

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, pregnant women, 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 overall burden seasonal influenza varies from year to year. During 2010–11 through 2015–16, it is estimated that the seasonal impact of influenza ranged from 9.2 million to 35.6 million illnesses; 4.3 million to 16.7 million medical visits; 140,000 to 710,000 hospitalizations; and 12,000 to 56,000 deaths.⁶

II. Background

Influenza viruses can be divided into 4 types; A, B, C, and D. Influenza type C viruses are not associated with severe disease, epidemics, or pandemics, and influenza D viruses primarily affect cattle and are not known to infect or cause illness in people, so neither will be discussed further here. Influenza type A viruses are divided into subtypes based on surface proteins called hemagglutinin (HA) and neuraminidase (NA).⁷ There are 16 hemagglutinin and 9 neuraminidase subtypes that circulate in a variety of avian species, and a restricted subgroup of these have infected other animals, such as pigs, horses, cats, ferrets, dogs, and marine mammals (seals and whales). A few bat species were recently shown to be infected by influenza viruses originally designated as new influenza A subtypes H17N10 and H18N11.^{8,9} However, these viruses were shown to be incompetent for reassortment with other influenza A viruses, a hallmark of the species, indicating that they are not true influenza A viruses.¹⁰

The two influenza A virus subtypes have cocirculated in human populations since 1977: influenza A (H1N1) and A (H3N2). Reassortment between 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, influenza A(H1N1)pdm09—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 B viruses are not divided into subtypes, but are further broken down into 2 lineages: Yamagata and Victoria.



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 efficiently transmitted 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, the influenza A (H1N1) pdm09 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 who do not have contraindications.¹¹ 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 (no hierarchy implied by the order of listing):¹¹

- Children 6 months of age through 4 years (59 months) of age
- Persons 50 years of age and older
- Adults and children with chronic pulmonary (including asthma), cardiovascular (except isolated 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
- Women who are or will be pregnant during the influenza season
- 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
- Residents of nursing homes and other long-term care facilities that house persons of any age with chronic medical conditions
- American Indians and Alaska Natives
- Persons who are extremely obese (body-mass index [BMI] ≥ 40)
- Health-care personnel, including physicians, nurses, and other workers in inpatient and outpatient-care settings, medical emergency-response workers (e.g., paramedics and emergency medical technicians), employees of nursing home and long-term care facilities who have contact with patients or residents, and students in these professions who will have contact with patients.
- Household contacts and caregivers of children <5 years of age and adults ≥ 50 years of age, particularly contacts of children <6 months of age. (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.)
- Household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications of influenza

In the United States, a variety of influenza vaccine products are licensed and available from several different manufacturers. As of March 2017, these include 1) unadjuvanted, egg-based trivalent and quadrivalent inactivated influenza vaccines (IIV3s and IIV4s, respectively); 2) adjuvanted trivalent egg-based inactivated influenza vaccines (aIIV3); 3) a high-dose trivalent egg-based inactivated influenza

vaccine (HD-IIV3); 4) a quadrivalent cell culture-based inactivated influenza vaccine (ccIIV4); and 5) a recombinant trivalent influenza vaccine (RIV3). Inactivated and recombinant vaccines are administered by intramuscular injection, with the exception of one that is administered intradermally. Each vaccine is approved for a specific age group. Information regarding the age group for whom a given vaccine is recommended can be found in the package insert. Vaccines are available that are licensed for persons as young as 6 months of age. For many vaccine recipients, more than 1 type or brand of vaccine might be appropriate within licensed indications and Advisory Committee on Immunization Practices (ACIP) recommendations. In such cases, any licensed, age-appropriate influenza vaccine product should be used.

The live attenuated influenza vaccine (LAIV), which is administered intranasally, is approved for use in healthy persons 2 through 49 years of age. However, in light of low effectiveness against influenza A(H1N1)pdm09 in the United States during the 2013–14 and 2015–16 seasons, ACIP (June, 2016) made the interim recommendation that LAIV not be used during the 2016–17 and 2017–2018 seasons.¹¹ As more information becomes available, this interim recommendation will be updated if necessary.

