Influenza, Influenza-Associated Pediatric Mortality, and Novel Influenza A

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Overview(1,2)

Influenza is a contagious upper respiratory tract disease that begins with the sudden onset of fever, headache, extreme tiredness, cough (usually dry), sore throat, body aches and nasal congestion. As the disease progresses the cough becomes more prominent. Less common symptoms such as abdominal pain, nausea vomiting, and diarrhea are more likely to occur in children. Symptoms usually resolve in 5-7 days.

Cases of influenza occur in greater numbers during the winter months usually peaking in January and February with 5% to 20% of the population becoming ill each flu season. Some people such as senior citizens, young children, especially children <2 years of age, and persons with certain health conditions are at high risk for serious flu complications. Bacterial pneumonia, ear infections, sinus infections, dehydration, and worsening of chronic medical conditions such as congestive heart failure, asthma, or diabetes may occur. Children may have severe neurologic complications that range from febrile seizures to severe encephalopathy and encephalitis. Reye syndrome has also been associated with influenza infection.

Influenza is spread mainly person-to-person through droplets created with coughing and sneezing by persons infected with the virus. The flu virus can survive for hours on solid surfaces, particularly in lower temperatures and lower humidity. Infection occurs when a person has contact with the droplets in the air or touching contaminated surfaces then touching mouth or nose. The incubation period is usually 1 to 4 days with a mean of 2 days. A healthy adult is infectious from one day before symptoms to 5 to 7 days after symptoms begin. Children may be contagious for a longer period of time.

Three types of seasonal influenza virus are recognized: A, B, and C. Influenza A and B cause the greatest disease burden in humans and are included in the seasonal vaccine. Influenza A is divided into subtypes based on two surface glycoproteins: hemagglutinin (H) and neuraminidase (N). Aquatic birds are generally the reservoir for influenza A. Influenza A viruses have infected many different animals, including ducks, chickens, pigs, whales, horses, and seals. However, certain subtypes of influenza A virus are specific to certain species, except for birds, which are hosts to all known subtypes of influenza A. Subtypes that have caused widespread illness in people either in the past or currently are H3N2, H2N2, H1N1, and H1N2. H1N1 and H3N2 subtypes also have caused outbreaks in pigs, and H7N7 and H3N8 viruses have caused outbreaks in horses. Influenza A viruses normally seen in one species sometimes can cross over and cause illness in another species. For example, until 1998, only H1N1 viruses circulated widely in the U.S. pig population. Influenza B is not divided into subtypes. Humans are the primary reservoir of the B virus.

**Influenza Pandemics:** A pandemic is defined by the emergence and global spread of a new influenza A virus subtype to which the population has little or no immunity and that spreads
rapidly from human to human. Pandemics, therefore, can lead substantially to increased morbidity and mortality rates compared with seasonal influenza. During the 20th century, there were 3 influenza pandemics, in 1918 (H1N1), 1957 (H2N2), and 1968 (H3N2). The pandemic in 1918 killed at least 20 million people in the United States and perhaps as many as 50 million people worldwide. A severe pandemic could overwhelm the health care system and disrupt critical societal functions. 2009 H1N1 (referred to as “swine flu” early on) is a new influenza virus causing illness in people. This new virus was first detected in people in the United States in April 2009. On June 11, 2009, the World Health Organization (WHO) signaled that a global pandemic of 2009 H1N1 influenza was underway by raising the worldwide pandemic alert level to Phase 6. This action was a reflection of the spread of the new 2009 H1N1 virus, not the severity of illness caused by the virus. At the time, more than 70 countries had reported cases of 2009 H1N1 infection and there were ongoing community level outbreaks of 2009 H1N1 in multiple parts of the world.

For a more complete description of Influenza, refer to the following texts:

- Control of Communicable Diseases Manual (CCDM)
- Red Book, Report of the Committee on Infectious Diseases
- Epidemiology and Prevention of Vaccine-Preventable Diseases, Centers for Disease Control and Prevention

Case Definition - Influenza

**Clinical description:**
Influenza is an acute viral disease of the respiratory tract characterized by abrupt onset of fever, myalgia, headache, severe malaise, nonproductive cough, sore throat and rhinitis. Without laboratory confirmation, influenza is referred to as “influenza-like illness” (ILI).

**Clinical case definition:**
Without laboratory confirmation, the ILI case definition used by CDC for national surveillance is fever $\geq 100^\circ$ Fahrenheit or $37.8^\circ$ Celsius and cough and/or sore throat (in the absence of a known cause). Influenza is commonly recognized by epidemiologic characteristics. Influenza illness may be indistinguishable from other viral respiratory illnesses based on symptoms alone.

