

Chapter 6: Influenza

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I. Disease Description

Influenza is an acute respiratory disease caused by infection with influenza 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. Because influenza seasons are unpredictable and often fluctuate in length and severity, the number of seasonal influenza-associated deaths varies from year to year. It is estimated that from the 1976-1977 season to the 2006-2007 influenza season, influenza-associated deaths ranged from 3,000 to 49,000 people.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, epidemics or pandemics 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, cats, ferrets, dogs, and whales. While influenza A viruses of only a few HA subtypes have been isolated from mammals, all of the known HA and NA subtypes have been isolated from avian species. The two influenza A virus 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) virus during the 2001–02 and 2002–03 influenza seasons. In April 2009, a novel influenza A (H1N1) virus, 2009 influenza A (H1N1), which was different from currently circulating influenza A (H1N1) viruses, emerged and its subsequent spread resulted in the first pandemic of the 21st century.

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 viruses 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 infect humans. A novel HA protein can include a virus of the same subtype but be dramatically antigenically different, as was seen during the

2009 H1N1 pandemic, where the HA likely came from a swine reservoir. 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. If the novel influenza A virus causes disease and is transmissible among humans, a worldwide epidemic called a pandemic may result. Novel influenza A viruses, but not influenza B viruses can cause influenza pandemics. During the 20th century, pandemics occurred in 1918 (A[H1N1]), 1957 (A[H2N2]), and 1968 (A[H3N2]). In April 2009, 2009 influenza A (H1N1) virus emerged to cause the first influenza pandemic in more than 40 years.

III. Vaccination

Annual influenza vaccination is recommended for all persons 6 months of age and older.⁸ Protection of persons at higher risk for influenza-related complications should continue to be a focus of vaccination efforts. When vaccine supply is limited, efforts should focus on delivering vaccination to protect persons at higher risk for severe influenza related complications, including the following groups:

- Children aged 6 months through 4 years (59 months)⁸⁻¹²
- Persons 50 years of age and older
- Women who are or will be pregnant during the influenza season
- Residents of nursing homes and other long-term care facilities that house persons of any age with chronic medical conditions
- Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Persons who are immunosuppressed, including immunosuppression caused by medications or by human immunodeficiency virus
- 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
- American Indians and Alaska Natives
- Persons who are morbidly obese (body-mass index ≥ 40)
- Health-care personnel
- Household contacts and caregivers of children aged <5 years and adults aged ≥ 50 years, particularly contacts of children aged < 6 months. (The pediatric group at greatest risk of complications is children younger than six months old. Influenza vaccines are not approved by the Food and Drug Administration [FDA] for use among children younger than six months.)⁸
- Household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications of influenza

In the United States, both inactivated and live attenuated influenza vaccines are available. The live attenuated influenza vaccine (LAIV), which is administered intranasally, is approved for use in healthy persons age 2 through 49 years. Inactivated vaccine (also called trivalent inactivated vaccine, or TIV) is administered by injection. Inactivated vaccines are available for use in persons 6 months of age and older. However, inactivated vaccines are available from several different manufacturers, and the recommended ages for individual brands of vaccines vary. For the 2010-11 influenza season, a newly approved inactivated TIV containing 60 mcg of HA per influenza vaccine virus strain (Fluzone High-Dose [Sanofi Pasteur]) was approved as an alternative inactivated vaccine for persons aged ≥ 65 years.⁸ An intradermal vaccine was licensed by the Food and Drug Administration (FDA) for use in adults 18-64 years beginning in the 2011-2012 influenza season. Information regarding the age group for whom a given vaccine is recommended can be found in the package insert.

Both LAIV and TIV are trivalent vaccines, containing three different influenza virus strains: influenza A (H3N2), influenza A (H1N1), and influenza B. Each year, vaccine strains are 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 effectiveness of influenza vaccines varies from season to season, and depends upon a number of factors. One factor is how well the vaccine strains match the viruses that actually circulate during the season. In addition, vaccine effectiveness is affected by the recipient's age, immunocompetence, and previous exposure to influenza viruses.

The best estimates of influenza vaccine efficacy come from randomized controlled trials (RCTs) that compare the rates of laboratory-confirmed influenza or an influenza-related outcome in persons who receive vaccine as with those who receive a placebo. It is not always feasible to perform randomized trials, however. For example, once a vaccine is recommended for use in a certain group, it is considered unethical to perform studies in which some people receive placebo, particularly among people who are recommended to receive vaccine (such as pregnant women, high risk individuals or people 65 years of age and older), because withholding vaccine from these groups could place them at risk for serious complications from influenza. For this reason, estimates of vaccine efficacy are usually derived from observational studies of vaccine effectiveness.