Trivalent vaccines contain 3 different influenza virus strains: influenza A (H3N2), influenza A (H1N1), and influenza B. Quadrivalent vaccines include the same influenza virus strains as trivalent vaccines plus a virus strain from the other influenza B lineage. Each year, vaccine strains are selected to represent the strains judged most likely to circulate during the influenza season in the United States. Typically, 1 or 2 of the 3 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. During the 2015–16 season, it was estimated that influenza vaccine prevented 5 million influenza illnesses; 2.5 million medical visits; 71,000 influenza hospitalizations; and 3,000 pneumonia and influenza deaths. The total number of influenza-associated respiratory and circulatory deaths is between 2 and 4 times greater than the estimates for pneumonia and influenza deaths.⁶

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. However, once a vaccine is recommended for use in a population, it is difficult to perform randomized trials, 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.

Estimates of influenza vaccine effectiveness are also affected by the outcome under study. Historically, many studies of influenza vaccine efficacy and effectiveness have used nonspecific outcomes, such as influenza-like illness (ILI), hospitalizations, and all-cause mortality, or serologic evidence of influenza virus infection. However, the most accurate influenza vaccine efficacy and effectiveness estimates come from studies that use influenza-specific outcomes, such as laboratory-confirmed (e.g., by culture or reverse transcription polymerase chain reaction [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.

In 2012, a systematic review and meta-analysis of influenza vaccine efficacy and effectiveness was conducted. Efficacy of trivalent inactivated influenza vaccine was found in 8 of 12 seasons analyzed in 10 randomized controlled trials, with a pooled efficacy against RT-PCR or culture-confirmed influenza of 59% for adults 8 through 65 years of age.¹² The RCTs described in this analysis estimated vaccine effectiveness of approximately 50%–70% among adults in this age group during some seasons in which the vaccines' influenza A strains were well-matched to circulating influenza A viruses,^{13–15} However, vaccine effectiveness can be lower, or not statistically significant, even in seasons of apparently good match.^{15, 16} Moreover, the benefits of vaccination may be of substantially reduced or of no benefit during seasons in which the vaccine strains are poorly matched to the circulating viruses (as was noted, Examples of this dies conducted were the 2004–05 and 2014–15 influenza seasons, where in case control studies found that the predominant viruses were drift variants of the influenza H3N2 vaccine virus.^{17–19} In addition, there is some evidence that prior season vaccination may affect current season vaccine effectiveness however the impact noted, if any, varies by season and study.^{20–27}

Most data concerning vaccine effectiveness among community-dwelling older adults comes from observational studies. One large randomized controlled trial was conducted among a community-dwelling population of adults 60 years of age and older during the 1991–92 influenza season, a season in which the vaccine strains were considered to be well matched to circulating strains. This study reports a vaccine efficacy of 58% (95% CI = 26%–77%) against serologically defined influenza illness.²⁸ Rather than culture or RT-PCR confirmation of influenza infection, influenza illness in this study is defined as seroconversion in the setting of symptomatic illness compatible with influenza. Concern has been raised that use of such outcomes may lead to overestimation of vaccine effectiveness. A 2010 review of studies of community-dwelling elderly found that IIV3 was not significantly effective against laboratory confirmed influenza or ILI.²⁹ A re-analysis of these data using a different stratification method and outcomes measure estimated vaccine effectiveness for laboratory-confirmed influenza of approximately 49%.³⁰ A 2014 published systematic review, which included pooled data from 35 case-control studies of community-dwelling elderly, found influenza vaccine was effective against laboratory confirmed influenza during periods of regional or widespread influenza activity.³¹ A case-control study of community-dwelling adults ≥65 years of age found that influenza vaccine during the 2010–11 season was associated with an overall 42% reduction in hospitalizations for laboratory confirmed influenza, with a higher reduction for influenza A(H1N1) (90%) than for influenza A(H3N2) (40%).³² The desire to improve vaccine effectiveness among adults ≥65 years of age has led to the development and licensure of vaccines intended to promote a better immune response in this population including a high-dose and adjuvanted trivalent vaccine. A large randomized comparative efficacy trial of high-dose versus standard-dose trivalent vaccine in persons ≥65 years of age during the 2011–12 and 2012–13 seasons found 24.2% greater relative efficacy for the high-dose for protection against laboratory confirmed influenza caused by any viral type or subtype associated with protocol-defined ILI.³³

