Seasonal Influenza in Adults and Children—Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America

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Guidelines for the treatment of persons with influenza virus infection were prepared by an Expert Panel of the Infectious Diseases Society of America. The evidence-based guidelines encompass diagnostic issues, treatment and chemoprophylaxis with antiviral medications, and issues related to institutional outbreak management for seasonal (interpandemic) influenza. They are intended for use by physicians in all medical specialties with direct patient care, because influenza virus infection is common in communities during influenza season and may be encountered by practitioners caring for a wide variety of patients.

EXECUTIVE SUMMARY

Background

Influenza virus infection causes significant morbidity and mortality in the United States each year [1, 2]. The majority of persons infected with influenza virus exhibit self-limited, uncomplicated, acute febrile respiratory symptoms or are asymptomatic. However, severe disease and complications due to infection, including hospitalization and death, may occur in elderly persons, in very young persons, in persons with underlying medical conditions (including pulmonary and cardiac disease, diabetes, and immunosuppression), and in previously healthy persons. Early treatment with antiviral medications may reduce the severity and duration of symptoms, hospitalizations, and complications (otitis media, bronchitis, pneumonia), and may reduce the use of outpatient services and antibiotics, extent and quantity of viral shedding, and possibly mortality in certain populations. Vaccination is the best method for preventing influenza, but antivirals may also be used as primary or secondary means of preventing influenza transmission in certain settings.

The Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices and the American Academy of Pediatrics provide

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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recommendations on the appropriate use of trivalent inactivated and live, attenuated influenza vaccines, as well as information on diagnostics and antiviral use for treatment and chemoprophylaxis [3–5]. The CDC's influenza Web site (http://www.cdc.gov/flu) also summarizes up-to-date information on current recommendations for influenza diagnostic testing and antiviral use. The Infectious Diseases Society of America's (IDSA's) influenza guideline provides an evidence-based set of recommendations and background on influenza with contributions from many sources, including the CDC, the American Academy of Pediatrics, the American College of Physicians, the American Academy of Family Physicians, the Pediatric Infectious Diseases Society, the Society for Healthcare Epidemiology of America, practicing clinicians, and the IDSA, to guide decision-making on these issues. The current guideline development process included a systematic weighting of the quality of the evidence and the grade of recommendation (table 1) [6]. These guidelines apply to seasonal (interpandemic) influenza and not to avian or pandemic disease. Clinical management guidelines for sporadic human infections due to avian A (H5N1) viruses have been published by the World Health Organization [7, 8].

DIAGNOSTIC ISSUES

Who Should Be Considered to Have Influenza?

1. During influenza season (defined as periods when influenza viruses are circulating in the community), the diagnosis of influenza should be considered in the following patients, regardless of vaccination status:

a. Immunocompetent and immunocompromised persons (both adults and children), including health care personnel, with fever and the acute onset of respiratory signs and symptoms (A-II).

b. Persons with fever and acute exacerbation of underlying chronic lung disease (A-II).

c. Infants and young children with fever and no other signs or symptoms (A-II).

d. Elderly persons with new or worsening respiratory symptoms, including exacerbation of congestive heart failure or altered mental status, with or without fever (A-II).

e. Severely ill persons with fever or hypothermia (A-II).

f. Hospitalized children admitted without fever and acute respiratory symptoms who subsequently develop fever or febrile respiratory illness after hospital admission (A-II).

g. Hospitalized adults admitted without fever and acute respiratory symptoms who subsequently develop febrile respiratory illness after hospital admission (A-II).

2. During any time of the year, influenza should be considered in immunocompetent and immunocompromised persons with acute febrile respiratory symptoms who are epidemiologically linked to an influenza outbreak (e.g., health care personnel at, residents of, or visitors to an institution experiencing an influenza outbreak; 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) (A-II).

Who Should Be Tested for Suspected Influenza?

3. If the result will influence clinical management (decisions on initiation of antiviral treatment, impact on other diagnostic testing, antibiotic treatment decisions, and infection control practices), with consideration for the sensitivity and specificity of the test used and information about local influenza virus circulation, the following persons should be considered for influenza testing (table 2):

Table 1. Infectious Diseases Society of America–US Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from Canadian Task Force on the Periodic Health Examination [6].

Table 2. Persons who should be tested for influenza.

During influenza season, testing should occur in the following persons if the result will influence clinical management
Outpatient immunocompetent persons of any age at high risk of developing complications of influenza (e.g., hospitalization or death) presenting with acute febrile respiratory symptoms, within 5 days 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
At any time of the year, testing should occur 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 (e.g., 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

During Influenza Season

a. Outpatient immunocompetent persons of any age at high risk for complications of influenza (e.g., hospitalization or death) (table 3) presenting with acute febrile respiratory symptoms, within 5 days of illness onset, when virus is usually being shed (A-II).

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

c. 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 from illness onset (A-II).

d. Elderly persons and infants presenting with suspected sepsis or fever of unknown origin, irrespective of time from illness onset (A-III).

e. Children with fever and respiratory symptoms presenting for medical evaluation, irrespective of time from illness onset (A-II).

f. Persons of any age who develop fever and respiratory symptoms after hospital admission, irrespective of time from illness onset (A-II).

g. 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 (A-III).

During Any Time of the Year

h. 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 (A-II).

i. Persons who are epidemiologically linked to an influenza outbreak (e.g., 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 (A-II).

What Specimens Should Be Collected for Influenza Tests from Persons with Suspected Influenza?

4. In immunocompetent persons, respiratory tract specimens should be obtained as close to illness onset as possible, preferably within 5 days after illness onset. Collection of specimens >5 days after illness onset may result in false-negative results because of substantially decreased viral shedding, especially in older children and adults. Infants and young children commonly shed influenza viruses for $\geq$1 week. In infants and young children, optimal specimens are nasal aspirates and swabs. In older children and adults, nasopharyngeal aspirates and swabs are preferred specimens. Oropharyngeal specimens (e.g., throat swabs) and sputum specimens may have a lower yield for detection of human influenza viruses but may still produce positive results (A-II).

5. Immunocompromised persons of any age with influenza virus infection may shed influenza viruses for weeks to months, even without fever or respiratory symptoms. Therefore, collection of upper and lower respiratory tract specimens (e.g., with bronchoalveolar lavage) within 5 days after illness onset may still be useful for influenza testing in these persons (A-II).

6. Upper and lower respiratory tract samples should be obtained from patients undergoing mechanical ventilation within 5 days after illness onset, although test results may be positive

Table 3. Persons at high risk of complications from influenza who should be considered for antiviral therapy.

Unvaccinated infants aged 12–24 months
Persons with asthma or other chronic pulmonary diseases, such as cystic fibrosis in children or chronic obstructive pulmonary disease in adults
Persons with hemodynamically significant cardiac disease
Persons who have immunosuppressive disorders or who are receiving immunosuppressive therapy
HIV-infected persons
Persons with sickle cell anemia and other hemoglobinopathies
Persons with diseases that requiring long-term aspirin therapy, such as rheumatoid arthritis or Kawasaki disease
Persons with chronic renal dysfunction
Persons with cancer
Persons with chronic metabolic disease, such as diabetes mellitus
Persons with neuromuscular disorders, seizure disorders, or cognitive dysfunction that may compromise the handling of respiratory secretions
Adults aged >65 years
Residents of any age of nursing homes or other long-term care institutions

NOTE. Although sufficient data do not exist to precisely define the extent of increased risk of influenza in these different groups of patients, there are data to suggest that the highest risk of both mortality and serious morbidity (e.g., hospitalization) occurs for severely immunocompromised patients (e.g., hematopoietic stem cell transplant patients) and very elderly (age, >85 years) residents of nursing homes; infants aged <24 months also have high hospitalization rates but lower case-fatality rates than do the other 2 groups. Data are from [3, 5].

even after this period. Lower respiratory tract samples include endotracheal aspirates and washes and bronchoalveolar lavage fluid (A-II).

7. Respiratory specimens should be tested for influenza as soon as possible after collection and should be refrigerated (but not frozen) pending testing (A-II).

8. Clinicians should consult test instructions for the recommended clinical specimens for each specific influenza test (A-II).

9. Acute-phase serum specimens should not be obtained for diagnostic purposes. Paired acute- and convalescent-phase serum specimens are needed for determination of antibody titers (by hemagglutinin inhibition, ELISA, or complement fixation, available only through reference laboratories), but results cannot be attained in a timely fashion and will not influence clinical management (A-II).

What Influenza Tests Should Be Used for Persons with Suspected Influenza?

10. Tests that yield results in a timely manner that can influence clinical management (decisions on initiation of antiviral treatment, impact on other diagnostic testing, antibiotic treatment decisions, and infection control practices) are recommended to guide patient care. Results of testing should take into account the a priori likelihood of influenza infection based on the patient's signs and symptoms, the sensitivity and specificity of the test used, and information on circulation of influenza in the community. An in-depth description of influenza testing methods is also available at the CDC's Seasonal Flu Web site (http://www.cdc.gov/flu/professionals/diagnosis/labprocedures.htm).

In order of priority, the following influenza tests are recommended, if available:

a. ***RT-PCR.*** This is currently the most sensitive and specific of testing modalities for influenza, with results available within 4–6 h after specimen submission. RT-PCR shows greater sensitivity than viral culture, may be used as a confirmatory test, and is useful for quickly differentiating between influenza types and subtypes. RT-PCR is also the preferred test for specimens obtained from persons with a history of exposure to animals with possible influenza illness (e.g., influenza A [H5N1] in poultry in Eurasia or Africa or swine influenza in any part of the world, including North America) (A-II).

b. ***Immunofluorescence.*** Direct fluorescent antibody or indirect fluorescent antibody staining for influenza antigen detection are used as screening tests. Immunofluorescence exhibits slightly lower sensitivity and specificity than viral isolation in cell culture, but results are available within hours after specimen submission. Performance of these assays depends heavily on laboratory expertise and the quality of the specimen collected (i.e., specimens must include respiratory epithelium cells) (A-II).

c. ***Commercial rapid influenza diagnostic tests.*** The currently available antigen detection tests provide results in 10–30 min but exhibit decreased sensitivity (70%–90% in children and <40% to 60% in adults), compared with RT-PCR and with viral culture (table 4). Performance of these assays depends heavily on patient age, duration of illness, sample type, and perhaps viral type. Given the lower sensitivity of immunofluorescence and commercial rapid tests, follow-up testing with

Table 4. Influenza testing methods.

Test	Time to results	Comments
RT-PCR (conventional gel-based PCR, real-time RT-PCR, and multiplex PCR)	2 h	High sensitivity and very high specificity; highly recommended
Immunofluorescence[a]		Moderately high sensitivity and high specificity; recommended
Direct fluorescent antibody staining	2–4 h	Detects and distinguishes between influenza A and B and between A/B and other respiratory viruses
Indirect fluorescent antibody staining	2–4 h	Detects and distinguishes between influenza A and B and between A/B and other respiratory viruses
Rapid influenza diagnostic tests[b]		Low-to-moderate sensitivity and high specificity; recommended; limitations of the test should be recognized when interpreting results
Antigen detection (EIA)	10–20 min	Depending on which EIA test is used, will either detect influenza A only, will detect and distinguish between influenza A and B, or will detect but not distinguish between influenza A and B
Neuraminidase detection assay	20–30 min	Detects but does not distinguish between influenza A and B
Viral culture		Moderately high sensitivity and highest specificity; this test is important for confirming screening test results and for public health surveillance, but it is not useful for timely clinical management
Shell vial culture	48–72 h	…
Isolation in cell culture	3–10 days	…
Serologic tests (hemagglutinin inhibition, ELISA, complement-fixation, and neutralization)[c]		Only available in reference laboratories; not useful for timely clinical management; recommended only for retrospective diagnosis, surveillance, or research purposes

[a] Requires fluorescent microscope.
[b] Includes moderately complex and Clinical Laboratory Improvement Amendments (CLIA)–waived tests.
[c] Requires paired acute- and convalescent-phase serum samples.