Historically, many studies of influenza vaccine efficacy and effectiveness have used nonspecific outcomes, such as influenza-like illness (ILI), hospitalizations, and all-cause mortality. Serologic evidence of influenza virus infection is also commonly used. The most accurate influenza vaccine efficacy and effectiveness estimates come from studies that use influenza-specific outcomes, such as laboratory-confirmed (e.g., by serology or RT-PCR) influenza virus infection. Such tests can be costly and take time to perform. As more and better diagnostic tests become available, more accurate and consistent assessments of influenza vaccine efficacy and effectiveness may be possible.

Recent RCTs of inactivated influenza vaccine among adults under 65 years of age have estimated 50-70% efficacy during seasons in which the vaccines' influenza A strains were well-matched to circulating influenza A viruses¹³⁻¹⁵ which is the usual situation. The benefits of vaccination may be reduced during seasons in which the vaccine strains are poorly matched to the circulating strains. For example, in a case-control study among persons during the 2004-2005 influenza season, where the predominant virus recovered from study patients was a drift variant of the influenza H3N2 vaccine strain, inactivated influenza vaccine effectiveness against laboratory confirmed influenza was 5% among study participants.¹⁶

Only one large randomized controlled trial of influenza vaccine has been conducted among an elderly population. During the 1991-1992 influenza season, a study of Dutch community dwelling people aged 60 years of age and older reported a vaccine efficacy of 58% (95% CI = 26% - 77%) against laboratory-confirmed influenza illness during a season which the vaccine strains were considered to be well-matched to circulating strains.¹⁷ There are no published studies of the efficacy or effectiveness of influenza vaccines in preventing laboratory-confirmed, serious outcomes of influenza such as hospitalization in the elderly.

Estimates of vaccine efficacy among children aged ≥ 6 months have varied by season and study design. In a randomized controlled trial among children aged 1-15 years, inactivated influenza vaccine efficacy was determined to be 77% against influenza A (H3N2) and 91% against influenza A (H1N1) virus infection.¹⁸ A randomized, double-blind, placebo-controlled trial conducted during two influenza seasons among children aged 6-24 months indicated that inactivated influenza vaccine had 66% efficacy against culture-confirmed influenza illness during the 1999-2000 influenza season but did not reduce culture-confirmed influenza illness substantially during the 2000-2001 influenza season.¹⁹

In a randomized, double-blind, placebo-controlled experimental influenza virus challenge study among 92 healthy adults aged 18-41 years, the efficacy of inactivated and live attenuated influenza vaccines in preventing laboratory-confirmed influenza was 71% and 85%, respectively. The difference in efficacy between the two types of vaccines was not statistically significant.²⁰

IV. Antiviral Drugs

Antiviral medications with activity against influenza viruses are an important adjunct to influenza vaccine in the control of influenza. Antiviral treatment can reduce the risk of complications from influenza and is recommended as early as possible for any patient with confirmed or suspected influenza who is hospitalized, has severe, complicated, or progressive illness, or is at higher risk for influenza complications. The benefits of antiviral treatment are likely to be greatest if treatment is started as soon as possible after illness onset, and evidence for benefit is strongest in studies in which treatment was started within 48 hours of illness onset.²¹ Antiviral treatment might still be beneficial in patients with severe, complicated, or progressive illness and in hospitalized patients when administered >48 hours from illness onset.²¹ In such cases, decisions on starting antiviral treatment should not wait for laboratory confirmation of influenza.

Four antiviral medications in two drug classes are currently approved for use in the United States: the adamantanes—amantadine and rimantadine—and the neuraminidase inhibitors—zanamivir and oseltamivir. However, only zanamivir and oseltamivir are currently recommended for use to prevent or treat influenza, due to high levels of influenza virus resistance to adamantanes among circulating influenza virus A strains.

Resistance of influenza A viruses to adamantanes can occur spontaneously or emerge rapidly during treatment.²² After the 2005–06 influenza season, resistance of influenza A (H3N2) viruses to amantadine and rimantadine increased dramatically and currently viruses of this subtype are resistant to these drugs. Almost all 2009 influenza A (H1N1) viruses are also resistant to amantadine and rimantadine. Because of this, CDC has recommended that the adamantanes not be used for treatment or chemoprophylaxis of influenza A virus infections.²³⁻²⁴ The adamantanes have no activity against influenza B virus infections.

