Chapter 6: Influenza

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I. Disease Description

Influenza is an acute respiratory disease caused by influenza type A or B viruses. The incubation period ranges from 1 to 4 days. Peak virus shedding usually occurs from 1 day before onset of symptoms to 3 days after. Typical features of influenza include abrupt onset of fever and respiratory symptoms such as cough (usually nonproductive), sore throat, and coryza, as well as systemic symptoms such as headache, muscle aches, and fatigue. The clinical severity of infection can range from asymptomatic illness to primary viral pneumonia and death. Acute symptoms generally last 2–7 days, although malaise and cough may continue for 2 weeks or longer. Complications of influenza infection include secondary bacterial pneumonia and exacerbation of underlying chronic health conditions. Complications occurring in children can include otitis media, febrile seizures, encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye syndrome.[1–5] Aspirin and other salicylate-containing medications are contraindicated for children and adolescents with influenza like illness, as their use during influenza infection has been associated with the development of Reye syndrome.

The sharp rise in influenza-associated acute respiratory illnesses that occurs during annual seasonal epidemics results in increased numbers of visits to physicians' offices, walk-in clinics, and emergency departments. Hospitalizations for pneumonia and other complications also increase. Persons 65 years of age and older, young children, and persons of any age with certain underlying health problems are at increased risk for complications of influenza and hospitalization. Influenza epidemics, particularly epidemics caused by influenza A (H3N2) viruses, are associated with increased mortality. From the 1990–91 through the 1998–99 influenza seasons, an average of 36,000 influenza-associated excess deaths occurred each year.[6] More than 90% of influenza-associated deaths occur among persons age 65 years and older.

II. Background

Influenza viruses can be divided into three types; A, B, and C. Influenza type C viruses are not associated with severe disease or outbreaks and will not be discussed further. Influenza type A viruses are divided into subtypes based on surface proteins called hemagglutinin (HA) and neuraminidase (NA).[7] There are 16 known hemagglutinin and 9 known neuraminidase subtypes. Influenza viruses can infect a wide range of animals, such as pigs, birds, horses, dogs, and whales. While only a few influenza A subtypes have been isolated from mammals, all the known subtypes have been isolated from avian species. The two influenza A subtypes that have cocirculated in human populations since 1977 are influenza A (H1N1) and A (H3N2). A reassortment of the influenza A (H1N1) and A (H3N2) viruses resulted in the circulation of A (H1N2) viruses during the 2001–02 and 2002–03 influenza seasons.

Influenza A and B viruses both undergo gradual, continuous change in the HA and NA proteins, known as antigenic drift. As a result of these antigenic changes, antibodies produced to influenza as a result of infection or vaccination with earlier strains may not be protective against viruses circulating in later years. Consequently, yearly epidemics usually occur in populations, and multiple infections can occur over a person's lifetime. Antigenic changes also necessitate frequent updating of influenza vaccine components to ensure that the vaccine is matched to circulating viruses. In addition to antigenic drift, influenza type A viruses can undergo a more dramatic and abrupt type of antigenic change called an antigenic shift, which occurs when viruses belonging to a new influenza A subtype bearing either a novel HA protein or novel HA and NA proteins begin circulating. While antigenic drift occurs continuously, antigenic shift occurs infrequently. When antigenic shift does occur, a large proportion, or even all, of the world's population has no antibody against the new virus. This can result in a worldwide epidemic called a pandemic. During the 20th century, pandemics occurred in 1918 (type A [H1N1]), 1957 (A [H2N2]), and 1968 (A [H3N2]). The recent emergence of avian influenza A (H5N1) as a cause of widespread illnesses in wild birds and poultry and sporadic illnesses in humans has increased concerns about the likelihood of an influenza pandemic.