RT-PCR and/or viral culture should be considered to confirm negative test results (A-II).

11. Viral isolation (in standard cell culture and shell vial culture) is not a screening test, but during periods of low influenza activity (late spring, summer, and early fall), it should be performed on respiratory specimens collected from persons with suspected influenza that present for medical care within 5 days after illness onset, especially if such persons are known to be epidemiologically linked to an influenza outbreak. During influenza season, viral culture should be performed with respiratory specimens obtained from a subset of persons for routine virologic surveillance purposes and to confirm some negative test results from rapid antigen and immunofluorescence testing, particularly in the setting of institutional outbreaks (A-II).

12. Serologic testing is usually not recommended to detect evidence of human influenza virus infection for management of acute illness. Influenza serologic test data for a single serum specimen cannot be reliably interpreted. Paired acute- and convalescent-phase serum samples are needed for determination of antibody titers (by hemagglutinin inhibition, ELISA, or complement fixation, available only through reference laboratories), but results cannot be attained in a timely fashion and will not influence clinical management. Paired serum specimens are useful only for retrospective diagnosis and for research purposes (A-II).

How Are Influenza Test Results Interpreted?

13. To properly interpret test results, clinicians should consider and understand the limitations of influenza tests, especially for screening tests such as immunofluorescence and commercially available rapid influenza tests, as well as the level of influenza activity among the population being tested (table 5). Clinicians should also consider that a positive influenza test result does not exclude bacterial coinfection and evaluation for the potential need for antibiotics (A-II).

a. A positive screening test result is most likely to be truly positive during periods of peak influenza activity in the population tested.

b. A positive screening test result is most likely to be falsely positive during periods of low influenza activity in the population tested, including early and late in the influenza season. A confirmatory test such as PCR or viral culture should be considered.

c. A negative screening test result is most likely to be truly negative during periods of low influenza activity in the population tested.

d. A negative screening test result is most likely to be falsely negative during periods of peak influenza activity in the population tested. A confirmatory test, such as PCR or viral culture, should be considered.

ANTIVIRALS FOR TREATMENT

Who Should Be Treated with Antivirals?

14. Treatment is recommended for both adults and children with influenza virus infection who meet the following criteria:

a. Persons with laboratory-confirmed or highly suspected influenza virus infection at high risk of developing complications (table 3), within 48 h after symptom onset. Benefits have been best evaluated mostly among otherwise healthy adults with uncomplicated influenza whose treatment was initiated within 48 h after symptom onset, although smaller numbers of persons with conditions that increase the risk of influenza complications have also been included in trials. Fewer data are available by which to make recommendations regarding treatment of persons >48 h after symptom onset. Treatment is recommended regardless of influenza vaccination status and regardless of severity of illness (A-II).

b. Persons requiring hospitalization for laboratory-confirmed or highly suspected influenza illness, regardless of underlying illness or influenza vaccination status, if treatment can be initiated within 48 h after onset of symptoms (A-II). However, persons who require hospitalization for laboratory-confirmed influenza whose positive laboratory test result for influenza is from a specimen obtained >48 h after the onset of illness may also benefit from treatment (B-II).

15. Treatment should be considered for both adults and children with influenza virus infection who meet the following criteria:

a. Outpatients at high risk of complications (table 3) with illness that is not improving and who have a positive influenza test result from a specimen obtained >48 h after onset of symptoms (C-III).

b. Outpatients with laboratory-confirmed or highly suspected influenza virus infection who are not at increased risk of complications, whose onset of symptoms is <48 h before presentation, and who wish to shorten the duration of illness and further reduce their relatively low risk of complications (A-I) or who are in close contact with persons at high risk of complications secondary to influenza infection (table 3). Those whose onset of symptoms occurred >48 h before presentation with persisting moderate to severe illness may also benefit from treatment, but safety and efficacy in this population have not been evaluated prospectively (B-III).

What Antiviral Drug Should Be Used for Treatment?

16. Influenza viruses and their susceptibilities to available antiviral medications evolve rapidly. Clinicians should maintain familiarity with local patterns of influenza circulation in their communities throughout influenza season. Current and frequently updated information on antiviral resistance and recommendations on antiviral use may be found at the CDC's influenza Web site (http://www.cdc.gov/flu). On the basis of antiviral susceptibility patterns current as of March 2009, infection with an influenza A (H1N1) virus should be treated with either zanamivir or an adamantine (preferably rimantadine, because of its more favorable adverse effect profile); oseltamivir should not be used to treat infection with influenza A (H1N1). Infection with an influenza A (H3N2) virus should be treated with oseltamivir or zanamivir; the adamantanes should not be used to treat influenza A (H3N2). If subtype information is unavailable, influenza A should be treated either with zanamivir or with a combination of oseltamivir and rimantadine. Infection with an influenza B virus should be treated only with oseltamivir or zanamivir. Table 6 provides detailed information on antiviral regimens in appropriate age groups (A-II).

ANTIVIRALS FOR CHEMOPROPHYLAXIS

Who Should Be Considered for Antiviral Chemoprophylaxis to Prevent Influenza?

17. Influenza vaccination is the primary tool to prevent influenza, and antiviral chemoprophylaxis is not a substitute for influenza vaccination. When influenza viruses are circulating in the community, chemoprophylaxis can be considered for high-risk persons during the 2 weeks after vaccination before an adequate immune response to inactivated vaccine develops (6 weeks for children who were not previously vaccinated and who require 2 doses of vaccine) (A-I).

18. Antiviral chemoprophylaxis should be considered for adults and children aged ⩾1 year who are at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are significantly immunocompromised) (B-II). Contraindications to vaccination include anaphylactic hypersensitivity to eggs or other vaccine components; moderate-to-severe febrile illness; and, as a precaution, a history of Guillain-Barré syndrome within 6 weeks after receipt of a prior influenza vaccination [5].

19. Antiviral chemoprophylaxis (in conjunction with prompt administration of the inactivated vaccine) should be considered for adults and children aged ⩾1 year who are at high risk of developing complications from influenza virus infection (table 3) and have not yet received influenza vaccine when influenza activity has already been detected in the community. Whenever possible, influenza vaccine should be administered, and vaccination should continue for recommended

Table 5. Interpretation of rapid influenza antigen test results for specimens obtained from patients with influenza-like illness.

Influenza activity	Positive predictive value[a,b]	Negative predictive value[b,c]
Very low (summer)	Very low	Very high
Low (early or late season)	Low to moderate	High
High (community outbreaks)	High	Low to moderate
Peak activity	Very high	Low

[a] Proportion of persons with positive test results who have influenza.
[b] Influenced by screening test sensitivity, specificity, and prevalence of influenza (community influenza activity) in the population being tested; assumes median sensitivity of 70%–75% and median specificity of 90%–95%, compared with viral culture or RT-PCR. Sensitivity for children (70%–90%) is much higher than that for adults (<40% to 60%).
[c] Proportion of persons with negative test results who do not have influenza.

persons until influenza is no longer in community circulation (B-II).

20. Antiviral chemoprophylaxis may be considered for unvaccinated adults, including health care workers, and for children aged ⩾1 year who are in close contact with persons at high risk of developing influenza complications during periods of influenza activity. Whenever possible, influenza vaccine should be administered; 2 weeks after administration, chemoprophylaxis may be discontinued (6 weeks for children who were not previously vaccinated and who require 2 doses of vaccine) (B-III).

21. Antiviral chemoprophylaxis is recommended for all residents (vaccinated and unvaccinated) in institutions, such as nursing homes and long-term care facilities, that are experiencing influenza outbreaks (A-I).

22. The strongest consideration for use of antiviral chemoprophylaxis should be given to persons at the highest risk of influenza-associated complications. The risk of influenza-associated complications is not identical among all high-risk persons, and antiviral chemoprophylaxis is likely to have the greatest benefit among those at highest risk of influenza complications and death, such as recipients of hematopoietic stem cell transplants (B-III).

23. Antiviral chemoprophylaxis should be considered for persons at high-risk of developing complications from influenza if influenza vaccine is not available due to shortage. If vaccine is available, it should be administered to these persons (A-I).

24. Antiviral chemoprophylaxis can be considered for high-risk persons (table 3) in situations in which there is documented low influenza vaccine clinical effectiveness because of the circulation of influenza virus strains that are antigenically distant from the vaccine strains, such that a substantial increase in vaccine failures is anticipated, as determined by federal, state, and local public health authorities (C-II).

When Should Antiviral Chemoprophylactic Regimens Be Started?

25. In persons at high risk of complications who are not adequately protected as a result of poor immune responses (e.g., in persons who are significantly immunocompromised), lack of influenza vaccination, or ineffective vaccine (e.g., when antigenically distant strains are circulating), antiviral chemoprophylaxis should be initiated at the onset of sustained community influenza activity, as determined by local public health authorities (B-II).

26. Antiviral chemoprophylaxis use for appropriate persons within households should be initiated when 1 family member develops suspected or confirmed influenza and any other family member is at high risk of complications secondary to infection, including infants aged <6 months (table 3). In this setting, all noninfected family members should receive antiviral chemoprophylaxis. Ideally, all eligible family members in such settings should be vaccinated, making chemoprophylaxis unnecessary (A-I).

27. Antiviral chemoprophylaxis and other control measures should be initiated in institutions, such as hospitals and long-term care facilities (e.g., nursing homes), when an influenza outbreak is detected or when influenza is strongly suspected but the etiology of the outbreak has yet to be determined (A-II).

How Long Should Chemoprophylaxis Continue?

28. If inactivated influenza vaccine is administered, antiviral chemoprophylaxis can generally be stopped 2 weeks after vaccination for persons in noninstitutional settings. Children aged <9 years who receive inactivated influenza vaccine for the first time require 2 doses of vaccine, with the second dose administered at least 4 weeks after the first dose; the immune response peaks 2 weeks after receipt of the second dose. Thus, a minimum of 6 weeks of chemoprophylaxis (i.e., chemoprophylaxis for at least 4 weeks after the first dose of vaccine and an additional 2 weeks of chemoprophylaxis after the second dose) would be needed, depending on the length of the delay between administration of the 2 vaccine doses (B-II).

29. When antiviral chemoprophylaxis is used in a household after the diagnosis of influenza in 1 family member, chemoprophylaxis should be continued for 10 days (A-I).

30. In persons at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are significantly immunocompromised), chemoprophylaxis should continue for the duration that influenza viruses

are circulating in the community during influenza season (B-III).

What Antiviral Drugs Should Be Used for Chemoprophylaxis?

31. Influenza viruses and their susceptibilities to available antiviral medications evolve rapidly. Clinicians should maintain familiarity with local patterns of influenza circulation in their communities throughout the influenza season. Current and frequently updated information on antiviral resistance and recommendations on antiviral use may be found at the CDC's influenza Web site (http://www.cdc.gov/flu). On the basis of antiviral susceptibility patterns current as of March 2009, either zanamivir or an adamantane (preferably rimantadine because of its more favorable adverse effect profile) should be used for influenza A (H1N1) chemoprophylaxis; oseltamivir should not be used for influenza A (H1N1) chemoprophylaxis. Either oseltamivir or zanamivir should be used for influenza A (H3N2) chemoprophylaxis; the adamantanes should not be used for influenza A (H3N2) chemoprophylaxis. If subtype information is unavailable, either zanamivir or a combination of oseltamivir and rimantadine should be used for influenza A chemoprophylaxis. Only oseltamivir or zanamivir should be used for influenza B chemoprophylaxis. Table 6 provides detailed information on antiviral regimens in appropriate age groups (A-I).

OUTBREAK MANAGEMENT IN INSTITUTIONAL SETTINGS

When Should an Influenza Outbreak Be Suspected in an Institution?