Estimates of vaccine efficacy among children ≥6 months of age have varied by season and study design. In a randomized controlled trial among children 1–15 years of age, inactivated influenza vaccine efficacy was determined to be 77% against influenza A (H3N2) and 91% against influenza A (H1N1) virus infection.³⁴ A single season placebo controlled study of children 3–19 years of age using culture or serology to identify influenza infection found the efficacy of inactivated vaccine was 56% among those 3–9 years of age and 100% for those 10–18 years of age.³⁵ A randomized, double-blind, placebo-controlled trial conducted during 2 influenza seasons indicated that, among children 6–24 months of age, 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 2000–01 influenza season.³⁶

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; evidence for benefit is strongest in studies in which treatment was started within 48 hours of illness onset.^{37–41} 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.³⁷ In such cases, decisions on starting antiviral treatment should not wait for laboratory confirmation of influenza.

Five licensed antiviral medications in 2 drug classes are currently available in the United States: the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (zanamivir, oseltamivir, and peramivir). However, only the neuraminidase inhibitors are currently recommended for use to prevent or treat influenza, due to high levels of resistance to adamantanes among circulating influenza virus A strains.^{42,43} The adamantanes have no activity against influenza B virus infections. Zanamivir, oseltamivir, and peramivir are active against both influenza A and B viruses. Zanamivir is an inhaled antiviral 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 an oral drug approved by the Food and Drug Administration (FDA) for treatment of acute uncomplicated influenza in persons 14 days and older, and for chemoprophylaxis of influenza in persons 1 year of age and older. Although it is not included in the drug's FDA-approved indications, use of oral oseltamivir for treatment of influenza in

infants 3 months to 1 year of age, is recommended by the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics. If a child is younger than 3 months old, use of oseltamivir for chemoprophylaxis is not recommended unless the situation is judged critical, due to limited data in this age group.^{44,45} 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.^{46–50} A third neuraminidase inhibitor, peramivir, is given as an intravenous infusion and is approved for treatment of uncomplicated influenza in persons 18 years of age and older.

The majority of recently circulating influenza viruses are susceptible to the neuraminidase inhibitor antiviral medications, oseltamivir, zanamivir, and peramivir; however, rare sporadic instances of resistant viruses have been detected worldwide.^{41–53} It is also possible that some influenza viruses become resistant to oseltamivir and peramivir during antiviral treatment with 1 of these agents and remain susceptible to zanamivir; this has been reported most often for influenza A (H1N1) viruses.^{54–57} It is important to review annual recommendations and updates published by CDC before prescribing influenza antiviral medications (see <https://www.cdc.gov/flu/professionals/antivirals/index.htm>).

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

- children <5 years of age (especially those <2 years of age);
- adults ≥65 years of age;
- 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);
- persons with immunosuppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons ≤18 years of age 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 ILI 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 6 months of age 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 18 years of age and older in long-term or nursing homes, health care personnel, and pregnant women.⁵⁸
- Increase the number of public health laboratories monitoring influenza-virus resistance to antiviral agents.⁵⁸

VIII. Case Definitions

Definitive diagnosis of influenza requires laboratory confirmation in addition to signs and symptoms. Case definitions for influenza-like illness are nonspecific 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 ILI 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,
- use of immunohistochemistry [IHC], and
- serologic testing using hemagglutination inhibition or microneutralization.^{59,60}

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.”

Specimen collection

Specimen collection and shipping are important steps in obtaining laboratory diagnosis or disease confirmation. Guidelines have been published for specimen collection and handling for viral and microbiologic agents (<https://stacks.cdc.gov/view/cdc/7590>). Information is also available on using CDC laboratories as support for reference and disease surveillance (<https://www.cdc.gov/nceid/dsr/specimen-management-branch.html>); this includes

- a central website (<https://www.cdc.gov/laboratory/specimen-submission/index.html>) for requesting lab testing;
- the form required for submitting specimens to CDC (See Appendix 23, Form # CDC 0.5034);

- information on general requirements for shipment of etiologic agents (Appendix 24; <https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix24-etiological-agent.pdf>)—although written to guide specimen submission to CDC, this information may be applicable to submission of specimens to other laboratories; and
- the CDC Infectious Diseases Laboratories Test Directory (<https://www.cdc.gov/laboratory/specimen-submission/list.html>), which contains not only a list of orderable tests for that institution, but also detailed information on appropriate specimen types, collection methods, specimen volume, and points of contact.