III. Vaccination

Annual influenza vaccination is recommended for persons 6 months of age and older who are at increased risk for influenza-associated complications and persons such as health-care providers and household contacts who have close contact with high-risk persons.[8]

Persons at high risk for severe influenza related complications include the following:

- Persons 65 years of age and older
- Residents of nursing homes and other long-term care facilities that house persons of any age with chronic medical conditions
- Adults and children with chronic pulmonary or cardiovascular disorders, including children with asthma
- Adults and children who required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications)
- Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration
- Children and adolescents (6 months–18 years of age) who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye syndrome after influenza
- Women who will be pregnant during the influenza season
- Children aged 6–23 months

Annual vaccination also is recommended for the following persons because of an increased risk for influenza-associated clinic, emergency department or hospital visits, particularly if they have a high-risk medical condition:

- Children aged 24–59 months[9–12]
- Persons aged 50–64 years

To prevent transmission of influenza to persons at increased risk for influenza-related complications, vaccination is also recommended for the following persons:

- Household contacts and out-of-home caretakers of persons at high risk for severe complications from influenza, and contacts and caretakers of children younger than 5 years old, particularly infants 0–5 months old. (The pediatric group at greatest risk of complications is children younger than 6 months old. However, influenza vaccines are not approved by the Food and Drug Administration [FDA] for use among children younger than 6 months.[8])
- Healthcare workers

In the United States, both inactivated and live attenuated influenza vaccines are available. The live attenuated vaccine is approved for use in healthy persons age 5 through 49 years. Inactivated vaccine is approved for use in all persons 6 months of age and older. Both are trivalent vaccines containing influenza A (H3N2), influenza A (H1N1), and influenza B strains selected to represent the strains judged most likely to circulate during the influenza season in the United States. Typically, one or two of the three vaccine components are updated each year to provide a better antigenic match with circulating viruses.

The efficacy of the vaccine depends on the match between the vaccine strains and the circulating strains as well as the recipient's age, immunocompetence, and previous exposure to influenza. In a randomized, double-blind, placebo-controlled challenge study among 92 healthy adults aged 18–41 years, the efficacy of inactivated and live attenuated influenza vaccines in preventing laboratory-documented influenza was 71% and 85%, respectively. The difference in efficacy between the two types of vaccine was not statistically significant.[13] In healthy persons younger than 65 years of age, inactivated influenza vaccine is approximately 70%–90% effective in preventing illness when the match between the vaccine strains and

circulating viruses is good.[14] The effectiveness of inactivated influenza vaccine in preventing hospitalization for pneumonia and influenza among persons 65 years of age and older living in settings other than nursing homes or similar long-term care facilities ranges from 30% to 70%.[15, 16] Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and death. Studies among this population have indicated that the inactivated vaccine can be 50%–60% effective in preventing hospitalization and pneumonia and 80% effective in preventing death, even though efficacy in preventing influenza illness may often be in the range of 30%–40%.[17, 18] Achieving a high rate of vaccination among nursing home residents can reduce the spread of infection in a facility through herd immunity, thus preventing disease.[19] Further, vaccination of nursing home staff has been associated with decreased mortality among residents, presumably by further lessening transmission from healthcare workers to patients.[20]

IV. Antiviral Drugs

Four antiviral medications in two classes are currently approved for use in the United States: the adamantanes—amantadine and rimantadine—and the neuraminidase inhibitors—zanamivir and oseltamivir. However, resistance of influenza A viruses to adamantanes can occur spontaneously or emerge rapidly during treatment.[21] During the 2005–06 influenza season, surveillance showed that more than 90% of influenza A(H3N2) viruses isolated in the United States were resistant to amantadine and rimatadine. Because of this, CDC recommended that the adamantanes not be used for treatment or chemoprophylaxis of influenza A infections.[22, 23] Testing of influenza virus isolates for antiviral resistance continues and these recommendations will be updated as needed.

Zanamivir and oseltamivir are active against both influenza A and B viruses. Zanamivir is approved for treatment of uncomplicated influenza in person 7 years of age and older and for chemoprophylaxis in persons 5 years of age and older. Oseltamivir is approved for treatment or chemoprophylaxis of influenza in persons 1 year of age and older. When administered prophylactically to healthy adults or children, oseltamivir and zanamivir are approximately 70%–90% effective in preventing illness from influenza A or B infection.[24–28] Resistance of influenza viruses to oseltamivir and zanamivir is also being monitored.