**Laboratory criteria for diagnosis:**
- Virus isolation by cell culture
- CLIA certified laboratory Immunofluorescence, Influenza Enzyme Immuno Assay (EIA), or Reverse transcription-polymerase chain reaction (RT-PCR)
- CLIA waived Commercial rapid non-culture diagnostic tests for influenza virus
- *Four-fold rise in antibody titer between the acute and convalescent serum specimens.
Case classification:
*Confirmed*: a case that is laboratory confirmed by virus culture, rapid diagnostic tests, or a four-fold rise in antibody titer between the acute and convalescent serum.

* Note: Serology tests available from reference laboratories that rely on the results of a single acute serum specimen are not to be considered confirmatory.

Case Definition - Influenza-Associated Pediatric Mortality

An influenza-associated death is defined for surveillance purposes as death resulting from a clinically compatible illness that was confirmed to be influenza by an appropriate laboratory or rapid diagnostic test. There should be no period of complete recovery between the illness and death. Influenza-associated deaths in all person ages <18 years should be reported.

*A death should not be reported if:*
- There is no laboratory confirmation of influenza virus infection.
- The influenza illness is followed by full recovery to baseline health status prior to death.
- The death occurs in a person 18 years or older.
- After review and consultation there is an alternative agreed upon cause of death.

Case classification:
*Confirmed*: A death meeting the clinical case definition that is laboratory confirmed. Laboratory or rapid diagnostic test confirmation is required as part of the case definition; therefore, all reported deaths will be classified as confirmed. Refer to the laboratory criteria for diagnosis noted above in the influenza case definition.

Case Definition – Novel A Infections, Human

Clinical description:
An illness compatible with influenza virus infection.

Laboratory Evidence:
A human case of infection with an influenza A virus subtype that is different from currently circulating human influenza H1 and H3 viruses. Novel subtypes include, but are not limited to, H2, H5, H7, and H9 subtypes. Influenza H1 and H3 subtypes originating from a non-human species or from genetic reassortment between animal and human viruses are also novel subtypes. Novel subtypes will be detected with methods available for detection of currently circulating human influenza viruses at state public health laboratories (e.g., real-time reverse transcriptase polymerase chain reaction [RT-PCR]). Non-human influenza viruses include avian subtypes (e.g., H5, H7, or H9 viruses), swine and other mammalian subtypes. Confirmation that an influenza A virus represents a novel virus will be performed by CDC’s influenza laboratory.
Criteria for epidemiologic linkage: a) the patient has had contact with one or more persons who either have or had the disease and b) transmission of the agent by the usual modes of transmission is plausible. A case may be considered epidemiologically linked to a laboratory-confirmed case if at least one case in the chain of transmission is laboratory confirmed.

**Case Classification:**
- **Confirmed:** A case of human infection with a novel influenza A virus confirmed by CDC’s influenza laboratory.
- **Probable:** A case meeting the clinical criteria and epidemiologically linked to a confirmed case, but for which no laboratory testing for influenza virus infection has been performed.
- **Suspected:** A case meeting the clinical criteria, pending laboratory confirmation. Any case of human infection with an influenza A virus that is different from currently circulating human influenza H1 and H3 viruses is classified as a suspected case until the confirmation process is complete.

**Comment**
For additional information about influenza or influenza surveillance, refer to CDC the CDC Influenza web site: [http://www.cdc.gov/flu/](http://www.cdc.gov/flu/).

An outbreak of infections with a new influenza A virus that demonstrates human-to-human transmission could signal the beginning of the next pandemic. Robust epidemiologic and laboratory surveillance systems are required for a coordinated public health response to infections with a novel influenza virus subtype. Early detection of an influenza virus with pandemic potential will permit identification of viral characteristics (e.g., genetic sequence, antiviral susceptibility, and virulence) that will affect clinical management and public health response measures. It should also facilitate development of a virus-specific vaccine and testing strategies.

All state public health laboratories have the capacity to test respiratory specimens for influenza viruses with sensitive and specific assays that can detect human and non-human influenza A viruses. They also have the capacity to subtype currently circulating human influenza A H1, H3, and avian H5 (Asian lineage) viruses. The detection or confirmation by a state public health laboratory of an influenza A virus that is unsubtypable with standard methods (e.g., real-time RT-PCR assays for human influenza A(H3) or (H1) viruses), or a non-human influenza virus (e.g., H5) from a human specimen, could be the initial identification of a virus with pandemic potential.
Information Needed for Investigation

Reported influenza cases do not typically require further investigation. However, there are situations when an investigation is necessary including influenza associated outbreaks, pediatric mortality, or identification of a novel influenza virus. Special circumstances may also arise with influenza surveillance that would necessitate further investigation. Additional investigation guidelines would be provided.