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. While most older human influenza viruses could be isolated in 10-day old fertilized chicken eggs or in specific cell cultures, contemporary human A(H3N2) viruses do not replicate well in eggs. The Madin-Darby canine kidney (MDCK) cell line and primary rhesus or cynomolgus monkey kidney cells generally support the replication of influenza viruses. Specialized MDCK cells that express high level of mammalian type receptors are needed for contemporary H3N2 viruses. Virus isolation has the advantage of producing quantities of virus sufficient for full antigenic characterization, which is required for determining if the current vaccine elicits antibodies that neutralize circulating strains and for 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.⁵³

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 levels below the limit of detection by virus isolation. RT-PCR can be used for detection of influenza viruses in original respiratory samples taken from patients with ILI, or for the characterization of viruses grown in cell culture or embryonated eggs. RT-PCR testing of original clinical respiratory samples can be performed under biosafety level 2 conditions; however, all work with potentially infectious material should be performed in a biosafety cabinet and with appropriate personal protective equipment.

Antigen detection assays

Several methods exist for the diagnosis of influenza infection directly from clinical material: 1) cells from a clinical specimen can be stained using an immunofluorescent antibody that reveals the presence of viral antigen; 2) nasal washes, nasopharyngeal aspirates, nasal and throat swabs, transtracheal aspirates, and bronchoalveolar lavages are suitable clinical specimens; and 3) commercially available rapid diagnostic kits test for the presence of viral antigens, although these tests are usually less sensitive (generally approximately 50%–70%) than RT-PCR testing.^{61–64} Currently available rapid influenza diagnostic tests fall into 2 groups: the tests that either detect both influenza type A and B viruses but do not differentiate between virus types, or 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 or microneutralization tests are most commonly used for serodiagnosis. A positive result is a 4-fold or greater rise in titer between the acute- and convalescent-phase samples to 1 type or subtype of virus. For example, if the initial serum dilution is 1:10, 2-fold serial dilutions would result in serum concentrations of 1:10, 1:20, 1:40, 1:80, etc. A 4-fold 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 2-fold increase between the 2 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 and Case Notification

Case reporting within a jurisdiction

Each state and territory has regulations and laws governing the reporting of diseases and conditions of public health importance.⁶⁵ These regulations and laws list the diseases that are to be reported, and describe those persons or institutions responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Detailed information on reportable conditions in each state is available through the Council of State and Territorial Epidemiologists.

Case notification to CDC

Influenza-associated deaths among children younger than 18 years of age and human infection with a novel influenza A virus are nationally notifiable conditions 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. Case notification should not be delayed because of incomplete information or lack of confirmation. The state in which the patient resides at the time of diagnosis should submit the case notification to CDC.

Influenza surveillance in the United States consists of 5 categories of information collected from 9 data sources:

- Viral surveillance
 - U.S. WHO collaborating laboratories
 - National Respiratory and Enteric Virus Surveillance System (NREVSS)
 - Novel influenza A reporting
- Outpatient illness surveillance
 - ILINet
- Mortality surveillance
 - National Center for Health Statistics (NCHS) mortality surveillance data
 - Influenza-associated pediatric mortality reporting
- Hospitalization surveillance
 - Influenza Hospitalization Network (FluSurv-NET)

- Summary of the geographic spread of influenza
 - State and territorial epidemiologists' reports of influenza activity level