Rapid diagnosis of influenza illness occurring early in the season can be used to prompt members of target groups to receive vaccine before illness becomes widespread in the community.

V. Importance of Rapid Case Identification

Rapid identification of influenza virus infection can assist healthcare providers in determining optimal strategies for preventing or treating influenza. In an institutional setting this may include the administration of antiviral drugs to reduce the spread of influenza. Rapid diagnosis of influenza illness occurring early in the season can be used to prompt members of target groups to receive vaccine before illness becomes widespread in the community.

VI. Importance of Surveillance

Because influenza viruses undergo constant antigenic change, both virologic surveillance (in which influenza viruses are isolated for antigenic analysis) and disease surveillance are necessary to identify influenza virus variants, to monitor their health impact in populations, and to inform selection of influenza vaccine components each year. Knowledge of the prevalent circulating virus type can also assist healthcare providers in making treatment decisions. For example, if influenza activity has been confirmed in a community, antiviral drugs may be used to treat patients with influenza-like illness within 48 hours of onset of symptoms to reduce the length and severity of illness. With the increased use of antiviral drugs, virologic surveillance also is important for the identification of drug-resistant strains of influenza viruses. Finally, disease surveillance allows for identification of high-risk persons and for determining the effectiveness of current prevention strategies, and is used for refining vaccine and antiviral recommendations each year.

VII. Importance of Vaccination

Annual vaccination of persons at high risk for influenza

Vaccination against influenza remains the most important method of prevention. Annual vaccination against influenza is recommended for persons or groups at increased risk for influenza-associated complications and their close contacts. Previous vaccination may offer little or no protection against strains that have undergone substantial antigenic drift. Even when a vaccine component remains the same, immunity induced by the vaccine declines over time and may not be protective during the next season. Finally, while antiviral agents can be a useful adjunct to vaccination, chemoprophylaxis is not a substitute for vaccination.

Disease reduction goals

The U.S. Department of Health and Human Services has established a *Healthy People 2010* goal of increasing rates of pneumococcal and influenza vaccination among institutionalized adults and all persons age 65 and older to at least 90%, and to at least 60% among noninstitutionalized, high-risk persons age 18–64 years.[29]

Influenza infection cannot be diagnosed accurately based on signs and symptoms alone. Laboratory testing is necessary to confirm the diagnosis.

VIII. Case Definitions

Definitive diagnosis of influenza requires laboratory confirmation in addition to signs and symptoms. Case definitions for influenza-like illness vary depending on the purpose for which they are used. A case definition of fever 100°F or greater and cough or sore throat is used by CDC in its sentinel provider surveillance system, in which healthcare providers report the total number of patient visits and the number of patients seen for influenza like-illness each week.

IX. Laboratory Testing

Influenza infection cannot be diagnosed accurately based on signs and symptoms alone. Laboratory testing is necessary to confirm the diagnosis.

Although influenza infection generally leads to more severe illness among adults than other respiratory viruses, individual cases of influenza infection cannot be distinguished from other respiratory virus infections based on clinical information alone. Laboratory testing is necessary to confirm the diagnosis. Methods available for the diagnosis of influenza include virus isolation (standard methods and rapid culture assays), molecular detection (reverse transcriptase polymerase chain reaction [RT-PCR]), detection of viral antigens (enzyme immunoassays [EIA], immunofluorescent antibody [IFA] testing), commercially available rapid diagnostic kits, and less frequently, electron microscopy, and serologic testing.[30, 31] The state health department should be contacted for information regarding the availability of testing and the methods used.

For additional information on laboratory support for surveillance of vaccine preventable diseases, see Chapter 22, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases."

Virus isolation and rapid culture assays

Virus isolation is the gold standard for influenza diagnosis. Appropriate clinical specimens include nasal washes, nasopharyngeal aspirates, nasal and throat swabs, transtracheal aspirates, and bronchoalveolar lavage. Specimens should be taken within 72 hours of onset of illness. Influenza viruses can be isolated in fertilized chicken eggs or in tissue culture. The Madin Darby canine kidney cell line and primary rhesus or cynomolgus monkey kidney cells support the growth of influenza viruses. Virus isolation has the advantage of producing quantities of virus sufficient for full antigenic characterization, which is required for determining vaccine match. Standard isolation procedures have the disadvantage of requiring several days to obtain results, thereby making them less useful to the clinician.