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. Antiviral medications are not currently approved by the Food and Drug Administration (FDA) for use in children aged <1 year.²¹ However, oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants aged <1 year when indicated at the discretion of the treating physician.²¹ When administered prophylactically to healthy adults or children, oseltamivir and zanamivir are 70%–90% effective in preventing illness from influenza A or B virus infection.^{25–29} Resistance of influenza viruses to oseltamivir and zanamivir is being monitored, and as of March 2011–low levels of resistance among influenza A and influenza B viruses have been reported.³⁰

Persons at higher risk for influenza-associated complications recommended for antiviral treatment include:

- children aged <5 years (especially those aged <2 years);
- adults aged ≥65 years;
- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury) (8);
- persons with immunosuppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons aged ≤18 years who are receiving long-term aspirin therapy;
- American Indians/Alaska Natives;
- persons who are morbidly obese (i.e., BMI ≥40); and
- residents of nursing homes and other chronic-care facilities.

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 and used for antigenic and genetic analysis as well as for antiviral resistance testing) and disease surveillance are necessary to identify influenza new virus variants, to monitor their health impact in populations, and to provide data necessary for selection of influenza vaccine components each year. Knowledge of the prevalent circulating virus type/subtype 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 to determine the level of drug-resistance among circulating influenza viruses. Finally, disease surveillance allows for identification of high-risk persons, determination of the effectiveness of current prevention strategies, and refinement of vaccine and antiviral recommendations each year.

VII. Importance of Vaccination

Annual vaccination of persons at high risk for influenza

Vaccination against influenza is the most important method of prevention. Annual vaccination against influenza is recommended for all persons aged 6 months or older. Previous vaccination may offer little or no protection against viruses 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, treatment with licensed drugs is not a substitute for influenza vaccination.

Disease reduction goals

The U.S. Department of Health and Human Services has established the following *Healthy People 2020* goals:

- Increase the proportion of children and adults who are vaccinated against seasonal influenza each year, including institutionalized adults aged 18 years and older in long-term or nursing homes, health care personnel, and pregnant women.³¹
- Increase the number of public health laboratories monitoring influenza-virus resistance to antiviral agents.³¹

VIII. Case Definitions

Definitive diagnosis of influenza requires laboratory confirmation in addition to signs and symptoms. Case definitions for influenza-like illness are non specific for influenza and vary depending on the purpose for which they are used. A case definition of fever 100°F or greater, oral or equivalent, and cough and/or sore throat is used by CDC in its U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), 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 virus infection cannot be diagnosed accurately based on signs and symptoms alone. Laboratory testing is necessary to confirm the diagnosis.

Although influenza virus infection generally leads to more severe illness among adults than other respiratory viruses, individual cases of influenza cannot be distinguished from other respiratory virus infections based on clinical information alone. Methods available for the diagnosis of influenza include virus isolation (standard methods and rapid culture assays), molecular detection (reverse transcription polymerase chain reaction [RT-PCR]), detection of viral antigens (enzyme immunoassays [EIA] and immunofluorescence [DFA/IFA] testing), detection by commercially available rapid influenza diagnostic tests, and less frequently, by use of immunohistochemistry [IHC], and serologic testing.³²⁻³³ 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, see Chapter 22, “Laboratory Support for Surveillance of Vaccine-Preventable Diseases.”

Virus isolation and rapid culture assays

Virus isolation is essential for virologic surveillance. Appropriate clinical specimens used for virus isolation include nasal washes, nasopharyngeal aspirates, nasal and throat swabs, tracheal aspirates, and bronchoalveolar lavages. Specimens should be taken within 72 hours of onset of illness. Influenza viruses can be isolated in fertilized chicken eggs or in tissue cell culture. The Madin-Darby canine kidney (MDCK) 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, and conducting testing for antiviral resistance. 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 virus culture.³³