In addition, outbreaks of influenza or ILI 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 100 public health and more than 300 clinical laboratories located throughout all 50 states, Puerto Rico, and the District of Columbia participate in virologic surveillance for influenza through either the U.S. World Health Organization (WHO) Collaborating Laboratories System or the National Respiratory and Enteric Virus Surveillance System (NREVSS). Influenza testing practices differ in public health and clinical laboratories and both sources provide valuable information for monitoring influenza activity. Clinical laboratories primarily test respiratory specimens for diagnostic purposes and data from these laboratories provide useful information on the timing and intensity of influenza activity. Public health laboratories primarily test specimens for surveillance purposes to understand which influenza viruses are circulating throughout their jurisdiction and the population groups being affected. A subset of specimens from clinical laboratories may be submitted to public health laboratories for further testing. In order to use each data source most appropriately and to avoid duplication, reports from public health and clinical laboratories have been presented separately in both FluView (<http://www.cdc.gov/flu/weekly/>) and FluView Interactive (<https://www.cdc.gov/flu/weekly/fluviewinteractive.htm>) beginning in the 2015–16 influenza season. All public health and clinical laboratories report each week to CDC the total number of respiratory specimens tested and the number positive for influenza viruses, along with age or age group of the person, if available. Data presented from clinical laboratories include the weekly total number of specimens tested, the number of positive influenza tests, and the percent positive by influenza virus type. Data presented from public health laboratories include the weekly total number of specimens tested, the number of positive influenza tests, and the number by influenza virus type, subtype, and influenza B lineage. In order to obtain enough specimens to produce this detailed information in an efficient manner, public health laboratories often receive samples that have already tested positive for an influenza virus at a clinical laboratory. As a result, monitoring the percent of specimens testing positive for an influenza virus in a public health laboratory is less useful (i.e., we expect a higher percent positive). Fortunately, it is not necessary to monitor this parameter when clinical laboratory data are available.

In addition, the age distribution of influenza positive specimens reported from public health laboratories is visualized in FluView and FluView Interactive. The number and proportion of influenza virus-positive specimens by influenza A virus subtype and influenza B virus lineage are presented by age group (0–4 years, 5–24 years, 25–64 years, and ≥ 65 years) each week and cumulative totals are provided for the season. A subset of the influenza viruses collected by public health laboratories are sent to CDC for further characterization, including antiviral resistance testing and antigenic and/or genetic characterization, and this information is presented in the antiviral resistance and virus characterization sections of the FluView report.

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 cannot be subtyped using the CDC Influenza rRT-PCR Diagnostic Panel. Rapid detection and reporting of human infections with novel influenza A viruses—viruses to which there is little to no pre-existing immunity—is very important as it facilitates prompt identification and characterization of influenza A viruses with pandemic potential and accelerates 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 ILI is collected through the ILINet, which consists of more than 3,000 healthcare providers in all 50 states, the District of Columbia, and the U.S. Virgin Islands that report more than 36 million patient visits each year. Each week, approximately 2000 outpatient

healthcare providers around the country report data to CDC on the total number of patients seen for any reason and the number of those patients with 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. The percentage of patient visits to healthcare providers for ILI reported each week is weighted on the basis of state population and compared to a national baseline.

Additionally, data collected in ILINet are used to produce a measure of ILI activity for all 50 states, Puerto Rico, the District of Columbia, and New York City. Activity levels are based on the percent of outpatient visits to in a jurisdiction due to ILI compared with the average percent of ILI visits that occur during weeks with little or no influenza virus circulation (non-influenza weeks). Because the number of sites reporting each week is variable, baselines are adjusted each week based on which sites within each jurisdiction provide data. To perform this adjustment, provider-level baseline ratios are calculated for those that have a sufficient reporting history. Providers that do not have the required reporting history they are assigned the baseline ratio for their practice type. The jurisdiction level baseline is then calculated using a weighted sum of the baseline ratios for each contributing provider. The activity levels compare the mean reported percent of visits due to ILI for the current week to the mean reported percent of visits due to ILI for non-influenza weeks. The 10 activity levels correspond to the number of standard deviations below, at or above the mean for the current week compared with the mean of the non-influenza weeks. There are 10 activity levels classified as minimal (levels 1–3), low (levels 4–5), moderate (levels 6–7), and high (levels 8–10). An activity level of 1 corresponds to values that are below the mean, level 2 corresponds to an ILI percentage less than 1 standard deviation above the mean, level 3 corresponds to ILI more than 1, but less than 2 standard deviations above the mean, and so on, with an activity level of 10 corresponding to ILI 8 or more standard deviations above the mean.