32. During influenza season, when ⩾2 institutional residents manifest signs and symptoms of influenza-like illness within 72 h of each other, testing for influenza should occur. When influenza viruses are circulating in the community, even 1 positive laboratory result in conjunction with other compatible illnesses on the unit indicates that an outbreak of influenza is occurring (A-II).

What Is the Role for Testing Institutional Residents with Influenza-Like Illness after a Diagnosis of Influenza Has Already Been Established in ⩾1 Resident?

33. After a single laboratory-confirmed case of influenza among residents has been identified in an institution, it is likely that subsequent cases of temporally associated influenza-like illness are also caused by influenza virus infection, although mixed outbreaks due to other respiratory pathogens may occur. Although it may not be possible to obtain specimens from all ill residents for influenza testing in the context of an outbreak, persons developing compatible symptoms >72 h after implementation of antiviral chemoprophylaxis or persons developing compatible symptoms who reside on previously unaffected units should be tested for influenza and other respiratory pathogens. If influenza test results are positive despite antiviral treatment, consider the possibility of a drug-resistant virus; the spread of influenza to previously unaffected areas of the facility where antiviral use has not been implemented; or multiple introductions of influenza from the community to facility residents (B-III).

Which Residents Should Be Treated with Antiviral Medications during an Outbreak?

34. All residents with laboratory-confirmed influenza virus infection should be treated with an appropriate influenza antiviral medication. After 1 case of laboratory-confirmed influenza is detected in a facility resident, all persons in the facility subsequently developing influenza-like illness or other signs or symptoms consistent with influenza (e.g., isolated altered mental status in an elderly resident) should be considered for treatment with an influenza antiviral medication (A-III).

Which Residents Should Receive Antiviral Chemoprophylaxis during an Outbreak?

35. During documented outbreaks of influenza in long-term care facilities, all residents should receive influenza antiviral chemoprophylaxis, regardless of influenza vaccination status. Ideally, chemoprophylaxis should be implemented on all floors and wards of the facility, because breakthrough cases frequently occur when antiviral medications are administered only to those persons on the affected unit or ward and not to all residents in the facility (A-I).

Which Health Care Personnel Should Receive Antiviral Chemoprophylaxis during an Outbreak?

36. For all institutional employees who are unable to receive influenza vaccine or for whom vaccine is contraindicated or when the vaccine is expected to be ineffective (e.g., because of the circulation of influenza virus strains that are antigenically distant from the vaccine strains, such that a substantial increase in vaccine failures is anticipated), antiviral medications should be used for chemoprophylaxis (B-III). Contraindications to vaccination include anaphylactic hypersensitivity to eggs or other vaccine components, moderate-to-severe febrile illness,

and, as a precaution, a history of Guillain-Barré syndrome within 6 weeks after a previous influenza vaccination [5].

How Long Should Antiviral Chemoprophylaxis Continue in Residents and Staff during an Outbreak?

37. In the setting of an institutional outbreak, antiviral chemoprophylaxis should be continued for 14 days or for 7 days after the onset of symptoms in the last person infected, whichever is longer (A-II).

INTRODUCTION

Influenza illness is caused by infection with 1 of 3 types of circulating RNA viruses: influenza A, B, or C virus [10]. Influenza C virus infection causes respiratory illness that is generally milder than that caused by influenza A and B virus infections [11], and diagnosis, treatment, and prevention are generally not pursued. This guideline focuses on clinical issues related to infection with seasonal influenza A and B viruses.

During influenza season, influenza viruses circulate ubiquitously in the population. Each year, 5%–20% of the population is infected with influenza viruses, and an estimated annual average of 36,000 deaths and >200,000 hospitalizations attributable to influenza virus infection occur in the United States [1, 2]. In addition, the impact of patients with influenza on outpatient services is significant [12, 13]. Although most ill persons experience an acute, self-limited febrile respiratory syndrome, certain groups are at increased risk of severe disease or death secondary to influenza virus infection. These groups include elderly persons, very young persons, and persons with underlying medical conditions, such as those with cardiopulmonary disease, those with diabetes, immunocompromised persons, and pregnant women [5].

Variation in practice patterns of both influenza diagnosis and treatment exist [14–16]. Appropriate use of diagnostic tests, along with timely administration of antiviral medications, may improve clinical outcomes of influenza virus infection, may reduce unnecessary diagnostic testing, may decrease duration of required medical care, and may reduce both appropriate (for presumed bacterial complications) and inappropriate use of antibacterial agents [17–23]. The current guideline addresses use of influenza diagnostic tests, including RT-PCR, immunofluorescence tests, commercially available rapid influenza diagnostic tests, and viral tissue cell culture. The guideline also addresses use of influenza antiviral medications, both for treatment and chemoprophylaxis, and use of diagnostic testing and antiviral medications in the context of an institutional outbreak.

PRACTICE GUIDELINES

Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances [6]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [6].

METHODS

Panel composition. The IDSA Standards and Practice Guidelines Committee convened experts in the diagnosis, treatment, chemoprophylaxis, and management of institutional outbreaks of seasonal influenza and included representatives from the following collaborating organizations: the American Academy of Family Physicians, the American Academy of Pediatrics, the American College of Physicians, the CDC, the Pediatric Infectious Diseases Society, and the Society for Healthcare Epidemiology of America. The Panel members are listed at the end of the text.

Literature review and analysis. Literature searches of the Medline database were performed for relevant English-language literature from the period 1966–2008. The following search terms were used: "influenza" or "influenza AND virus," "influenza AND infection," "influenza AND treatment," "influenza AND prophylaxis," "influenza AND chemoprophylaxis," and "influenza AND outbreak." The searches focused on human studies.

Process overview. In evaluating the evidence regarding the diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza, the Panel followed a process used in the development of other IDSA guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation (table 1) [6].

Consensus development based on evidence. The Panel met on 11 occasions via teleconference and in person to complete the work of the guideline. The purpose of the meetings was to discuss the questions to be addressed, make writing assignments, and discuss recommendations. All members of the panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. All collaborating organizations were also asked to provide feedback and endorse the guidelines. The following organizations endorsed the guidelines: the American Academy of Family Physicians, the American Academy of Pediatrics, American College of Physicians, the CDC, the Pediatric Infectious Diseases Society, and the Society for Healthcare Epidemiology of America. The guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee and the IDSA Board of Directors prior to dissemination.

Table 6. Influenza antiviral medication dosing recommendations.

Agent, group	Treatment	Chemoprophylaxis
Neuraminidase inhibitors		
Oseltamivir		
Adults	75-mg capsule twice per day for 5 days	75-mg capsule once per day[a]
Children (age, ⩾12 months), weight		
⩽15 kg	60 mg per day divided into 2 doses	30 mg once per day
15–23 kg	90 mg per day divided into 2 doses	45 mg once per day
24–40 kg	120 mg per day divided into 2 doses	60 mg once per day
>40 kg	150 mg per day divided into 2 doses	75 mg once per day
Zanamivir		
Adults	Two 5-mg inhalations (10 mg total) twice per day	Two 5-mg inhalations (10 mg total) once per day
Children	Two 5-mg inhalations (10 mg total) twice per day (age, ⩾7 years)	Two 5-mg inhalations (10 mg total) once per day (age, ⩾5 years)
Adamantanes[b]		
Rimantadine[c]		
Adults	200 mg per day, either as a single daily dose or divided into 2 doses	200 mg per day, either as a single daily dose or divided into 2 doses
Children, age		
1–9 years	6.6 mg/kg per day (maximum, 150 mg per day) divided into 2 doses	5 mg/kg per day once daily, not to exceed 150 mg
⩾10 years	200 mg per day, either as a single daily dose or divided into 2 doses	200 mg per day, either as a single daily dose or divided into 2 doses
Amantadine		
Adults	200 mg per day, either as a single daily dose or divided into 2 doses	200 mg per day, either as a single daily dose or divided into 2 doses
Children, age		
1–9 years	5–8 mg/kg per day divided into 2 doses or as a single daily dose (maximum, 150 mg per day)	5–8 mg/kg per day divided into 2 doses or as a single daily dose (maximum, 150 mg per day)
9–12 years	200 mg per day divided into 2 doses	200 mg per day divided into 2 doses

[a] For treatment duration, see the sections Antivirals for Chemoprophylaxis and Outbreak Management in Institutional Settings.
[b] On the basis of influenza surveillance data current as of March 2009, the adamantanes should be used only in situations in which influenza A (H1N1) infection or exposure is suspected. The adamantanes should not be used for infection or exposure to influenza A (H3N2) or influenza B. See the sections Antivirals for Treatment and Antivirals for Chemoprophylaxis.
[c] Rimantadine has not been approved by the US Food and Drug Administration for treatment of children, but published data exist on safety and efficacy in the pediatric population [9].

Guidelines and conflicts of interest. All members of the Expert Panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts are listed in the Acknowledgments section.

Revision dates. At annual intervals, the Panel Chair, the IDSA Standards and Practice Guidelines Committee liaison advisor, and the Chair of the IDSA Standards and Practice Guidelines Committee will determine the need for revisions to the guideline on the basis of an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revision of the guideline to the IDSA Standards and Practice Guidelines Committee and the IDSA Board for review and approval.

LITERATURE SEARCH RESULTS

In previously healthy adults and adolescents, a clinical diagnosis of influenza may be reasonably accurate (sensitivity, >70%) during periods of influenza virus circulation in the community. However, sensitivity and specificity are improved by employing certain influenza diagnostic laboratory tests, especially in children and hospitalized persons, because many other respiratory pathogens may present with similar symptomatology. Obtaining results from diagnostic tests may facilitate timely institution of antiviral treatment in infected patients and provide timely

information by which to prevent transmission by initiation of chemoprophylactic antiviral medications and other control measures.

Antiviral medications from 2 drug classes possess activity against influenza viruses: the adamantanes (amantadine and rimantadine), which are active against only influenza A viruses, and the neuraminidase inhibitors (oseltamivir and zanamivir), which are active against both influenza A and B viruses. Based on virologic surveillance data acquired during recent influenza seasons, a significant proportion of influenza A (H3N2) viruses are resistant to the adamantane drugs (but susceptible to both neuraminidase inhibitors), and a significant proportion of influenza A (H1N1) viruses are resistant to oseltamivir (but susceptible to zanamivir and the adamantanes). Monitoring local patterns of influenza A circulation in conjunction with local public health authorities and with the CDC (http://www.cdc.gov/flu) is of paramount importance as ongoing global surveillance for emerging patterns of antiviral resistance continues.

Under certain circumstances, both adults and children should receive antiviral medications if they are infected with influenza viruses. All hospitalized persons with influenza virus infection should be treated with antivirals. Administration of antivirals should preferably occur within 48 h after symptom onset for all infected adults and children at high risk of developing complications secondary to infection (table 3). Consideration may be given to administration of antivirals >48 h after symptom onset in certain circumstances in hospitalized patients. Antiviral administration may be considered in outpatients with influenza infection diagnosed 48 h after symptom onset if they are at high risk of developing complications secondary to infection and if their symptoms are not improving. Administration of antivirals may also be considered within 48 h after symptom onset in infected outpatients who are not at high risk of developing complications secondary to infection but who wish to shorten the duration of illness and further reduce their relatively low risk of complications. Administration of antivirals to outpatients whose onset of symptoms occurred >48 h prior to presentation and who have persisting moderate-to-severe illness may also benefit from treatment, but safety and efficacy in this population have not been evaluated prospectively. However, clinicians should still consider the possibility of bacterial coinfections and the need for antibiotics in influenza-positive patients.

