadine and rimantadine) have no activity against influenza B viruses and are not recommended for treatment of influenza A virus infection because currently circulating influenza A viruses (A[H1N1]pdm09 and A[H3N2]) are resistant to these drugs.

Randomized placebo-controlled trials of antiviral treatment of influenza in hospitalized patients are lacking. However, the CDC recommends prescribing neuraminidase inhibitor antiviral treatment to all hospitalized patients with confirmed or suspected influenza as soon as possible, without waiting for test results. Abundant observational data from hospitalized patients with influenza indicate that the greatest clinical benefit is achieved when antiviral treatment is started as close to illness onset as possible, although benefit is still possible when it is started 48 or more hours after onset compared with no treatment (59). For outpatients with suspected or confirmed influenza in a group at high risk for complications, and for those with progressive disease who do not require hospitalization, antiviral treatment is recommended even if more than 2 days have passed since illness onset. For otherwise healthy persons with suspected or confirmed uncomplicated influenza who are not at high risk for complications and who present within 2 days of illness onset, clinical judgment can be used to decide whether to prescribe antiviral treatment.

Randomized clinical trials in out-patients with uncomplicated influenza have established the efficacy of early (≤2 days after illness onset) neuraminidase inhibitor treatment to reduce the duration of illness by approximately 0.6–1 day (60, 61). A meta-analysis of randomized controlled trials of oseltamivir treatment versus placebo in adult outpatients reported that oseltamivir significantly reduced the risk for lower respiratory tract complications requiring antibiotic treatment as well as the risk for hospitalization for any cause but increased the risk for nausea and vomiting (60).

> A meta-analysis of individual observational data from 3376 patients of all ages at high risk for hospitalization with suspected or confirmed influenza A(H1N1)pdm09 virus infection reported that outpatient neuraminidase inhibitor treatment was associated with a significantly reduced likelihood of hospitalization compared with no antiviral treatment (62).

Although oseltamivir and zanamivir are pregnancy category C drugs, the CDC advises that pregnancy should not be considered a contraindication. Oseltamivir is recommended over inhaled zanamivir because of concerns about lower lung volumes in pregnancy causing reduced zanamivir distribution and potential bronchospasm (63). Cohort studies have concluded that oseltamivir treatment is safe and that there is no evidence that treatment of

pregnant women with this drug is associated with any adverse pregnancy or birth outcomes (64, 65).

An individual-patient-level meta-analysis (78 observational studies with >29 000 hospitalized patients with suspected or laboratory-confirmed influenza A[H1N1]pdm09 virus infection) reported that neuraminidase inhibitor treatment of adults was associated with reduced risk for death compared with no antiviral treatment. Treatment initiation within 2 days of illness onset was associated with reduced risk for death compared with starting treatment more than 2 days after onset (59). Similarly, when the analysis was limited to pregnant women, early initiation was associated with reduced risk for death compared with no treatment or later initiation of treatment, and neuraminidase inhibitor treatment at any time after illness onset was associated with reduced risk for death versus no treatment.

When should patients be hospitalized?

Hospitalization should be considered for patients with significant dehydration and severely ill persons who have complications of suspected or laboratory-confirmed illness, especially those with respiratory distress, hypoxemia, impaired cardiopulmonary function, or altered mental status. Likewise, patients who have an uncertain clinical course or are frail at baseline might require admission for close observation.

When should clinicians consult an infectious disease specialist or public health authority?

Diagnostic consultation may be useful in seriously ill patients in whom influenza is suspected but unproven, in patients with atypical presentations, when severe complications are suspected, and when the differential diagnosis is broad (e.g., immunosuppressed patients with pneumonia).

Infectious disease specialists can guide the use of antiviral agents and help determine the need for antimicrobial agents and should also be consulted if antiviral resistance is suspected. They can help manage severely immunosuppressed patients with influenza and guide use of investigational antivirals, either through a clinical trial or for compassionate use. Pulmonary or critical care specialists can help with procedures for maintaining oxygenation in critically ill patients and obtaining specimens for testing.