Influenza hospitalization network (FluSurv-NET)

FluSurv-NET conducts surveillance for population-based, laboratory-confirmed influenza related hospitalizations in children (persons less than 18 years of age) 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 3 additional states (MI, OH, and UT). Cases are identified by reviewing hospital laboratory and admission databases and infection control logs for patients hospitalized during the influenza season with a documented positive influenza test (viral culture, direct/indirect fluorescent antibody assay (DFA/IFA), molecular assays including RT-PCR, or a rapid influenza diagnostic test [RIDT]) conducted as a part of routine patient care. Data gathered are used to estimate age-specific hospitalization rates on a weekly basis during the influenza season and to describe characteristics of persons hospitalized with associated influenza illness. Laboratory-confirmation is dependent on clinician-ordered influenza testing. Therefore, the rates provided are likely to be underestimated as influenza-associated hospitalization can be missed, either because testing was not performed, or because cases may be attributed to other causes of pneumonia or other common influenza-related complications.

NCHS mortality surveillance data

NCHS collects death certificate data from state vital statistics offices for all deaths occurring in the United States. Pneumonia and influenza (P&I) deaths are identified based on ICD-10 multiple cause of death codes. NCHS surveillance data are aggregated by the week of death occurrence and as a result, P&I percentages based on the NCHS surveillance data are released 2 weeks after the week of death to allow for collection of enough data to produce a stable P&I percentage. The NCHS surveillance data based on P&I percentage for earlier weeks are continually revised and may increase or decrease as new and updated death certificate data are received from the states by NCHS. 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 5 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 of age) 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 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 5 categories of influenza surveillance are designed to provide a national assessment of influenza activity. FluSurv-NET data provides population-based, laboratory-confirmed estimates of influenza-related hospitalizations but the data are reported from limited geographic areas. NCHS mortality surveillance data are reported on the national, Department of Health and Human Services (HHS) regional, and state-level. Outpatient ILI and laboratory data are reported on a national level and by HHS 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 map display state-level information. Human infections with novel influenza A viruses and influenza-associated pediatric deaths are reported on the state-level but no personal identifying information is released.

It is important to maintain a comprehensive system for influenza surveillance for several reasons.

- Influenza viruses are constantly evolving to escape immune pressure and thus ongoing data collection and characterization of the strains are required.
- Influenza strains can rapidly undergo genetic and/or antigenic changes leading to annual epidemics and infrequent pandemics of influenza; surveillance of viruses will detect these changes.
- Vaccines must be administered annually and are updated regularly based on surveillance findings.
- Treatment for influenza is guided by laboratory surveillance for antiviral resistance.
- National responses to emerging pandemic strains are triggered by surveillance data.
- Varying segments of the population are affected by influenza and may require targeted interventions. These groups are determined through influenza surveillance.

It is important to remember the following about influenza surveillance in the United States.

- All influenza activity reporting by public health partners and health care providers is voluntary.
- The reported information answers the questions of where, when, and which influenza viruses are circulating. It can be used to determine if influenza activity is increasing or decreasing, but cannot be used to ascertain how many people have become ill with influenza during the influenza season. Estimates of disease burden are made using mathematical models.
- The system consists of 8 complementary surveillance components in 5 categories. These components include reports from more than 350 laboratories, 2,800 outpatient health care providers, NCHS, research and health care personnel at the FluSurv-NET sites, and influenza surveillance coordinators and state epidemiologists from all state, local, and territorial health departments.

- Influenza surveillance data collection is based on a reporting week that starts on Sunday and ends on Saturday of each week. Each surveillance participant is requested to summarize weekly data and submit it to CDC by Tuesday afternoon of the following week. Those data are then downloaded, compiled, and analyzed at CDC. FluView (<https://www.cdc.gov/flu/weekly>) and FluView Interactive (<https://www.cdc.gov/flu/weekly/fluviewintactive.htm>) are updated weekly each Friday.

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

Health care 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; see <https://www.cdc.gov/mmwr/index.html>).

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 to reserve aliquots of clinical specimens used for rapid influenza antigen testing for possible additional confirmation, such as by RT-PCR.

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. Guidelines are provided to state public health laboratories annually.

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 using CDC RT-PCR kits. Any influenza A virus that cannot be subtyped or that tests positive for a subtype other than H1N1pdm09 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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This document can be found at: www.cdc.gov/vaccines/pubs/surv-manual/chpt06-influenza.html

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