Rapid culture assays that use immunologic methods to detect viral antigens in cell culture are available. The results of these assays can be obtained in 18–40 hours compared with an average of 4.5 days to obtain positive results from standard culture.[31]

Molecular testing methods

The use of molecular techniques to directly detect virus in respiratory samples can provide rapid identification of viruses. RT-PCR is a powerful technique for identifying influenza virus genomes even when they are present at very low levels. PCR can be used for detection of influenza viruses in original respiratory samples taken from patients with influenza-like illness, or for the characterization of viruses grown in tissue culture or embryonated eggs. PCR testing can be performed under biosafety level 2 conditions even for viruses such as avian influenza A(H5N1), which require biosafety level 3 with enhancements for viral culture.

Antigen detection assays

Several methods exist for the diagnosis of influenza infection directly from clinical material. Cells from the clinical specimen can be stained using an immunofluorescent antibody that reveals the presence of viral antigen. Nasal washes, nasopharyngeal aspirates, nasal and throat swabs, gargling fluid, transtracheal aspirates, and bronchoalveolar lavage are suitable clinical specimens. Commercially available kits test for the presence of viral antigens. Currently available test kits fall into three groups; the first detects only influenza type A viruses, while the second detects both influenza type A and B viruses but does not differentiate between virus types, and the third detects both influenza type A and B viruses and distinguishes between the two. Results of these rapid antigen detection tests can be available in less than 1 hour. Another less frequently used antigen detection method is immunostaining and visualization of viral antigens by electron microscopy. This method may be used for detection of influenza antigens in postmortem tissue samples.

When direct antigen detection or molecular detection methods are used for the diagnosis of influenza, it is important to collect and save an aliquot of the clinical sample for possible further testing. These samples may be used for culture confirmation of direct test results and isolation for subtyping influenza A isolates by the state public health laboratory. For some rapid testing methods the medium used to store the specimen is inappropriate for viral culture; in this case, it is necessary to collect two separate specimens.

Full antigenic characterization of the virus may be performed by the U.S. World Health Organization (WHO) Collaborating Center for Surveillance, Epidemiology, and Control of Influenza, Influenza Division, CDC. Characterization of isolates is necessary for the detection and tracking of antigenic variants, an essential part of the selection of optimal influenza vaccine components.

Serologic testing

While serologic testing can be useful in certain situations where viral culture is not possible or in special studies, serologic diagnosis of influenza is not accepted for the purposes of national surveillance because of a lack of standardized methods for testing and interpretation. Paired serum specimens are required for serologic diagnosis of influenza infection. The acute-phase specimen should be collected within 1 week of the onset of illness, and preferably within 2–3 days. The convalescent-phase sample should be collected approximately 2–3 weeks later. Hemagglutination inhibition tests are the preferred method of serodiagnosis. A positive result is a fourfold or greater rise in titer between the acute- and convalescent-phase samples to one type or subtype of virus. For example, if the initial serum dilution is 1:10, twofold serial dilutions would result in serum concentrations of 1:10, 1:20, 1:40, 1:80, etc. A fourfold or higher increase in titer between the acute- and convalescent-phase sera (e.g., from 1:20 to 1:80 or higher) is considered positive. A twofold increase between the two sera (e.g., from 1:20 to 1:40) is within the variability of the test and is not considered a positive finding. Vaccination history of the patient must also be taken into account to ensure that a rise in titer reflects infection rather than a recent influenza vaccination. Because most human sera contain antibodies to influenza, diagnosis of influenza cannot be made from a single serum sample.

X. Reporting

Influenza-associated deaths among children younger than 18 years of age and human infection with a novel influenza A virus are reported through the National Notifiable Diseases Surveillance System (NNDSS). Other influenza infections are not nationally notifiable but may be reported in some states. Local health departments should contact the state health department for guidelines on reporting individual cases or outbreaks of influenza.