Public health authorities should be consulted if novel influenza A virus infection is suspected based on clinical presentation, reported exposure to animals or to a patient with such infection, and pertinent travel history. State health departments can use RT-PCR to test specifically for seasonal influenza A as well as novel influenza A viruses originating from animals, with confirmation at the CDC. Public health authorities are responsible for monitoring disease outbreaks, determining the source, evaluating possible human-to-human transmission, and instituting measures to limit further transmission in close contacts. Clinicians should view CDC recommendations on specimen collection and testing, antiviral treatment and chemoprophylaxis, infection prevention and control, and monitoring of close contacts.

Practice Improvement

What measures do stakeholders use to measure the quality of care?

The Centers for Medicare & Medicaid Services (CMS) requires participating nursing homes to offer influenza vaccine to all residents. For preventive care and screening, the CMS includes influenza vaccination screening of patients aged 6 months or older as a quality measure in its Merit-Based Incentive Payment System. It also requires acute care hospitals, ambulatory surgical centers, outpatient dialysis facilities, inpatient rehabilitation facilities, inpatient psychiatric facilities, and long-term acute care facilities to report data on influenza vaccination among health care personnel to the CDC (66).

The Joint Commission requires accredited organizations to establish an annual influenza vaccination program for all employees, including licensed independent practitioners and nonclinical staff, and to measure the screening of patients admitted to acute care hospitals during the influenza season (October through March) for vaccination before discharge, if indicated (67,68).

What do professional organizations recommend with regard to prevention and treatment?

The recommendations of most professional medical organizations are consistent with CDC recommendations. The CDC publishes the annual recommendations of the Advisory Committee on Immunization Practices for use of approved influenza vaccines in the United States and also provides updated antiviral recommendations for influenza on its Web site. The Infectious Diseases Society of America publishes recommendations for influenza testing and antiviral treatment. The recommendations listed in this article reflect those guidelines.

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Appendix

In the Clinic Tool Kit

Influenza

Clinical Guidelines—www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_By_Organism-28143/Viruses/Influenza

Guidelines from the Infectious Diseases Society of America.

www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Vaccination_of_the_Immunocompromised_Host

Guidelines from the Infectious Diseases Society of America for immunization in immunosuppressed patients.

www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf

Guidelines from the World Health Organization for pandemic influenza.

Patient Information—www.cdc.gov/flu/freeresources/print.htm

Information for patients and health care workers from the Centers for Disease Control and Prevention (CDC) (available in English and Spanish).

www.immunize.org/catg.d/p4208.pdf

Information for parents and patients.

www.acog.org/Patients/FAQs/The-Flu-Vaccine-and-Pregnancy

Information for pregnant women on influenza and influenza vaccination.

Information for Health Professionals From the CDC—www.cdc.gov/flu/index.htm

www.cdc.gov/flu/weekly/fluactivitysurv.htm

Surveillance.

www.cdc.gov/flu/professionals/acip/index.htm

Vaccine recommendations.

www.cdc.gov/flu/professionals/diagnosis/index.htm

Testing information, including information on interpretation of test results.

www.cdc.gov/flu/professionals/antivirals/index.htm

Antiviral information and current recommendations.

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Summary on antivirals.

www.cdc.gov/flu/avianflu/index.htm

Novel influenza A virus infections.

WHAT YOU SHOULD KNOW ABOUT INFLUENZA

What Is Influenza?

Influenza is a virus that makes you feel sick and can cause serious health problems. It's often called "the flu." The flu is spread when an infected person coughs or sneezes close to you. It is usually spread during the winter or cooler months but can be spread all year long.

What Are the Signs and Symptoms?

- High fever
- Feeling tired and weak
- Feeling sore and achy
- Sore throat
- Cough
- Headache

How Is It Diagnosed?