Molecular testing methods

RT-PCR is the most sensitive method for the detection of influenza virus and the gold standard for influenza diagnosis. 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. RT-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. RT-PCR testing with use of original clinical respiratory samples can be performed under biosafety level 2 conditions even for highly pathogenic viruses such as avian influenza A (H5N1) virus, which requires 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, transtracheal aspirates, and bronchoalveolar lavages are suitable clinical specimens. Commercially available rapid diagnostic kits test for the presence of viral antigens, although these tests are usually less sensitive than RT-PCR testing. Currently available rapid influenza diagnostic tests fall into two groups: tests that detect both influenza type A and B viruses but do not differentiate between virus types, and those that detect both influenza type A and B viruses and distinguish between the two. Results of these rapid influenza antigen detection tests can be available in 15 minutes or less. Another less frequently used antigen detection method is immunofluorescence using staining of respiratory specimens with monoclonal antibodies and visualization of viral antigens using a fluorescent microscope. This method and RT-PCR methods may also be used for detection of influenza antigens and nucleic acids, respectively, in postmortem respiratory 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 of 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 seasonal influenza using a single serum specimen is not accepted for the purposes of clinical diagnosis or national surveillance because of a lack of standardized methods for testing and interpretation. Paired serum specimens are required for serologic diagnosis of influenza virus 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 most commonly used for 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 viruses, 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 virus 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 nine data sources:

- Viral surveillance
 - U.S. WHO collaborating laboratories
 - National Respiratory and Enteric Virus Surveillance System (NREVSS)
 - Novel influenza A reporting
- Outpatient illness surveillance
 - U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet)
- Mortality surveillance
 - 122 Cities Mortality Reporting System
 - Influenza-associated pediatric mortality reporting
- Hospitalization surveillance
 - Influenza Hospitalization Network (FluSurv-NET)
 - Aggregate Hospitalization and Death Reporting Activity (AHDRA)
- 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

Approximately 80 U.S. **World Health Organization (WHO) Collaborating Laboratories** and 60 **National Respiratory and Enteric Virus Surveillance System (NREVSS)** laboratories located throughout the United States participate in virologic surveillance for influenza viruses. All state public health laboratories participate as U.S. WHO collaborating laboratories along with some county public health laboratories and some large tertiary care or academic medical centers. Most NREVSS laboratories participating in influenza surveillance are hospital laboratories. The U.S. WHO and NREVSS collaborating laboratories report the total number of respiratory specimens tested and the number positive for influenza virus types A and B each week to CDC. Most of the U.S. WHO collaborating laboratories also report the influenza A subtype (H1 or H3) of the viruses they have isolated and the ages of the persons from whom the specimens were collected. The majority of NREVSS laboratories do not report the influenza A virus subtype. Reports from both sources are combined and the weekly total number of positive influenza tests, by virus type/subtype, and the percent of specimens testing positive for influenza are presented in the weekly influenza update, FluView (<http://www.cdc.gov/flu/weekly/>). A subset of the influenza viruses collected by U.S. WHO collaborating laboratories are sent to CDC for further characterization, including gene sequencing, antiviral resistance testing and antigenic characterization.

Novel influenza A reporting

In 2007, human infection with a novel influenza A virus became a nationally notifiable condition. Novel influenza A virus infections include all human infections with influenza A viruses that are different from currently circulating human influenza H1 and H3 viruses. These viruses include those that are subtyped as nonhuman in origin and those that are unsubtypeable with standard laboratory methods and reagents. Rapid reporting of human infections with novel influenza A viruses will facilitate prompt detection and characterization of influenza A viruses and accelerate the implementation of effective public health responses.

U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet)

Information on patient visits to health care providers for influenza-like illness is collected through the **U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet)**. ILINet consists of more than 3,000 healthcare providers in all 50 states, the District of Columbia and the U.S. Virgin Islands reporting over 25 million patient visits each year. Each week, approximately 1,800 outpatient care sites around the country report data to CDC on the total number of patients seen and the number of those patients with influenza-like illness (ILI) by age group (0-4 years, 5-24 years, 25-49 years, 50-64 years, and ≥ 65 years). For this system, ILI is defined as fever (temperature of 100°F [37.8°C] or greater) and a cough and/or a sore throat in the absence of a KNOWN cause other than influenza. Sites with electronic records use an equivalent definition as determined by state public health authorities.

Additionally, data reports collected in ILINet are used to produce a measure of ILI activity by state. Activity levels range from minimal to intense and are arranged on a scale of 1-10 with 1 being the least intense and 10 being the most intense. The activity levels correspond with the given proportion of visits to outpatient clinics due to ILI, and the number of standard deviations from the mean proportion during non-influenza weeks the given value is. An activity level of 1 corresponds to values that are below the mean and an activity level of 10 corresponds with values that are 8 or more standard deviations above the mean. Because data at the state or jurisdiction level are variable, baselines are adjusted on a weekly basis based on which sites within each state or jurisdiction provide data. To perform this adjustment, provider level baseline ratios are calculated for providers that have a sufficient reporting history, and for providers that do not have the required reporting history they are assigned the baseline ratio for their practice type. The state level baseline is then calculated using a weighted sum of the baseline ratios for each contributing provider.