Influenza surveillance in the United States consists of five categories of information collected from 10 data sources:

- Viral surveillance
  - U.S. WHO collaborating laboratories
  - National Respiratory and Enteric Virus Surveillance System (NREVSS)
  - Novel influenza A reporting
- Outpatient illness surveillance
  - Influenza Sentinel Provider Surveillance Network
  - BioSense Department of Veterans Affairs and Department of Defense Outpatient Surveillance
- Mortality surveillance
  - 122 Cities Mortality Reporting System
  - Influenza-associated pediatric mortality reporting
- Hospitalization surveillance
  - Emerging Infections Program (EIP)
  - New Vaccine Surveillance Network (NVSN)
- Summary of the geographic spread of influenza
  - State and territorial epidemiologists' reports of influenza activity level

In addition, outbreaks of influenza or influenza like illness may be reported to CDC from other sources, such as a state health department, a collaborating hospital or university laboratory, or an institution experiencing an outbreak.

WHO and NREVSS collaborating laboratories

Each week approximately 130 US WHO and NREVSS collaborating laboratories report the total number of specimens received for respiratory virus testing and the number of positive isolations of influenza A (H1N1), A (H3N2), A (not subtyped), or B. WHO collaborating laboratories report these data by age group (in years, less than 1, 1–4, 5–24, 25–44, 45–64, 65 and older, or unknown). The laboratories participating are in state or local health departments, universities, and hospitals. The information gathered through this system is either recorded on facsimile forms (CDC form CDC 55.31) and faxed to CDC, or transmitted to CDC via the Internet or the Public Health Laboratory Information System (PHLIS). A subset of the isolates obtained in these laboratories is submitted to the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at CDC for complete antigenic characterization and antiviral resistance testing.

Novel influenza A reporting

Human infection with a novel influenza A virus became a nationally notifiable condition in 2007. Cases can be reported through NNDSS

Influenza Sentinel Provider Surveillance Network

Each week from October through May, approximately 1,300 healthcare providers report the number of patient visits for the week and the number of those patients examined for influenza-like illness by age group in years (0–4, 5–24, 25–64, 65 and older). A subset of the providers continue to report year-round. The participating healthcare provider may collect nasal and throat swabs for virus isolation. Data are reported electronically to CDC either by Internet or fax (CDC form CDC 55.20) each week.

BioSense Department of Veterans Affairs (VA) and Department of Defense (DoD) Outpatient Surveillance

Approximately 350 DoD and 800 VA treatment facilities transmit information on outpatient visits by active military personnel and their dependents and veterans daily in the form of ICD-9 codes. The percentage of patient visits with any ICD-9 code for an acute respiratory infection is calculated by age group each week.

Emerging Infections Program

The EIP Influenza Project conducts surveillance for laboratory-confirmed influenza related hospitalizations in persons less than 18 years of age in 60 counties covering 12 metropolitan areas of 10 states (San Francisco CA, Denver CO, New Haven CT, Atlanta GA, Baltimore MD, Minneapolis/St. Paul MN, Albuquerque NM, Las Cruces NM, Albany NY, Rochester NY, Portland OR, and Nashville TN). Cases are identified by reviewing hospital laboratory and admission databases and infection control logs for children with a documented positive influenza test conducted as a part of routine patient care.

New Vaccine Surveillance Network (NVSN)

The New Vaccine Surveillance Network (NVSN) provides population-based estimates of laboratory-confirmed influenza hospitalization rates for children less than 5 years old residing in three counties: Hamilton County OH, Davidson County TN, and Monroe County NY. Children admitted to NVSN hospitals with fever or respiratory symptoms are prospectively enrolled and respiratory samples are collected and tested by viral culture and RT–PCR. NVSN estimated rates are reported every 2 weeks during the influenza season.

122 Cities mortality reporting system

Each week throughout the year the vital statistics offices of 122 cities report the total number of death certificates filed due to all causes for that week and the number of deaths for which pneumonia or influenza was mentioned in any position on the certificate. This information is reported to CDC each week by fax form or voice mail. A seasonal baseline is calculated, and if the proportion of deaths due to pneumonia and influenza (P&I) for a given week exceeds the baseline value for that week by a statistically significant amount, influenza related deaths are said to be above the epidemic threshold.