Your doctor will ask you questions about your symptoms. This is generally all the information your doctor needs to diagnose the flu; however, in some cases, you may need a physical examination or tests.

Can It Cause Health Complications?

Usually the flu is not serious, and you will start to feel better after 3 to 5 days and fully recover within 1 to 2 weeks. However, in some persons it can cause serious health complications resulting in a hospital stay or even death. You are at higher risk for flu complications if you are:

- Aged 65 years and older
- Pregnant
- Living in a nursing home
- American Indian or Alaska Native
- Obese

You are also at higher risk if you have certain health problems. These include:

- Lung disease
- Heart disease
- Weakened immune system

How Is It Treated?

Your doctor may prescribe antiviral treatment for the flu. All of the following are ways to feel better:

- Rest.
- Stay hydrated by drinking lots of clear fluids.
- Use over-the-counter medicines, like acetaminophen or ibuprofen, to help bring your fever down. These medicines can also help aches.
- Avoid taking aspirin.

If you are at risk for complications, your doctor may prescribe medicines called antivirals that help your body fight the flu virus. They may work best if they are started within 2 days of getting flu symptoms, but may still be helpful if they are started after that time.

Should I Get a Flu Shot?

Everyone 6 months and older should get a flu shot, preferably by the end of October each year. There are different types of vaccines available. Ask your health care provider which is best for you. If you have severe allergies to eggs, you may get a flu shot but you should be watched by a health care provider afterwards to make sure you do not develop a bad reaction. You should not get the flu shot if you ever had a serious allergic reaction to it in the past.

How Can I Prevent Spreading the Flu?

- If you think you have the flu, stay home from work or school.
- Use a facemask or tissue to cover your mouth and nose when coughing.
- Wash your hands often.
- Stay away from others until your fever is gone and your cough is better.

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

Centers for Disease Control and Prevention

https://www.cdc.gov/flu/index.htm

World Health Organization

www.who.int/mediacentre/factsheets/fs211/en/

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Groups at Greatest Risk for Influenza-Related Complications and Hospitalization

Children aged <5 y, especially <2 y

Adults aged ≥65 y

Residents of nursing homes and long-term care facilities

Pregnant women

Persons aged <19 y receiving long-term aspirin therapy

American Indians and Alaska Natives

Persons of any age with the following chronic medical conditions:

- Pulmonary disease (including asthma, chronic obstructive pulmonary disease, cystic fibrosis)
- Cardiac disease (excluding isolated hypertension)
- Neurologic and neurodevelopmental conditions
- Hematologic disorders
- Endocrine disorders
- Renal disorders
- Hepatic disease
- Metabolic disease
- Immunosuppression (due to disease or medication)
- Extreme obesity (body mass index ≥40 kg/m^2)

CLINICAL BOTTOM LINE

Prevention...

Annual influenza vaccination is recommended for all persons aged 6 months and older in the United States, including health care personnel. Vaccination is moderately effective in preventing influenza.Recent studies have suggested that it may also help to reduce the risk for some complications associated with influenza, including hospitalization and death. Antiviral chemoprophylaxis can be an adjunct to influenza vaccination under some circumstances.

CLINICAL BOTTOM LINE

Diagnosis...

Clinical diagnosis of uncomplicated influenza based on abrupt onset of fever, cough, and myalgia is usually reliable when influenza activity is present in the community. Complications of influenza should be considered in high-risk persons, including those with certain chronic comorbidities, young children, pregnant women, elderly persons, extremely obese persons, residents of long-term care facilities, and American Indians and Alaska Natives. In outpatients, influenza testing can be considered if the results will change clinical management decisions. Molecular assays with high sensitivity and specificity can help guide management decisions in individual patients, including those with severe disease. Clinical decisions and management, especially related to initiation of antiviral treatment and implementation of infection prevention and control measures, should not be delayed pending test results. Proper interpretation of test results, especially negative results, is important to successful clinical management.