Vaccination remains the primary tool for influenza prevention. Because of the high frequencies of adamantane resistance in currently circulating influenza A (H3N2) viruses and of the high frequencies of oseltamivir resistance occurring in currently circulating influenza A (H1N1) viruses, local patterns of circulation of influenza viruses by type and subtype should be considered, if available, when prescribing influenza antiviral chemoprophylaxis. Persons who should receive influenza antiviral chemoprophylaxis include the following groups if they are unable to receive influenza vaccine: adults and children aged ⩾1 year at high risk of complications secondary to infection (table 3), close contacts of high-risk persons, employees in institutions experiencing outbreaks of influenza, and all vaccinated and unvaccinated residents of institutions experiencing influenza outbreaks. Not all persons at high risk of developing complications are at equal risk, and consideration should be given to administering chemoprophylaxis to those at highest risk (e.g., hematopoietic stem cell transplant recipients). Finally, antiviral chemoprophylaxis should be considered in certain persons during influenza seasons if influenza vaccine viruses are not well-matched to circulating viruses or if vaccine is unavailable because of a shortage.

For persons aged ⩾9 years who receive chemoprophylaxis, when inactivated influenza vaccine is administered, the duration of the regimen should be 2 weeks. Children aged <9 years who receive inactivated influenza vaccine for the first time require 2 doses of vaccine, with the second dose administered at least 4 weeks after the first dose. The immune response peaks 2 weeks after administration of the second dose. Thus, a minimum of 6 weeks of chemoprophylaxis (i.e., chemoprophylaxis for at least 4 weeks after the first dose of vaccine and an additional 2 weeks of chemoprophylaxis after the second dose) is needed, depending on the length of delay between the 2 vaccine doses. Live, attenuated influenza vaccine should not be used for persons receiving antiviral medications because of the possibility of decreased vaccine effectiveness. Influenza antiviral medications should be stopped 48 h prior to the administration of live, attenuated influenza vaccine, and antivirals should not be given for 2 weeks after administration of live, attenuated influenza vaccine, if possible. Persons who receive live, attenuated influenza vaccine demonstrate rapid protection against influenza infection [24–26]. If chemoprophylaxis is administered to household contacts of persons infected with influenza, antivirals should be continued for 10 days. During institutional influenza outbreaks, chemoprophylaxis should be administered for 14 days or for 7 days after onset of symptoms in the last person infected, whichever is longer.

Outbreaks of influenza in institutional settings contribute to significant viral transmission, morbidity, and mortality. Influenza testing should occur in any facility in which ⩾2 residents experience new respiratory symptoms within a 72-h period during influenza season. During periods when influenza viruses are in community circulation, a single laboratory-confirmed case of influenza in the context of ⩾2 persons presenting with influenza-like illness should lead to implementation of facility-wide influenza outbreak control measures.

GUIDELINE RECOMMENDATIONS FOR DIAGNOSIS, TREATMENT, CHEMOPROPHYLAXIS, AND INSTITUTIONAL OUTBREAK MANAGEMENT OF INFLUENZA

DIAGNOSTIC ISSUES

Who Should Be Considered to Have Influenza?

Recommendations

1. During influenza season (defined as periods when influenza viruses are circulating in the community), the diagnosis of influenza should be considered in the following patients, regardless of vaccination status:

a. Immunocompetent and immunocompromised persons (both adults and children), including health care personnel, with fever and the acute onset of respiratory signs and symptoms (A-II).

b. Persons with fever and acute exacerbation of underlying chronic lung disease (A-II).

c. Infants and young children with fever and no other signs or symptoms (A-II).

d. Elderly persons with new or worsening respiratory symptoms, including exacerbation of congestive heart failure or altered mental status, with or without fever (A-II).

e. Severely ill persons with fever or hypothermia (A-II).

f. Hospitalized children admitted without fever and acute respiratory symptoms who subsequently develop fever or febrile respiratory illness after hospital admission (A-II).

g. Hospitalized adults admitted without fever and acute respiratory symptoms who subsequently develop febrile respiratory illness after hospital admission (A-II).

2. During any time of the year, influenza should be considered in immunocompetent and immunocompromised persons with acute febrile respiratory symptoms who are epidemiologically linked to an influenza outbreak (e.g., health care personnel at, residents of, or visitors to an institution experiencing an influenza outbreak; 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) (A-II).

Evidence summary. During periods of influenza activity, community epidemics are common. Abrupt onset of fever with cough is most predictive of uncomplicated influenza in adult outpatients, with a sensitivity >70% during influenza season [27–29]. Influenza is associated with a variety of signs and symptoms that may vary by age, underlying chronic disease, complications, and host immune status. Young infants may present with fever and suspected sepsis [30, 31]. Diarrhea may occur in up to 28% of infected infants and young children [32–34]. Although upper respiratory symptoms with systemic symptoms constitute the most common presentation, severe nonpulmonary manifestations (e.g., myocarditis [35, 36], rhabdomyolysis [37–39], encephalitis [40–44], hypovolemic shock with hyperthermia or hypothermia [45–50]), and invasive bacterial coinfection may occur (with *Staphylococcus aureus, Streptococcus pneumoniae,* group A streptococci, and others) [35, 51–53]. Secondary bacterial pneumonia due to methicillin-resistant *S. aureus* is becoming more prevalent and has been a common finding in recent pediatric influenza-associated deaths [45, 52, 54, 55]. Exacerbation of chronic disease is common (e.g., chronic obstructive pulmonary disease, asthma, and congestive cardiac failure) [36, 56–59]. Elderly persons with influenza may not always have fever [60–64]. Persons at greatest risk of developing complications and being hospitalized in association with influenza include young infants, elderly individuals, persons who are immunocompromised, and persons with certain chronic underlying diseases, such as cardiac, pulmonary, or neurological disease [1, 5, 65–76]. Elderly persons have the highest mortality rates attributable to influenza [2]. Influenza vaccine effectiveness varies by age, host immune status, and the match between circulating and vaccine virus strains [77]. Because influenza vaccine is not 100% effective, vaccinated and unvaccinated persons may manifest influenza-like illness symptoms due to influenza or cocirculating noninfluenza pathogens (e.g., rhinovirus, adenovirus, respiratory syncytial virus, parainfluenza virus, bocavirus, non–severe acute respiratory syndrome coronaviruses, human metapneumovirus, *Bordetella pertussis, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and bacterial causes of community-acquired pneumonia). Nosocomial influenza should be considered for persons who experience an onset of fever ⩾48 h after hospital admission during influenza season [78–83]. During summer months, a diagnosis of influenza should be considered for ill international travelers or their ill contacts [84–89], because influenza viruses circulate year-round in the tropics and would also be circulating in the opposite hemisphere at that time. In addition, travelers returning from countries affected by avian influenza who have febrile respiratory symptoms, combined with a history of exposure to sick, dying, or dead birds in that country, should prompt consultation with the local health department for possible avian influenza testing. Frequently updated information on avian influenza may be obtained at the CDC's Avian Influenza (Bird Flu) Web site (http://www.cdc.gov/flu/avian/index.htm) and the World Health Organization's Avian Influenza Web site (http://www.who.int/csr/disease/avian_influenza/en/). Swine influenza infections may also occur in people; most persons infected with swine influenza have a history of being in close proximity to pigs. Swine influenza is endemic in pig herds in North America and worldwide.

Who Should Be Tested for Suspected Influenza?

Recommendations

3. If the result will influence clinical management (decisions on initiation of antiviral treatment, impact on other diagnostic testing, antibiotic treatment decisions, and infection control practices), with consideration for the sensitivity and specificity of the test used and information about local influenza virus circulation, the following persons should be considered for influenza testing (table 2):

During Influenza Season

a. Outpatient immunocompetent persons of any age at high risk for complications of influenza (e.g., hospitalization or death) (table 3) presenting with acute febrile respiratory symptoms, within 5 days of illness onset, when virus is usually being shed (A-II).

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

c. 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 from illness onset (A-II).

d. Elderly persons and infants presenting with suspected sepsis or fever of unknown origin, irrespective of time from illness onset (A-III).

e. Children with fever and respiratory symptoms presenting for medical evaluation, irrespective of time from illness onset (A-II).

f. Persons of any age who develop fever and respiratory symptoms after hospital admission, irrespective of time from illness onset (A-II).

g. 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 (A-III).

During Any Time of the Year

h. 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 (A-II).

i. Persons who are epidemiologically linked to an influenza outbreak (e.g., 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 (A-II).

Evidence summary. Testing should be performed if the results might influence clinical management or infection control procedures. However, when interpreting results, clinicians must consider the sensitivity of the diagnostic test used, the patient's clinical presentation, and available information on influenza virus circulation in the region. Most persons will have detectable influenza viral shedding for 5 days after illness onset [65, 79]. Young infants can shed influenza viruses for as long as 10 days [90, 91]. Immunocompromised persons can shed influenza viruses for weeks to months after becoming infected [92, 93]. Identification of influenza virus infection in newly admitted patients or in patients with nosocomially-acquired influenza can facilitate implementation of infection control measures to prevent and control influenza transmission in hospitals [78–83, 94]. Detection of influenza virus infection can reduce inappropriate antibiotic use, facilitate antiviral treatment, and decrease length of emergency room visits, use of other laboratory tests, and health care costs [17, 19, 20, 22, 23]. However, presence of bacterial coinfection and the need for antibiotics should be considered for influenza-positive patients as well as influenza-negative patients. Influenza can also occur in persons who have traveled to areas experiencing influenza outbreaks [84–89], including outbreaks of avian or swine influenza, as noted above.

What Specimens Should Be Collected for Influenza Tests from Persons with Suspected Influenza?

Recommendations

4. In immunocompetent persons, respiratory tract specimens should be obtained as close to illness onset as possible, preferably within 5 days after illness onset. Collection of specimens >5 days after illness onset may result in false-negative results because of substantially decreased viral shedding, especially in older children and adults. Infants and young children commonly shed influenza viruses for ⩾1 week. In infants and young children, optimal specimens are nasal aspirates and swabs. In older children and adults, nasopharyngeal aspirates and swabs are preferred specimens. Oropharyngeal specimens (e.g., throat swabs) and sputum specimens may have a lower yield for detection of human influenza viruses but may still produce positive results (A-II).

5. Immunocompromised persons of any age with influenza virus infection may shed influenza viruses for weeks to months, even without fever or respiratory symptoms. Therefore, collection of upper and lower respiratory tract specimens (e.g., with bronchoalveolar lavage) within 5 days after illness onset may still be useful for influenza testing in these persons (A-II).

6. Upper and lower respiratory tract samples should be obtained from patients undergoing mechanical ventilation within 5 days after illness onset, although test results may be positive even after this period. Lower respiratory tract samples include

endotracheal aspirates and washes and bronchoalveolar lavage fluid (A-II).

7. Respiratory specimens should be tested for influenza as soon as possible after collection and should be refrigerated (but not frozen) pending testing (A-II).

8. Clinicians should consult test instructions for the recommended clinical specimens for each specific influenza test (A-II).

9. Acute-phase serum specimens should not be obtained for diagnostic purposes. Paired acute- and convalescent-phase serum specimens are needed for determination of antibody titers (by hemagglutinin inhibition, ELISA, or complement fixation, available only through reference laboratories), but results cannot be attained in a timely fashion and will not influence clinical management (A-II).

Evidence summary. To maximize detection of human influenza viruses, respiratory tract specimens should be collected from ill persons as close to illness onset as possible. Although nasopharyngeal swab or aspirate specimens are the optimal specimens, nasal swab, aspirate, or wash specimens—especially from young children—are almost as good as nasopharyngeal specimens for detection of influenza viruses [95–99]. Throat specimens have lower yield for detection of human influenza viruses [100] but appear to be superior to nasal specimens for detection of sporadic avian influenza A (H5N1) infections in humans [8]. The type of specimen probably matters most for rapid tests and direct fluorescent antibody; the increased sensitivity of PCR may improve the yield [97]. Induced sputum specimens have been tested by PCR but have not been compared with other respiratory specimens for influenza virus detection [101]. Influenza virus in sputum may also be detected by viral isolation [102], and lower respiratory tract specimens obtained from immunocompromised persons may be positive for influenza virus even when specimens obtained from higher in the respiratory tract do not yield positive results. No serologic assay has been validated to diagnose influenza virus infection with use of acute-phase serum specimens.