Influenza Hospitalization Network (FluSurv-NET)

FluSurv-NET conducts surveillance for population-based, laboratory-confirmed influenza related hospitalizations in children (persons less than 18 years) and adults. The network covers over 80 counties in the 10 Emerging Infections Program (EIP) states (CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN) and six additional states (ID, MI, OH, OK, RI and UT). Cases are identified by reviewing hospital laboratory and admission databases and infection control logs for children and adults with a documented positive influenza test (viral culture, direct/indirect fluorescent antibody assay (DFA/IFA), reverse transcription-polymerase chain reaction (RT-PCR), or a rapid influenza diagnostic test (RIDT)) conducted as a part of routine patient care. FluSurv-NET estimated hospitalization rates are reported every two weeks during the influenza season.

Aggregate Hospitalization and Death Reporting Activity (AHDRA)

States and territories collecting reports of laboratory-confirmed influenza-associated hospitalizations and deaths in their jurisdictions voluntarily share the reports with the Influenza Division at CDC. AHDRA reporting by state health departments allows tracking of detailed data and trends in severe disease with greater geographic representativeness than is possible with existing systems alone and informs decision-making at the state and national levels. States report laboratory-confirmed hospitalizations and deaths as aggregate weekly counts to a secure website with the following age groups: 0-4 years, 5-17 years, 18-49 years, 50-64 years, and ≥ 65 years.

122 Cities mortality reporting system

Each week, the vital statistics offices of 122 cities across the United States report the total number of death certificates received and the number of those for which pneumonia or influenza was listed as the underlying or contributing cause of death by age group (under 28 days, 28 days –1 year, 1-14 years, 15-24 years, 25-44 years, 45-64 years, 65-74 years, 75-84 years, and ≥ 85 years). The percentage of deaths due to pneumonia and influenza (P&I) are compared with a seasonal baseline and epidemic threshold value calculated for each week. The seasonal baseline of P&I deaths is calculated using a periodic regression model that incorporates a robust regression procedure applied to data from the previous five years. An increase of 1.645 standard deviations above the seasonal baseline of P&I deaths is considered the “epidemic threshold,” i.e., the point at which the observed proportion of deaths attributed to pneumonia or influenza was significantly higher than would be expected at that time of the year in the absence of substantial influenza-related mortality.

Influenza-associated pediatric mortality reporting

Influenza-associated deaths in children (persons less than 18 years) were added as a nationally notifiable condition in 2004. Any laboratory-confirmed influenza-associated death in a child is reported through this system. Demographic and clinical information are collected on each case and are transmitted to CDC.

State and territorial epidemiologists' reports

State health departments report the estimated level of spread of influenza activity in their states each week through the **State and Territorial Epidemiologists Reports**. States report influenza activity as no activity, sporadic, local, regional, or widespread. These levels are defined as follows:

- **No Activity:** No laboratory-confirmed cases of influenza and no reported increase in the number of cases of ILI.
- **Sporadic:** Small numbers of laboratory-confirmed influenza cases or a single laboratory-confirmed influenza outbreak has been reported, but there is no increase in cases of ILI.
- **Local:** Outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in a single region of the state.

- **Regional:** 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 with recent laboratory evidence of influenza in those regions.
- **Widespread:** Outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in at least half the regions of the state with recent laboratory evidence of influenza in the state.

Together, the five categories of influenza surveillance are designed to provide a national assessment of influenza activity. Human infections with novel influenza A viruses, pneumonia and influenza mortality from the 122 Cities Mortality System, influenza-associated pediatric deaths and AHDRA are reported on a national level only. FluSurv-NET data provides population-based, laboratory-confirmed estimates of influenza-related hospitalizations but are reported from limited geographic areas. Outpatient influenza-like illness and laboratory data are reported on a national level and by region. Outpatient influenza-like illness activity levels are reported by state. The state and territorial epidemiologists' reports of the geographic spread of influenza activity and the ILI activity indicator display state-level information. 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 virus 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 methods, accuracy, and limitations of laboratory testing for influenza virus infection 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/overview.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 explore the inclusion of electronic records in ILINet and to increase the number of ILINet providers 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 additional confirmation, including by RT-PCR or virus isolation.

XII. Case Investigation

Any influenza A virus that cannot be subtyped using standard methods and reagents 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 virus 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 or H1N1 antisera included in the influenza reagent kit distributed by CDC or by CDC 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 during business hours. After hours, please contact the CDC emergency response hotline at 770-488-7100.

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