CLINICAL BOTTOM LINE

Treatment...

The mainstay of influenza treatment is early initiation of antiviral agents in outpatients with suspected or confirmed influenza who are at high risk for complications or have progressive disease and in hospitalized patients with suspected or confirmed influenza. Supportive care of complications should be provided, with prompt implementation of recommended infection prevention and control measures.

Table 1.

Approved Influenza Vaccines for U.S. Adults, 2017–2018 Season [*]

Description	Approved Ages	Dose/Route	Recommendation/Notes[†]
Inactivated, standard dose, egg-grown, trivalent (IIV3s)[‡]	≥18 y	0.5 mL/intramuscular	Contains 15 mcg of each HA antigen per 0.5-mL dose (45 mcg total); one manufacturer's syringe tip cap on prefilled syringes might contain natural rubber latex (potential issue for persons with latex allergy)
Inactivated, standard dose, egg-grown, quadrivalent (IIV4s)[‡]	≥18 y	0.5 mL/intramuscular	Contains 15 mcg of each HA antigen per 0.5-mL dose (60 mcg total)
Inactivated, standard dose, cell culture-grown, quadrivalent (ccIIV4)[‡]	≥18 y	0.5 mL/intramuscular	Contains 15 mcg of each HA antigen per 0.5-mL dose (60 mcg total)
Inactivated, standard dose, egg-grown, quadrivalent, intradermal (IIV4s)[‡]	18–64 y	0.1 mL/intradermal	Contains 9 mcg of each HA antigen per 0.1-mL dose (36 mcg total); preferred injection site is over the deltoid muscle using the prefilled microinjection device
Inactivated, high dose, egg-grown, trivalent (IIV3)[‡]	≥65 y	0.5 mL/intramuscular	Contains 60 mcg of each HA antigen per 0.5-mL dose (180 mcg total)
Adjuvanted inactivated, standard dose, cell culture-grown, trivalent (aIIV3)[‡]	≥65 y	0.5 mL/intramuscular	Contains 15 mcg of each HA antigen per 0.5-mL dose (45 mcg total) with an oil-in-water emulsion adjuvant; manufacturer's syringe tip cap on prefilled syringes might contain natural rubber latex (potential issue for persons with latex allergy)
Recombinant trivalent (RIV3)	>18 y	0.5 mL/intramuscular	Contains 45 mcg of each HA antigen per 0.5-mL dose (135 mcg total)
Recombinant quadrivalent (RIV4)	>18 y	0.5 mL/intramuscular	Contains 45 mcg of each HA antigen per 0.5-mL dose (180 mcg total)
Live attenuated, egg-grown, quadrivalent (LAIV4)	2–49 y	Intranasal	Not recommended for the 2017–2018 season

HA = hemagglutinin.

[*] Contraindicated in persons with prior severe allergic reaction (e.g., anaphylaxis) to any vaccine component. Updated information and recommendations on use of influenza vaccines are available on the Web site of the Centers for Disease Control and Prevention (CDC) (www.cdc.gov/flu/professionals/vaccination/index.htm).

[†] Caution in persons with moderate to severe acute illness (with or without fever) and in those with a history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.

[‡] Contraindicated in persons with prior severe allergic reactions (e.g., anaphylaxis) to any vaccine component or after previous influenza vaccination. The Advisory Committee on Immunization Practices and the CDC state that any licensed, recommended, and appropriate inactivated influenza vaccine or recombinant influenza vaccine can be administered to persons with egg allergy of any severity.

Table 2.