What Influenza Tests Should Be Used for Persons with Suspected Influenza?

Recommendations

10. Tests that yield results in a timely manner that can influence clinical management (decisions on initiation of antiviral treatment, impact on other diagnostic testing, antibiotic treatment decisions, and infection control practices) are recommended to guide patient care. Results of testing should take into account the a priori likelihood of influenza infection based on the patient's signs and symptoms, the sensitivity and specificity of the test used, and information on circulation of influenza in the community. An in-depth description of influenza testing methods is also available at CDC's Seasonal Flu Web site (http://www.cdc.gov/flu/professionals/diagnosis/labprocedures.htm).

In order of priority, the following influenza tests are recommended, if available:

a. ***RT-PCR.*** This is currently the most sensitive and specific of testing modalities for influenza, with results available within 4–6 h after specimen submission. RT-PCR shows greater sensitivity than viral culture, may be used as a confirmatory test, and is useful for quickly differentiating between influenza types and subtypes. RT-PCR is also the preferred test for specimens obtained from persons with a history of exposure to animals with possible influenza illness (e.g., influenza A [H5N1] in poultry in Eurasia or Africa or swine influenza in any part of the world, including North America) (A-II).

b. ***Immunofluorescence.*** Direct fluorescent antibody or indirect fluorescent antibody staining for influenza antigen detection are used as screening tests. Immunofluorescence exhibits slightly lower sensitivity and specificity than viral isolation in cell culture, but results are available within hours after specimen submission. Performance of these assays depends heavily on laboratory expertise and the quality of the specimen collected (i.e., specimens must include respiratory epithelium cells) (A-II).

c. ***Commercial rapid influenza diagnostic tests.*** Currently available antigen detection tests provide results in 10–30 min but exhibit decreased sensitivity (70%–90% in children and <40% to 60% in adults), compared with RT-PCR and with viral culture (table 4). Performance of these assays depends heavily on patient age, duration of illness, sample type, and perhaps viral type. Given the lower sensitivity of immunofluorescence and commercial rapid tests, follow-up testing with RT-PCR and/or viral culture should be considered to confirm negative test results (A-II).

11. Viral isolation (in standard cell culture and shell vial culture) is not a screening test, but during periods of low influenza activity (late spring, summer, and early fall), it should be performed on respiratory specimens collected from persons with suspected influenza that present for medical care within 5 days after illness onset, especially if such persons are known to be epidemiologically linked to an influenza outbreak. During influenza season, viral culture should be performed with respiratory specimens obtained from a subset of persons for routine virologic surveillance purposes and to confirm some negative test results from rapid antigen and immunofluorescence testing, particularly in the setting of institutional outbreaks (A-II).

12. Serologic testing is usually not recommended to detect evidence of human influenza virus infection for management of acute illness. Influenza serologic test data for a single serum specimen cannot be reliably interpreted. Paired acute- and con-

valescent-phase serum samples are needed for determination of antibody titers (by hemagglutinin inhibition, ELISA, or complement fixation, available only through reference laboratories), but results cannot be attained in a timely fashion and will not influence clinical management. Paired serum specimens are useful only for retrospective diagnosis and for research purposes (A-II).

Evidence summary. To influence clinical management, influenza tests that provide accurate and timely results are recommended. RT-PCR is highly sensitive and very accurate for detection of influenza A and B viruses in respiratory clinical specimens and can provide results within a few hours, but timely results may not be available in many clinical settings. Multiplex RT-PCR assays may be used in some settings to detect a range of respiratory viral pathogens.

Rapid antigen tests have lower accuracy to detect influenza virus infection, compared with RT-PCR or viral culture; thus, negative test results in particular can be difficult to interpret [103–109], although these tests can yield results in minutes to a few hours. Immunofluorescence is often available at hospital laboratories and has moderately high sensitivity and high specificity, compared with viral culture, but it requires good specimen collection technique, a fluorescent microscope, and a trained clinical laboratory scientist [99]. Immunofluorescent staining of cytocentrifuged respiratory secretions may provide higher sensitivities than do standard direct fluorescent antibody, indirect fluorescent antibody, or rapid influenza tests [110]. Multiple-antigen immunofluorescent respiratory viral panels, which are available in some settings, will also detect parainfluenza viruses 1–3, respiratory syncytial virus, adenovirus, and human metapneumovirus. Commercially available rapid influenza diagnostic tests are widely available, are simple to use, can be used as point-of-care tests at the patient's bedside, and can yield results in 10–30 min. However, not all clinical specimens are suitable for rapid influenza tests, and the package insert and manufacturer's instructions should be followed. In addition, although rapid influenza tests have reasonable specificities, their sensitivities range from poor to moderate, compared with RT-PCR or viral culture [99, 106, 107, 111, 112]. Neither rapid antigen tests nor immunofluorescent assays determine influenza A subtype. Most importantly, limitations to interpreting results should be considered (see How Are Influenza Test Results Interpreted? below). Traditionally, viral culture (including shell vial culture) has been considered the "gold standard" for detection of infection with human influenza viruses. Although viral culture does not provide timely results, it is essential as a source of virologic data on strain characteristics, such as antigenic comparison to influenza vaccine strains and antiviral susceptibility, that are important for clinicians and public health. Results may not be useful for clinical management decisions but could be helpful for identifying influenza virus infection when other screening tests yield false-negative results and as confirmation of a subset of negative rapid influenza test results, particularly in the context of an institutional outbreak. Characterization and detailed analyses of influenza viruses isolated during out-of-season activity are particularly important for public health surveillance purposes (for monitoring antigenic drift, influenza vaccine strain selection, influenza vaccine effectiveness, and appearance of novel influenza strains) and may also allow for diagnoses of other viruses that may be of special importance in immunocompromised populations. Antiviral susceptibility testing is likely to be of increasing importance over time but currently is available only in a limited number of reference laboratories. Antiviral susceptibility test results currently are not generally available in a timely manner to contribute to clinical management.

How Are Influenza Test Results Interpreted?

Recommendations

13. To properly interpret test results, clinicians should consider and understand the limitations of influenza tests, especially for screening tests such as immunofluorescence and commercially available rapid influenza tests, as well as the level of influenza activity among the population being tested (table 5). Clinicians should also consider that a positive influenza test result does not exclude bacterial coinfection and evaluation for the potential need for antibiotics (A-II).

a. A positive screening test result is most likely to be truly positive during periods of peak influenza activity in the population tested.

b. A positive screening test result is most likely to be falsely positive during periods of low influenza activity in the population tested, including early and late in the influenza season. A confirmatory test such as PCR or viral culture should be considered.

c. A negative screening test result is most likely to be truly negative during periods of low influenza activity in the population tested.

d. A negative screening test result is most likely to be falsely negative during periods of peak influenza activity in the population tested. A confirmatory test, such as PCR or viral culture, should be considered.

Evidence summary. Influenza test results are influenced by the level of influenza activity in the population being tested (i.e., the prevalence), the characteristics of a test compared to a gold standard, pretest probability, whether the person has signs and symptoms of influenza, whether the influenza virus is actively replicating in the person, proper collection and transport of specimens, and proper test procedures [99]. Interpretation of test results relies on the predictive values of a test (i.e.,

the positive and negative predictive values). Positive and negative predictive values are influenced primarily by the prevalence of influenza viruses in the population tested and on the sensitivity and specificity of the test to detect influenza virus infection versus a gold standard [99, 105]. The sensitivity and specificity of an influenza test are fixed parameters, whereas the prevalence of circulating influenza viruses changes over time in any community (table 5). False-positive and false-negative results are possible with available screening tests, depending on the characteristics of the test, the quality of the specimen collected, the level of influenza activity in the population, and other factors [99]. For example, although it is unlikely that persons receiving live, attenuated influenza vaccine would require influenza testing soon after vaccine administration, persons who receive live, attenuated influenza vaccine can shed vaccine virus strains in the upper respiratory tract for up to 7 days after intranasal vaccination and can test positive for influenza during this period [113, 114].

ANTIVIRALS FOR TREATMENT

Who Should Be Treated with Antivirals?

Recommendations

14. Treatment is recommended for both adults and children with influenza virus infection who meet the following criteria:

a. Persons with laboratory-confirmed or highly suspected influenza virus infection at high risk of developing complications (table 3), within 48 h after symptom onset. Benefits have been best evaluated mostly among otherwise healthy adults with uncomplicated influenza whose treatment was initiated within 48 h after symptom onset, although smaller numbers of persons with conditions that increase the risk of influenza complications have also been included in trials. Fewer data are available by which to make recommendations regarding treatment of persons >48 h after symptom onset. Treatment is recommended regardless of influenza vaccination status and regardless of severity of illness (A-II).

b. Persons requiring hospitalization for laboratory-confirmed or highly suspected influenza illness, regardless of underlying illness or influenza vaccination status, if treatment can be initiated within 48 h after onset of symptoms (A-II). However, persons who require hospitalization for laboratory-confirmed influenza whose positive laboratory test result for influenza is from a specimen obtained >48 h after the onset of illness may also benefit from treatment (B-II).

15. Treatment should be considered for both adults and children with influenza virus infection who meet the following criteria:

a. Outpatients at high risk of complications (table 3) with illness that is not improving and who have a positive influenza test result from a specimen obtained >48 h after onset of symptoms (C-III).

b. Outpatients with laboratory-confirmed or highly suspected influenza virus infection who are not at increased risk of complications, whose onset of symptoms is <48 h before presentation, and who wish to shorten the duration of illness and further reduce their relatively low risk of complications (A-I) or who are in close contact with persons at high risk of complications secondary to influenza infection (table 3). Those whose onset of symptoms occurred >48 h before presentation with persisting moderate to severe illness may also benefit from treatment, but safety and efficacy in this population have not been evaluated prospectively (B-III).

What Antiviral Drug Should Be Used for Treatment?

Recommendation

16. Influenza viruses and their susceptibilities to available antiviral medications evolve rapidly. Clinicians should maintain familiarity with local patterns of influenza circulation in their communities throughout influenza season. Current and frequently updated information on antiviral resistance and recommendations on antiviral use may be found at the CDC's influenza Web site (http://www.cdc.gov/flu). On the basis of antiviral susceptibility patterns current as of March 2009, infection with an influenza A (H1N1) virus should be treated with either zanamivir or an adamantane (preferably rimantadine, because of its more favorable adverse effect profile); oseltamivir should not be used to treat infection with influenza A (H1N1). Infection with an influenza A (H3N2) virus should be treated with oseltamivir or zanamivir; the adamantanes should not be used to treat influenza A (H3N2). If subtype information is unavailable, influenza A should be treated either with zanamivir or with a combination of oseltamivir and rimantadine. Infection with an influenza B virus should be treated only with oseltamivir or zanamivir. Table 6 provides detailed information on antiviral regimens in appropriate age groups (A-II).

Antivirals available for treatment of influenza. Historically, adamantanes (amantadine and rimantadine) were inhibitory for most influenza A but not for influenza B viruses. However, widespread high levels of resistance to amantadine and rimantadine among influenza A (H3N2) and limited resistance among influenza A (H1N1) viruses have been reported since 2006 [115–117].

Neuraminidase inhibitors (oseltamivir and zanamivir) have activity against both influenza A and B viruses. Reduced effectiveness of oseltamivir occasionally has been reported for treatment of influenza B [118, 119]. Although the rate of re-

sistance to neuraminidase inhibitors was generally low prior to 2007 [120, 121], the emergence of oseltamivir resistance among influenza A (H1N1) virus strains was reported in many countries starting in 2007–2008 [122–131]. Both zanamivir and the adamantanes are active against oseltamivir-resistant A influenza (H1N1) viruses. Rimantadine is preferred over amantadine because of its more favorable adverse effect profile. Ongoing surveillance for antiviral resistance is occurring in laboratories worldwide. Clinicians who treat patients with influenza should be aware of local public health data, when available, on the type and subtypes of influenza circulating in their area. Current and frequently updated information on antiviral resistance and recommendations on antiviral use can be found at the CDC's influenza Web site (http://www.cdc.gov/flu).