Verify the diagnosis. Determine the basis of the diagnosis. What laboratory tests were conducted? What were the results? What are the case’s clinical symptoms?

Establish the extent of illness. If the patient works outside the home, attends school or childcare, or resides in a health care facility, determine if co-workers, schoolmates, other patients, or family members have been ill with the same set of symptoms. This can be done by questioning the patient, the patient’s family, the school or childcare facility, or the health care facility management.

Notification

- Contact the **District Communicable Disease Coordinator**, or the **Senior Epidemiology Specialist**, or the Department of Health and Senior Services’ Situation Room (DSR) at 800-392-0272 (24/7) immediately if an outbreak is suspected, or when cases are in high-risk settings such as health care facilities or among the children or employees of child care centers.
- Contact the Bureau of Environmental Health Services at (573) 751-6095 and the Section for Child Care Regulation at (573) 751-2450, if the case is associated with a child care center.
- Contact the Section for Long Term Care Regulation at (573) 526-8524, if cases are associated with a long term-care facility.
- Contact the Bureau of Health Services Regulation at (573) 751-6303, if cases are associated with a hospital, hospital-based long-term care facility, or ambulatory surgical center.

Control Measures

General control measures to prevent additional cases include:

- Get vaccinated against the flu: The best way to protect against the flu – seasonal or 2009 H1N1 – is to get vaccinated. **Importantly, infants less than 6 months of age** represent a particularly vulnerable group because they are too young to receive the seasonal or 2009 H1N1 influenza vaccine; as a result, individuals responsible for caring for these children constitute a high-priority group for early vaccination.
Immunizations:

**Seasonal Influenza**

Yearly flu vaccination is the best way to prevent becoming ill with influenza. The two types of vaccine are inactivated vaccine given as a shot and nasal-spray flu vaccine made with live, weakened flu viruses. Although anyone who wants to reduce their chances of getting the flu can get vaccinated, those persons at high risk of having serious flu-related complications or because they live with or care for high risk persons should have yearly vaccinations. CDC has yearly recommendations for high risk groups. Refer to the Morbidity and Mortality Weekly Report (MMWR), Prevention and Control of Influenza: Recommendations of the Advisory committee on Immunization Practices (ACIP). (This is published annually in April at: http://www.cdc.gov/vaccines/pubs/ACIP-list.htm

**2009 H1N1 Influenza**

Influenza A is subject to reassortant of genes creating flu virus that people have little or no immunity and for which there is no vaccine. Since availability of vaccine could be limited, prioritized groups are established with each new virus.

No shortage of 2009 H1N1 vaccine is expected, but vaccine availability and demand can be unpredictable and there is some possibility that initially, the vaccine will be available in limited quantities. So, the ACIP has made recommendations regarding which people should be prioritized if the vaccine is initially available in extremely limited quantities. The groups recommended to receive the 2009 H1N1 influenza vaccine include:

- **Pregnant women** because they are at higher risk of complications and can potentially provide protection to infants who cannot be vaccinated;
- **Household contacts and caregivers for children younger than 6 months of age** because younger infants are at higher risk of influenza-related complications and cannot be vaccinated. Vaccination of those in close contact with infants younger than 6 months old might help protect infants by “cocooning” them from the virus;
- **Healthcare and emergency medical services personnel** because infections among healthcare workers have been reported and this can be a potential source of infection for vulnerable patients. Also, increased absenteeism in this population could reduce healthcare system capacity;
- **All people from 6 months through 24 years of age:**
  - Children from 6 months through 18 years of age because cases of 2009 H1N1 influenza have been seen in children who are in close contact with each other in school and day care settings, which increases the likelihood of disease spread, and
  - Young adults 19 through 24 years of age because many cases of 2009 H1N1 influenza have been seen in these healthy young adults and they often live, work, and study in close proximity, and they are a frequently mobile population; and
- **Persons aged 25 through 64 years who have health conditions associated with higher risk of medical complications from influenza.**

For more information see http://www.cdc.gov/h1n1flu/vaccination/acip.htm
• Educate ill persons to stay home when ill.
• Encourage hand hygiene and respiratory etiquette of both people who are well and those who have any symptoms of flu: Wash hands frequently with soap and water when possible; keep hands away from your nose, mouth, and eyes; and cover noses and mouths with a tissue when coughing or sneezing (or a shirt sleeve or elbow if no tissue is available).
• Persons at high risk for flu complications who become ill with flu-like illness should call their health care provider as soon as possible to determine if they need antiviral treatment. Early treatment (within 48 hours of the onset of illness) with antiviral medications can decrease the risk of severe illness from influenza.