Influenza-associated pediatric mortality reporting

Influenza-associated pediatric mortality was added as a nationally notifiable condition in 2004. Laboratory-confirmed influenza-associated deaths in children less than 18 years old are reported through NNDSS.

State and territorial epidemiologists' reports

Each week from October through May, epidemiologists from each state and territory report the estimated level of influenza activity in their area as "no activity," "sporadic," "local," "regional," or "widespread." Sporadic activity is defined as small numbers of laboratory-confirmed influenza cases or a single influenza outbreak, but no increase in cases of influenza-like illness (ILI). Local activity is outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in a single region of the state. Regional activity is outbreaks of influenza or increases in ILI and recent laboratory-confirmed influenza in at least two but less than half the regions of the state. Widespread activity is outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in at least half the regions of the state. These reports come to National Center for Public Health Informatics (NCPHI), CDC, via the National Electronic Telecommunications System for Surveillance (NETSS).

The information sources used to make this determination vary from state to state. Reports of laboratory-diagnosed influenza and ILI reports from the sentinel provider network are used by most states. Some states may also include reports of increased visits for respiratory illness to hospital emergency departments, school or worksite absenteeism reporting, or nursing home surveillance. Local health departments should contact their state health department for state surveillance and reporting procedures.

XI. Enhancing Surveillance

A number of activities can improve the detection and reporting of influenza infections as well as the comprehensiveness, timeliness, and quality of reporting.

Expanding reporting period

Healthcare providers should be made aware that influenza cases can occur during any month of the year and that collecting and testing respiratory specimens during the summer months may provide valuable information about viruses likely to circulate during the upcoming influenza season.

Promoting awareness

Healthcare providers should also be aware of the ease with which influenza infection can be confirmed by laboratory tests and of the importance of reporting influenza surveillance information at local, state, and national levels. They should also know about the sources for influenza surveillance information.

Influenza surveillance information is available through the Internet at http://www.cdc.gov/flu/weekly/fluactivity.htm.

Influenza activity updates are also published periodically in the *Morbidity and Mortality Weekly Report (MMWR).*

Expanding sources of surveillance

Efforts should be made by state health departments to increase the number of sentinel physicians reporting influenza-like illness data each week to one participating physician per 250,000 population. Efforts should also be made to ensure that surveillance sites are geographically representative and cover all age groups.

Increasing awareness of local surveillance practices

State health departments should invite local health departments and healthcare providers to participate in existing surveillance systems. In addition, healthcare providers and surveillance personnel may be reminded of the importance of prompt reporting and reserving aliquots of clinical specimens used for rapid influenza antigen testing for possible virus isolation.

XII. Case Investigation

Any influenza A virus that cannot be subtyped should be sent by the state health department to the CDC Influenza Division immediately.

Individual cases of influenza typically are not investigated. Exceptions to this are severe or fatal illnesses from unusual complications of influenza infection (e.g., encephalitis, myocarditis, rhabdomyolysis). Individual cases should also be investigated when the infecting virus is suspected or confirmed to be of animal origin (most frequently swine or avian), and the state health department and CDC should be notified immediately. In such cases, investigators should attempt to identify exposure to animals and determine if the virus has been transmitted from human to human. Generally, animal influenza viruses are identified as influenza A viruses that cannot be subtyped by hemagglutination inhibition testing using the standard H3N2 and H1N1 antisera included in the influenza reagent kit distributed by CDC or by RT-PCR. Any influenza A virus that cannot be subtyped or that tests positive for a subtype other than H1N1 or H3N2 should be sent through the state health department to the CDC Influenza Division immediately. At the direction of the state health department, the Influenza Division may be contacted at 404-639-3591. Finally, guidelines for testing of suspect human cases of avian influenza A (H5N1), published by CDC in June 2006, are available at http://www2a.cdc.gov/han/ArchiveSys/ViewMsgV.asp?AlertNum=00246.

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