Both currently licensed neuraminidase inhibitors are approved for use in adults and children. Oseltamivir is approved for treatment of influenza in infants and children aged ⩾1 year in both tablet and suspension formulations, and zanamivir is approved for treatment of influenza in children aged ⩾7 years in the same inhalational powder formulation used in adults. Oseltamivir is not approved for therapy in children aged <1 year because of the lack of adequate safety and efficacy data and because of concerns regarding CNS toxicity in newborn rats. However, limited retrospective data on the safety and efficacy of oseltamivir in this young age group have not demonstrated age-specific drug-attributable toxicities to date [132, 133]. In one additional unpublished study, the safety of oseltamivir in infants aged <1 year was retrospectively reviewed by the National Institutes of Health Collaborative Antiviral Study Group at 15 pediatric health care institutions. One hundred eighty infants aged <1 year who received influenza antiviral therapy with either oseltamivir or an adamantane were identified. Sixty-four percent received oseltamivir; one-third (62 infants) were <6 months of age. Neurologic events during and 1 month after completion of therapy were compared between oseltamivir- and adamantane-treated infants, with no statistically or clinically significant differences noted between groups [134]. Prospective evaluation for both safety and efficacy of oseltamivir in this age group is being conducted currently.

Influenza A and B viruses are susceptible to ribavirin in vitro. Aerosolized ribavirin has been used for treatment of influenza, although data in humans are limited, and aerosolized ribavirin may be considered for critically ill patients who are unable to receive medications orally or by diskhaler [135–139]. Oral ribavirin has also been shown to be effective in uncomplicated disease, although higher dosing is important [140]. Intravenous ribavirin, although investigational, may also be of clinical utility in cases of severe illness, especially in combination with other antiviral agents [141–143].

Evidence of benefits of treatment with neuraminidase inhibitors in adults. In a meta-analysis of randomized, controlled trials, early treatment of uncomplicated influenza in healthy adults with neuraminidase inhibitors reduced both complications (OR in the intention-to-treat analysis, 0.43) and nasal influenza viral titers at 24 h [144]. Oseltamivir was shown to significantly reduce the rate of all-cause hospitalizations within 30 days in one pooled analysis of randomized, controlled trials that enrolled adults and adolescents who were either previously healthy or at high risk of developing complications from 1.7% to 0.7% (relative reduction, 59%) overall [145]. A retrospective claims analysis found a significant decrease in hospitalizations (1.3% vs. 0.9%) when oseltamivir was used to treat influenza-like illness [146]. A retrospective chart review identified a reduced duration of hospital stay among hospitalized elderly patients with influenza treated within 48 h after symptom onset [147].

On the basis of randomized trials including only persons treated within 48 h after symptom onset, neuraminidase inhibitors reduce the duration of symptoms of uncomplicated influenza by ~1 day among outpatients. Treatment also reduces the time to alleviation of influenza symptoms (hazard reduction for intention-to-treat analyses, 1.2) and time to return to normal activity (hazard reduction for intention-to-treat analyses, 1.23) [148]. In one meta-analysis, use of relief medications and antibiotics was not reduced in treated patients [148]. In contrast, pooled analyses of randomized, controlled trials of zanamivir and oseltamivir by different investigators found significant absolute reductions in antibiotic use by 5% for each (18% vs. 13% [149]; 10% vs. 5% for the incidence of influenza-related lower respiratory tract complications resulting in antibiotic use [145]). Another pooled analysis of zanamivir found a significant 9% (i.e., 25% vs. 16%) reduction in the rate of complications requiring antibiotic use among high-risk persons [150]. A retrospective claims analysis found a significant decrease in antibiotic use of 2.4% (19.4% vs. 17%) associated with oseltamivir use [146]. Other observational studies have indicated that oseltamivir treatment is associated with reductions in hospitalizations and lower respiratory tract complications in selected high-risk populations with influenza, including nursing home residents, patients with leukemia, and hematopoietic stem cell transplant recipients [151–154]. Retrospective analyses using large insurance databases of persons with clinical influenza diagnoses have reported reductions in hospitalizations among outpatients aged ⩾1 year with influenza-like illness who were treated with oseltamivir (26%; 95% CI, 10%–39%) [146], fewer hospitalizations among previously healthy persons aged ⩾13 years who were treated for ⩽1 day (22%; 95% CI, 9%–33%) [155], and fewer all-cause hospitalizations among in diabetic persons aged ⩾18 years who were treated for ⩽1 day (30%; 95% CI, 6%–48%) [156].

Studies of high-risk persons are more limited in size. In the pooled analysis of the randomized, controlled trials of oselta-

mivir mentioned above, oseltamivir treatment was associated with a significant reduction in the rate of hospitalization for influenza from 3.2% to 1.6% (relative reduction, 50%) in high-risk persons. In a pooled analysis of high-risk persons, zanamivir use was associated with a significantly earlier return to activities of 3 days and a 9% reduction in antibiotic use [150]. In a meta-analysis involving studies of high-risk persons, zanamivir (but not oseltamivir) was found to reduce the time to alleviation of symptoms [157]. An observational study demonstrated improved outcomes in patients with leukemia who were treated for influenza [152].

It is important to note that all randomized trials conducted to date included only patients treated within 48 h after the onset of symptoms. In most persons, influenza is a self-limited illness. In otherwise healthy adult outpatients, viral titers are already decreasing by 48 h after the onset of illness [158–160]. As expected, in such patients, the benefit of antivirals is greatest when given early [161, 162]. In a prospective, open-label study of oseltamivir therapy started within 48 h after the onset of symptoms, therapy started <6 h after the onset of symptoms reduced the duration of symptoms by 3.1 days, compared with commencement of therapy >36 h after illness onset [161]. Thus, in otherwise healthy adults who are not seriously ill, treatment given >48 h after illness onset may be of little benefit.

There are currently few data to assess whether there is benefit in treating patients with severe illness, including those who require hospital admission for influenza or its complications, >48 h after symptom onset. No prospective, adequately controlled clinical trials have been completed that involve patients who are seriously ill with influenza or that involve those who are documented to be shedding influenza virus >48 h after the onset of symptoms. One cohort study among hospitalized adults with influenza reported that oseltamivir treatment, including treatment in persons >48 h after illness onset, resulted in a significant reduction in mortality within 15 days after illness onset [163]. Of note, nearly 90% of the oseltamivir-treated patients had positive rapid antigen test results. Oseltamivir treatment, even when delayed, has been associated with improved survival in patients with influenza A (H5N1) illness, many of whom have presented with viral pneumonia [8]. The cost and safety profile of oseltamivir are sufficiently favorable, such that many experts recommend that patients who require hospital admission for influenza should routinely receive therapy with antivirals [163].

Evidence of benefits of treatment with neuraminidase inhibitors in children. Oseltamivir was investigated in otherwise healthy children aged 1–12 years with uncomplicated influenza in a prospective, randomized, double-blind, placebo-controlled study in which entry criteria specified that enrolled children were required to have had influenza symptoms for ≤48 h [164]. A 5-day treatment course with oseltamivir, compared with placebo, was associated with a decrease in the median time to resolution of overall clinical illness of 36 h. A significant decrease in viral shedding was also noted in treated children, with almost complete resolution of shedding documented within 4 days for treated children, compared with 6 days for control children. Complications of influenza were also reduced in oseltamivir-treated children; the incidence of physician-diagnosed acute otitis media was reduced by 44%, compared with the incidence among placebo recipients.

In studies of children aged 6–12 years with asthma who received oseltamivir or placebo for uncomplicated influenza infection, a significant improvement in pulmonary function was noted on day 6 after treatment, although no difference in the median time to resolution of illness was documented [165].

One retrospective review of the use of health care services by children who received a clinical diagnosis of influenza reported that children 1–12 years of age who received prescriptions for oseltamivir within 24 h after diagnosis experienced a 52% reduction in the rate of subsequent medical encounters for clinically diagnosed pneumonia, compared with children who were not treated (relative risk, 0.483; 95% CI, 0.326–0.717). In addition, significant reductions in antibiotic use and in outpatient and emergency department visits were also observed [166].

In a randomized, double-blind, prospective study of inhaled zanamivir administered twice daily for 5 days to children aged 4–12 years, symptomatic illness was reduced by 1.25 days in influenza-infected children who received zanamivir, compared with placebo recipients [167]. In 3 trials of subjects aged ≥12 years, zanamivir treatment decreased the duration of symptoms by 1–2.5 days in influenza-positive subjects [168–170]. In a multicenter, prospective study of subjects whose therapy was started within 30 h after symptom onset, resolution of major symptoms occurred 3 days earlier in the treatment group, compared with the control group [162]. One nonrandomized, open-label trial of zanamivir versus oseltamivir found no difference in time to reduction of the febrile period in pediatric outpatients infected with influenza A (H1N1), influenza A (H3N2), or influenza B [171]. In hospitalized children, treatment with either oseltamivir or zanamivir decreased the duration of fever significantly, compared with placebo, for children infected with circulating A (H3N2) and B viruses, with the decrease shown to be equivalent for both antivirals. Although use of neither oseltamivir nor zanamivir decreased the duration of culture positivity for circulating A (H3N2) viruses in this study, zanamivir decreased the duration of shedding for B viruses, compared with no treatment [91].

One trial compared zanamivir and oseltamivir and found no difference between the 2 with regard to the time to reduction of the febrile period in pediatric outpatients with influenza A (H1N1), influenza A (H3N2), or influenza B [171].

Antiviral resistance. Widespread high levels of resistance to amantadine and rimantadine among influenza A (H3N2), and limited resistance among influenza A (H1N1) viruses has been reported since 2006 [115–117]. Only neuraminidase inhibitors should be used for treatment of or chemoprophylaxis for infection with influenza A (H3N2) viruses. Resistance to neuraminidase inhibitors arises by single-step mutations, and isolation of oseltamivir-resistant viruses has been reported during and after treatment, especially in children [164, 172, 173]. In immunocompromised hosts, the emergence of resistant variants has been associated with lack of virologic response and progressive disease [174, 175]. Detection of oseltamivir-resistant influenza A or B viruses among circulating community isolates previously had been uncommon, even in countries like Japan, where there are high levels of oseltamivir use [121, 176]. However, starting in 2007–2008, oseltamivir-resistant influenza A (H1N1) virus strains associated with a specific H274Y mutation in the neuraminidase gene were reported in many countries [122–131]. Circulation of these resistant variants was not associated with oseltamivir use, and associated infections had clinical features and outcomes similar to those for infections due to oseltamivir-susceptible influenza A (H1N1) viruses. However, progressive viral replication and fatal outcome, despite receipt of oseltamivir, have been reported in patients infected with resistant influenza A (H1N1) virus [177]. These strains retained susceptibility to zanamivir and the adamantanes. Current and frequently updated information on antiviral resistance and recommendations on antiviral use can be found at the CDC's influenza Web site (http://www.cdc.gov/flu).

Adverse events. One meta-analysis of antiviral treatment of influenza in adults concluded that neuraminidase inhibitors were not associated with any major adverse effects [148]. Nausea and vomiting are the most common adverse event associated with oseltamivir therapy and were reported in 9%–10% of adults receiving treatment [178]. In children, adverse effects after oseltamivir administration are also principally gastrointestinal, with 14% of oseltamivir-treated children reporting vomiting, compared with 8% of influenza-infected, placebo-treated children [164]. In Japan, neuropsychiatric adverse events were reported at a frequency of ~1 in 100,000 oseltamivir prescriptions, mainly in adolescents [179]. It is not clear whether these events were associated with oseltamivir, influenza, or some combination that may include genetic susceptibility to these adverse events. More recently, an unpublished Japanese study assessed oseltamivir use in 10,000 persons aged <18 years and found no evidence of neuropsychiatric events in this population [180]. Neuropsychiatric events have occasionally been reported in adults taking oseltamivir [181]. The package inserts for both oseltamivir and zanamivir in the United States contain warnings about potential adverse neuropsychiatric events [178, 182].