Influenza Diagnostic Tests*

Name	Method	Time to Results	Performance	Notes
Rapid diagnostic test	Antigen detection	10 min	Low to moderate sensitivity; high specificity	Negative results may not rule out influenza; most assays are approved for point-of-care use
Rapid molecular assay	Viral RNA detection	15–20 min	Moderate to high sensitivity; high specificity	Negative results may not rule out influenza; some assays are approved for point-of-care use
Immunofluorescence assay	Antigen detection	2–4 h	Moderate sensitivity; high specificity	Negative results may not rule out influenza; requires trained laboratory personnel with fluorescent microscope in a moderately sophisticated clinical laboratory
Molecular assay	Viral RNA detection	60–80 min for some assays; up to 4–6 h for others	High sensitivity; high specificity	Negative results may not always rule out influenza, especially in critically ill patients
Tissue cell viral culture	Virus isolation	3–10 d	High sensitivity; high specificity	Negative results may not always rule out influenza; molecular assays have higher sensitivity

* Respiratory tract specimens should be collected as close to illness onset as possible for testing. Serologic testing is not recommended. Updated information and guidance on the use of influenza diagnostic tests and interpretation of results are available on the Web site ofthe Centers for Disease Control and Prevention (www.cdc.gov/flu/professionals/diagnosis/index.htm).

Table 3.

Recommended Antiviral Drugs for Treatment and Chemoprophylaxis of Influenza in Adults*

Agent	Mechanism of Action	Dosage	Benefits	Adverse Effects and Notes
Zanamivir	Inhibits influenza virus neuraminidase to block release of virus particles from infected respiratory tract cells	*Treatment:* 2 inhalations (10 mg) twice daily for 5 d *Chemoprophylaxis:* 2 inhalations (10 mg) once daily; duration based on ongoing exposure	Early treatment shortens duration of symptoms by 1 d; chemoprophylaxis is approximately 70%−90% effective in preventing illness from influenza; activity against influenza A and B viruses; activity against some influenza A viruses resistant to other neuraminidase inhibitors	Postmarketing reports suggest rare bronchospasm; other adverse effects include oropharyngeal or facial edema, diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, and dizziness as well as ear, nose, and throat infections; contraindicated in persons with underlying airway disease; pregnancy category C; approved for early treatment of uncomplicated disease in outpatients; not recommended for hospitalized patients due to lack of data
Oseltamivir	Inhibits influenza virus neuraminidase to block release of virus particles from infected respiratory tract cells	*Treatment:* 75 mg orally twice daily for 5 d; longer duration may be indicated in severely ill patients *Chemoprophylaxis:* 75 mg orally once daily; duration based on ongoing exposure	Early treatment shortens duration of symptoms by 1 d *Chemoprophylaxis:* approximately 70% −90% effective in preventing illness from influenza; activity against influenza A and B viruses	Nausea and vomiting may occur infrequently; postmarketing reports of serious skin reactions and sporadic, transient neuropsychiatric events (self-injury or delirium, mainly among Japanese adolescents and adults); dosage reduction for creatinine clearance ≤60 mL/min; pregnancy category C; approved for early treatment of uncomplicated disease in outpatients; recommended by the Centers for Disease Control and Prevention for treatment of hospitalized patients with influenza; resistance may emerge, especially in severely immunosuppressed persons; reduced effectiveness reported for some influenza B virus infections
Peramivir	Inhibits influenza virus neuraminidase to block release of virus particles from infected respiratory tract cells	*Treatment:* One 600-mg dose, via intravenous infusion for 15–30 min	Single dose equivalent to 5 d of oseltamivir; activity against influenza A and B viruses; not for chemoprophylaxis	Diarrhea; postmarketing reports of serious skin reactions and sporadic, transient neuropsychiatric events (self-injury or delirium, mainly among Japanese adolescents and adults); approved for early treatment of uncomplicated disease in outpatients; insufficient data on efficacy for hospitalized patients

* Updated information and guidance on use of antiviral medications for treatment and chemoprophylaxis of influenza are available on the Web site of the Centers for Disease Control and Prevention (www.cdc.gov/flu/professionals/antivirals/index.htm).