There are no adverse events that have been reported to occur in >1% of zanamivir recipients [162, 183, 184]. However, zanamivir is an orally inhaled powder, and there are case reports of bronchospasm related to zanamivir treatment [185]. Concerns regarding bronchospasm and decreased pulmonary function after inhalation of zanamivir in pediatric and adult patients with underlying airway disease, including asthma and chronic obstructive pulmonary disease, prompted a warning not to administer zanamivir to these persons [182]. One prospective, randomized trial of patients with influenza who had mild-to-moderate asthma or chronic obstructive pulmonary disease found no differences in adverse events or spirometric measurements between zanamivir and placebo recipients; the zanamivir recipients had reduced time to illness alleviation and faster improvements in self-tested peak expiratory flow rates [186].

Adults and children with influenza can develop potentially severe complications due to bacterial coinfection. Particular attention should be paid to the possibility of influenza-associated complications in the vulnerable populations that generally reside in institutional settings. Persons at high risk of such complications (table 3) should be thoroughly evaluated for secondary bacterial pneumonia, a common cause of death in this population. Providers should also be aware of a significant increase in *S. aureus* coinfections (primarily methicillin-resistant *S. aureus* confections) among children with serious or fatal influenza in the United States [45, 52, 54, 55]. Antiviral treatment may be inadequate for therapy of seriously ill patients with influenza-associated complications, and appropriate antibiotic treatment should be administered and guided by results of microbiological tests and evidence-based recommendations if there is evidence for or strong suspicion of serious bacterial infection in hospitalized patients [187]. When patients are treated for influenza, clinicians should be alert to the possibility that persisting symptoms or deterioration may reflect bacterial infection and should counsel their patients appropriately.

ANTIVIRALS FOR CHEMOPROPHYLAXIS

Who Should Be Considered for Antiviral Chemoprophylaxis to Prevent Influenza?

Recommendations

17. Influenza vaccination is the primary tool to prevent influenza, and antiviral chemoprophylaxis is not a substitute for influenza vaccination. When influenza viruses are circulating in the community, chemoprophylaxis can be considered for high-risk persons during the 2 weeks after vaccination before an adequate immune response to inactivated vaccine develops (6 weeks for children who were not previously vaccinated and who require 2 doses of vaccine) (A-I).

18. Antiviral chemoprophylaxis should be considered for adults and children aged ⩾1 year who are at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are significantly immunocompromised) (B-II). Contraindications to vaccination include anaphylactic hypersensitivity to eggs or other vaccine components; moderate-to-severe febrile illness; and, as a precaution, a history of Guillain-Barré syndrome within 6 weeks after receipt of a prior influenza vaccination [5].

19. Antiviral chemoprophylaxis (in conjunction with prompt administration of the inactivated vaccine) should be considered for adults and children aged ⩾1 year who are at high risk of developing complications from influenza virus infection (table 3) and have not yet received influenza vaccine when influenza activity has already been detected in the community. Whenever possible, influenza vaccine should be administered, and vaccination should continue for recommended persons until influenza is no longer in community circulation (B-II).

20. Antiviral chemoprophylaxis may be considered for unvaccinated adults, including health care workers, and for children aged ⩾1 year who are in close contact with persons at high risk of developing influenza complications during periods of influenza activity. Whenever possible, influenza vaccine should be administered; 2 weeks after administration, chemoprophylaxis may be discontinued (6 weeks for children who were not previously vaccinated and who require 2 doses of vaccine) (B-III).

21. Antiviral chemoprophylaxis is recommended for all residents (vaccinated and unvaccinated) in institutions, such as nursing homes and long-term care facilities, that are experiencing influenza outbreaks (A-I).

22. The strongest consideration for use of antiviral chemoprophylaxis should be given to persons at the highest risk of influenza-associated complications. The risk of influenza-associated complications is not identical among all high-risk persons, and antiviral chemoprophylaxis is likely to have the greatest benefit among those at highest risk of influenza complications and death, such as recipients of hematopoietic stem cell transplants (B-III).

23. Antiviral chemoprophylaxis should be considered for persons at high-risk of developing complications from influenza if influenza vaccine is not available due to shortage. If vaccine is available, it should be administered to these persons (A-I).

24. Antiviral chemoprophylaxis can be considered for high-risk persons (table 3) in situations in which there is documented low influenza vaccine clinical effectiveness because of the circulation of influenza virus strains that are antigenically distant from the vaccine strains, such that a substantial increase in vaccine failures is anticipated, as determined by federal, state, and local public health authorities (C-II).

When Should Antiviral Chemoprophylactic Regimens Be Started?

Recommendations

25. In persons at high risk of complications who are not adequately protected as a result of poor immune responses (e.g., in persons who are significantly immunocompromised), lack of influenza vaccination, or ineffective vaccine (e.g., when antigenically distant strains are circulating), antiviral chemoprophylaxis should be initiated at the onset of sustained community influenza activity, as determined by local public health authorities (B-II).

26. Antiviral chemoprophylaxis use for appropriate persons within households should be initiated when 1 family member develops suspected or confirmed influenza and any other family member is at high risk of complications secondary to infection, including infants aged <6 months (table 3). In this setting, all noninfected family members should receive antiviral chemoprophylaxis. Ideally, all eligible family members in such settings should be vaccinated, making chemoprophylaxis unnecessary (A-I).

27. Antiviral chemoprophylaxis and other control measures should be initiated in institutions, such as hospitals and long-term care facilities (e.g., nursing homes), when an influenza outbreak is detected or when influenza is strongly suspected but the etiology of the outbreak has yet to be determined (A-II).

How Long Should Chemoprophylaxis Continue?

Recommendations

28. If inactivated influenza vaccine is administered, antiviral chemoprophylaxis can generally be stopped 2 weeks after vaccination for persons in noninstitutional settings. Children aged <9 years who receive inactivated influenza vaccine for the first time require 2 doses of vaccine, with the second dose administered at least 4 weeks after the first dose; the immune response peaks 2 weeks after receipt of the second dose. Thus, a minimum of 6 weeks of chemoprophylaxis (i.e., chemoprophylaxis for at least 4 weeks after the first dose of vaccine and an additional 2 weeks of chemoprophylaxis after the second dose) would be needed, depending on the length of the delay between administration of the 2 vaccine doses (B-II).

29. When antiviral chemoprophylaxis is used in a household after the diagnosis of influenza in 1 family member, chemoprophylaxis should be continued for 10 days (A-I).

30. In persons at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are significantly immunocompromised), chemoprophylaxis should continue for the duration that influenza viruses are circulating in the community during influenza season (B-III).

What Antiviral Drugs Should Be Used for Chemoprophylaxis?

Recommendation

31. Influenza viruses and their susceptibilities to available antiviral medications evolve rapidly. Clinicians should maintain familiarity with local patterns of influenza circulation in their communities throughout the influenza season. Current and frequently updated information on antiviral resistance and recommendations on antiviral use may be found at the CDC's influenza Web site (http://www.cdc.gov/flu). On the basis of antiviral susceptibility patterns current as of March 2009, either zanamivir or an adamantane (preferably rimantadine because of its more favorable adverse effect profile) should be used for influenza A (H1N1) chemoprophylaxis; oseltamivir should not be used for influenza A (H1N1) chemoprophylaxis. Either oseltamivir or zanamivir should be used for influenza A (H3N2) chemoprophylaxis; the adamantanes should not be used for influenza A (H3N2) chemoprophylaxis. If subtype information is unavailable, either zanamivir or a combination of oseltamivir and rimantadine should be used for influenza A chemoprophylaxis. Only oseltamivir or zanamivir should be used for influenza B chemoprophylaxis. Table 6 provides detailed information on antiviral regimens in appropriate age groups (A-I).

Evidence summary. Both neuraminidase inhibitors (zanamivir and oseltamivir) and the adamantanes (amantadine and rimantadine) have been extensively evaluated and have demonstrated efficacy in preventing influenza infection and disease when used for prophylaxis in family settings, community-dwelling elderly persons, and elderly persons in long-term care facilities [188, 189]. Efficacy has been demonstrated both for prophylaxis for the entire influenza season and for postexposure prophylaxis. However, the usefulness of amantadine and rimantadine is limited by the high prevalence of resistance to these agents among circulating strains of influenza A—especially H3N2 and, less often, H1N1 viruses [116, 117]—as well as the intrinsic lack of activity against influenza B. Moreover, when amantadine or rimantadine were used to treat index cases in families, there was no prophylactic efficacy, because of the rapid emergence and transmission of resistant virus [190]. Adamantanes may be considered for prophylactic use only if oseltamivir-resistant influenza A (H1N1) virus infection is suspected. When zanamivir was administered for 10–14 days to healthy adults and children after household exposure, it was 79%–81% effective at preventing laboratory-confirmed influenza illness, irrespective of concurrent treatment given to the ill index case patients [191, 192]. The efficacy of postexposure prophylaxis with oseltamivir was 68%–89% among household members exposed to influenza [193, 194].

To date, the development of resistance to neuraminidase inhibitors in immunocompetent persons using oseltamivir for prophylaxis has not been observed [192, 193]. Resistance can develop during treatment with any influenza antiviral medication, and future trends in resistance will need to be taken into account. Breakthrough influenza infection among persons receiving oseltamivir prophylaxis for >72 h should prompt discussion with the local public health department to consider the possibility of neuraminidase inhibitor resistance. To date, most clinical isolates of oseltamivir–resistant influenza A (H1N1) have remained fully susceptible to zanamivir and the adamantanes [129]. The choice of an antiviral drug should be determined by the age group, local antiviral resistance data, and the appropriateness of delivery by the oral (oseltamivir) or inhaled (zanamivir) route. Current and frequently updated information on antiviral resistance and recommendations on antiviral use can be found at the CDC's influenza Web site (http://www.cdc.gov/flu).

Several studies have demonstrated the effectiveness of antiviral chemoprophylaxis in nursing home settings, either for the duration of the influenza season or to control outbreaks [94, 195]. One research group administered oseltamivir to elderly persons in long-term care facilities for the duration of the influenza season and demonstrated 92% efficacy and a reduction in complications [196]. Other investigators reported the use of prophylaxis for all residents in 8 nursing home outbreaks in Ontario, Canada [151]; the outbreaks were promptly controlled in all facilities. Another study reported a similar experience in outbreaks among highly vaccinated residents of nursing homes in Michigan [197]. One comparative trial found significantly higher protection among nursing home residents with inhaled zanamivir than with oral rimantadine, in part because of emergence of resistance to adamantanes [198]. Influenza is associated with high mortality rates among recipients of hematopoietic stem cell transplants [199]. No prospective trials of chemoprophylaxis have been reported in this population, but a retrospective case-control study demonstrated that oseltamivir chemoprophylaxis was associated with prompt control of an outbreak among hematopoietic stem cell transplant recipients [200].

All persons at high risk of developing influenza-associated complications, as well as their close contacts, should receive an annual influenza vaccine. If influenza viruses are circulating in the community, chemoprophylaxis can be considered during

the 2 weeks after vaccination before an adequate immune response to inactivated vaccine develops (at least 6 weeks for children who were not previously vaccinated and who require 2 doses of vaccine, given at least 4 weeks apart and allowing for adequate immune response in the 2 weeks after administration of the second dose). Persons who receive antiviral chemoprophylaxis should be given only inactivated influenza vaccine, because antiviral medications may reduce the effectiveness of the live, attenuated influenza vaccine. Titers of antibody to influenza generally rise to protective levels, and efficacy against confirmed influenza infection can be demonstrated within 2 weeks after vaccination. Lower immunogenicity and efficacy of influenza vaccines have been demonstrated in the elderly population [201, 202]. Among persons with HIV infection, influenza vaccines appear to be immunogenic and effective, as determined on the basis of limited trials. However, lower immunogenicity and efficacy have been demonstrated among persons with CD4 cell counts <200 cells/mL [203–205]. Other persons in whom influenza vaccination may have poor effectiveness include those with immunodeficiencies caused by drugs to prevent transplant rejection and persons with severe congenital immunodeficiency (e.g., hypogammaglobulinemia, severe combined immunodeficiency syndrome, DiGeorge syndrome, and common variable immunodeficiency).

OUTBREAK MANAGEMENT IN INSTITUTIONAL SETTINGS

When Should an Influenza Outbreak Be Suspected in an Institution?

Recommendation

32. During influenza season, when ⩾2 institutional residents manifest signs and symptoms of influenza-like illness within 72 h of each other, testing for influenza should occur. When influenza viruses are circulating in the community, even 1 positive laboratory result in conjunction with other compatible illnesses on the unit indicates that an outbreak of influenza is occurring (A-II).

Evidence summary. Institutions are facilities that care for persons who are at increased risk of developing influenza-associated complications and in which influenza viruses may be more easily transmitted between such persons. Institutions may include—but are not limited to—hospitals, long-term care facilities for adults and children, prisons, and other similar congregate settings. Staff members in institutions should remain vigilant for cases of respiratory illness year-round, and close communication should be maintained with the local and state health departments regarding timing and local patterns of circulation of influenza and other respiratory pathogens, such as respiratory syncytial virus and parainfluenza virus [206–208].

Considering the high attack rate associated with influenza outbreaks in institutional settings [209], during influenza season, it is prudent to consider a single case of laboratory-confirmed disease in the context of ⩾2 cases of influenza-like illness occurring within 72 h of each other as an outbreak in the institutional setting, leading to prompt implementation of control measures, including vaccination and use of antivirals [94, 195, 210–213]. Because of the lower sensitivity of rapid influenza tests, negative results from such tests should prompt further testing with RT-PCR and/or viral culture to confirm that the outbreak is not due to influenza. For clusters of influenza-like illness occurring when influenza viruses are known to be circulating within the community, a low threshold (2 cases of influenza-like illness occurring within 72 h of each other) for instituting facility-wide outbreak control measures should be employed while awaiting laboratory confirmation of the diagnosis. During periods when influenza viruses are not circulating in the community, it is less likely that cases of influenza-like illness represent infection with influenza viruses, and use of influenza vaccine and antiviral chemoprophylaxis may be delayed until a definitive laboratory diagnosis is obtained. However, in such contexts, other infection control measures, such as isolation and cohorting of ill residents, restriction of ill staff and visitors, screening for ill staff members, and active surveillance for new cases, should be implemented and may help control the outbreak while awaiting confirmation of the etiology [5, 213, 214].

What Is the Role for Testing Institutional Residents with Influenza-Like Illness after a Diagnosis of Influenza Has Already Been Established in ⩾1 Resident?

Recommendation

33. After a single laboratory-confirmed case of influenza among residents has been identified in an institution, it is likely that subsequent cases of temporally associated influenza-like illness are also caused by influenza virus infection, although mixed outbreaks due to other respiratory pathogens may occur. Although it may not be possible to obtain specimens from all ill residents for influenza testing in the context of an outbreak, persons developing compatible symptoms >72 h after implementation of antiviral chemoprophylaxis or among persons developing compatible symptoms who reside on previously unaffected units should be tested for influenza and other respiratory pathogens. If influenza test results are positive despite antiviral treatment, consider the possibility of a drug-resistant virus; the spread of influenza to previously unaffected areas of the facility where antiviral use has not been implemented; or multiple introductions of influenza from the community to facility residents (B-III).

Evidence summary. Few data exist to determine whether

performing diagnostic tests for every resident who develops influenza-like illness in the context of an influenza outbreak leads to more timely control of the outbreak. However, once a case of influenza-like illness in an institution is confirmed to be caused by influenza, subsequently identified cases of influenza-like illness are also likely to be caused by influenza, although this is not always the case (e.g., influenza and other respiratory viruses may circulate simultaneously in the same facility, and coinfection may occasionally occur) [215]. Because the likelihood is high that such patients are infected with influenza virus [64], depending on availability of tests in a given facility, it may be impractical to test every patient who presents with influenza-like illness for influenza virus in the context of an influenza outbreak. Elderly patients may have atypical symptoms of influenza infection; testing for influenza may be important for afebrile residents with respiratory symptoms or new-onset altered mental status. Institutional residents are frequently at high risk of developing influenza-associated complications. If clinical suspicion for influenza infection is high, it is prudent to institute antiviral therapy and implement infection control measures while awaiting the results of influenza diagnostic tests.

Which Residents Should Be Treated with Antiviral Medications during an Outbreak?

Recommendation

34. All residents with laboratory-confirmed influenza virus infection should be treated with an appropriate influenza antiviral medication. After 1 case of laboratory-confirmed influenza is detected in a facility resident, all persons in the facility subsequently developing influenza-like illness or other signs or symptoms consistent with influenza (e.g., isolated altered mental status in an elderly resident) should be considered for treatment with an influenza antiviral medication (A-III). See Antivirals for Treatment and table 6 for regimen information.

Evidence summary. Few data exist to suggest that treatment of persons with confirmed influenza during an institutional outbreak, without implementation of facility-wide antiviral chemoprophylaxis and influenza vaccination, leads to quicker control of the outbreak. However, such persons are likely to be at risk of developing complications of influenza virus infection [5, 216] and should be treated with appropriate antiviral medications, as discussed in the Antivirals for Treatment section. Early treatment (within 2 days after onset) was associated with greater reductions in the risk of complications than was delayed administration in one retrospective study [151].

Which Residents Should Receive Antiviral Chemoprophylaxis during an Outbreak?

Recommendation

35. During documented outbreaks of influenza in long-term care facilities, all residents should receive influenza antiviral chemoprophylaxis, regardless of influenza vaccination status. Ideally, chemoprophylaxis should be implemented on all floors and wards of the facility, because breakthrough cases frequently occur when antiviral medications are administered only to those persons on the affected unit or ward and not to all residents in the facility (A-I).

Evidence summary. Little disagreement exists regarding whether residents in institutional settings should receive influenza antiviral chemoprophylaxis in the context of an institutional influenza outbreak. Observational data [151, 195, 197, 198, 217–221] evidence from randomized trials [219, 222] and recommendations from influenza experts and medical societies [5, 94, 188, 206, 211, 223, 224] support the use of influenza antivirals for residents in this setting. Instituting chemoprophylaxis also demonstrates economic benefit for the affected facility [225]. However, antivirals are frequently administered for chemoprophylaxis only to residents who occupy rooms on an affected floor or ward. This practice often leads to continuation of the outbreak, with cases occurring on other floors or wards of the facility after control measures have been implemented on the original unit. In light of this experience, if feasible, facility-wide chemoprophylaxis for all residents, regardless of whether they were previously vaccinated, should occur during the course of the outbreak [5, 214, 218].

Which Health Care Personnel Should Receive Antiviral Chemoprophylaxis during an Outbreak?

See Antivirals for Treatment for regimen information.

Recommendation

36. For all institutional employees who are unable to receive influenza vaccine or for whom vaccine is contraindicated or when the vaccine is expected to be ineffective (e.g., because of the circulation of influenza virus strains that are antigenically distant from the vaccine strains, such that a substantial increase in vaccine failures is anticipated), antiviral medications should be used for chemoprophylaxis (B-III). Contraindications to vaccination include anaphylactic hypersensitivity to eggs or other vaccine components, moderate-to-severe febrile illness, and, as a precaution, a history of Guillain-Barré syndrome within 6 weeks after a previous influenza vaccination [5].

Evidence summary. Although evidence exists that vaccination of health care workers reduces mortality in patients [226,

227], no studies have assessed the impact among residents of administration of antiviral chemoprophylaxis to health care workers. Every effort should be made to ensure that all health care staff are vaccinated each season. Unvaccinated staff may be the source of introduction of influenza virus from the community into facilities, and staff also become infected and serve as sources of transmission within institutions [228]. For these reasons, unvaccinated institutional staff should receive influenza antiviral chemoprophylaxis during influenza outbreaks. During seasons in which circulating viruses are not well matched with vaccine viruses, consideration should be given to administration of antiviral chemoprophylaxis to vaccinated staff as well. Antiviral chemoprophylaxis may be considered for vaccinated staff who are immunocompromised because vaccine may have significantly decreased efficacy [205]. If an employee receives influenza vaccine during an institutional outbreak, antiviral chemoprophylaxis should be given for 14 days after vaccination, until protective antibodies have developed. Ideally, chemoprophylaxis should be administered to unvaccinated staff facility-wide, because breakthrough cases may occur if antiviral medications are administered only to those persons who work in the affected unit or ward. Appropriate use of antiviral chemoprophylaxis in staff will be facilitated by rapid recognition of outbreaks, combined with information about the circulation of antigenically distant strains unlikely to be inhibited by the current vaccine.

How Long Should Antiviral Chemoprophylaxis Continue in Residents and Staff during an Outbreak?

Recommendation

37. In the setting of an institutional outbreak, antiviral chemoprophylaxis should be continued for 14 days or for 7 days after the onset of symptoms in the last person infected, whichever is longer (A-II).

Evidence summary. The CDC, numerous state and local public health agencies, and experts on influenza control recommend that antiviral chemoprophylaxis during an institutional influenza outbreak should be administered for no less than 14 days and that, if surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until 7 days after the last case has been identified [5, 94, 214, 229]. One randomized trial that compared 2 antiviral chemoprophylaxis protocols used during nursing home outbreaks of influenza A concluded that administration of antivirals to residents for a minimum of 14 days (and for 7 days after the last confirmed influenza case) was sufficient to prevent recrudescence of the outbreak [229].

LIMITATIONS OF THE LITERATURE AND ONGOING AND FUTURE STUDIES

In preparing these guidelines, the Expert Panel attempted to highlight areas in which the literature provides limited evidence. Many of these are highlighted in the evidence summary. However, we wish to highlight several crucial research needs. Additional studies are needed to demonstrate the role of diagnostic testing in improving the treatment of adults with influenza-like illness, both in the outpatient setting and in the hospital setting. A key outcome is the ability to reduce inappropriate antibiotic use and emergence of antibiotic resistance. There are limited data on the efficacy or optimal duration of treatment with neuraminidase inhibitors among hospitalized patients and among children aged <1 year. The recent emergence of circulating virulent strains of influenza A (H1N1) with high-level resistance to oseltamivir needs to be closely tracked. The prevalence of resistance and the availability of alternative agents will influence these recommendations in the future.

PERFORMANCE MEASURES

Performance indicators are tools to help users measure both the extent and the effects of implementation of guidelines. Such tools or measures can be indicators of the process itself, outcomes, or both. Deviations from the recommendations are expected in a proportion of cases, and compliance in 80%–95% of cases is generally appropriate, depending on the indicator.

Four measures have been selected for the influenza guidelines:

1. Influenza testing should be performed for all persons admitted to the hospital with acute febrile respiratory symptoms during periods of influenza activity in the community.
2. Antivirals should be administered to all persons requiring hospital admission for laboratory-confirmed influenza.
3. All health care personnel should receive annual influenza vaccination, unless medical contraindications exist for doing so. Contraindications to vaccination include anaphylactic hypersensitivity to eggs or other vaccine components, moderate-to-severe febrile illness, and as a precaution, a history of Guillain-Barré syndrome within 6 weeks after a previous influenza vaccination. If health care personnel decline vaccination, they should sign declination forms acknowledging their understanding of the risk they pose to patients in their facilities.
4. Health care institutions (including hospitals, long-term care facilities, and other institutions housing persons potentially at high risk of complications secondary to influenza infection) should offer influenza vaccine to and track the vaccination status of all employees.

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