Antivirals

Seasonal Influenza
In the United States, four prescription antiviral medications (oseltamivir, zanamivir, amantadine and rimantadine) are approved for treatment and chemoprophylaxis of influenza. Since January 2006, the neuraminidase inhibitors (oseltamivir, zanamivir) have been the only recommended influenza antiviral drugs because of widespread resistance to the adamantanes (amantadine, rimantadine) among influenza A (H3N2) virus strains. The neuraminidase inhibitors have activity against influenza A and B viruses while the adamantanes have activity only against influenza A viruses. In 2007-08, a significant increase in the prevalence of oseltamivir resistance was reported among influenza A (H1N1) viruses worldwide. During the 2007-08 influenza season, 10.9% of H1N1 viruses tested in the U.S. were resistant to oseltamivir.

2009 H1N1 Influenza
CDC recommends the use of oseltamivir or zanamivir for the treatment and/or prevention of infection with 2009 H1N1 influenza viruses. Oseltamivir (brand name Tamiflu®) is approved to both treat and prevent influenza A and B virus infection in people one year of age and older. Zanamivir (brand name Relenza®) is approved to treat influenza A and B virus infection in people 7 years and older and to prevent influenza A and B virus infection in people 5 years and older. Updated Interim Recommendations for the Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009-2010 Season may be found at: http://www.cdc.gov/h1n1flu/recommendations.htm

• 2009 H1N1 Flu Clinical and Public Health Guidance can be found at: http://www.cdc.gov/h1n1flu/guidance/
• If an outbreak is reported at a school, hospital, nursing home, or other group setting, and the facility is unable to arrange for rapid diagnostic influenza testing, contact the District Communicable Disease Coordinator or the State Influenza Coordinator to arrange for viral culture kits from the Missouri State Public Health Laboratory (SPHL). Instruct the facility to properly collect throat swabs of symptomatic patients, residents or staff, and send the specimens to the SPHL for virus culture testing and strain identification.
Laboratory Procedures

Laboratory testing at the SPHL is limited to sentinel site surveillance and outbreak investigations. Routine laboratory testing is not provided.

**Specimen Collection:**
Inadequate or inappropriate specimen collection, storage, and transport are likely to yield false negative test results. Training in specimen collection is highly recommended due to the importance of specimen quality.

Specimen types acceptable for influenza culture and RT-PCR testing include nasopharyngeal swabs, nasal swabs, throat swabs, nasal aspirates, and dual nasopharyngeal/throat swabs.

Specimens should be collected in the acute stage of the illness, kept in viral transport media, and refrigerated immediately. Whenever possible, specimens should be shipped so they will not arrive in the laboratory over the weekend or on a holiday, and will arrive within 7 days of collection. Postage-paid mailers are provided to sentinel sites, and the state laboratory courier service is provided free of charge. Click here for the “Collection and Submission of Seasonal Influenza Specimen” instructions and additional information regarding testing is available at: [http://health.mo.gov/lab/](http://health.mo.gov/lab/).

**Testing:**

Contact the District Communicable Disease Coordinator or District Senior Epidemiology Specialist when viral culture testing is indicated for a facility or community outbreak. Viral specimens should be collected on patients within the first 4 days of illness. The ideal time for viral culturing is within the first three days of symptom onset. Be sure to label the specimen with the date of collection and the patient’s name. Any specimens that are received by the laboratory without patient names will be discarded without testing.

- **Viral culture** testing is considered the gold standard and is performed at the SPHL. This avenue of testing is available during outbreaks and for Missouri physicians participating in the U.S. Influenza Sentinel Physician Surveillance Network. Viral culture testing may take up to 3 weeks for strain identification; therefore it is not suitable for diagnosis in determining treatment options.

- **PCR:** The same specimens submitted for viral culture testing will be used for PCR to test for influenza. The specimen submitted will be tested and reported within the week it is received. PCR testing is used to quickly identify influenza outbreaks or novel strains of influenza that may be circulating. Regardless of the PCR result, viral isolation will still be performed on the specimen since an isolate is still needed to do further antigenic typing.

- **Rapid Diagnostic Tests:** The sensitivity and specificity of these rapid tests is usually dependent on the type of test, the quality of specimen collected, the time it was collected and on the amount of virus collected in the specimen. Pharyngeal swabs and nasal washes or aspirates yield the best specimens, as these will contain more mucous and cellular material than a throat swab. Many of the rapid tests are done in physicians offices and are
now on the CLIA waived test list. Depending on the product, these tests can detect the presence of influenza A/B undifferentiated, influenza type A alone, or influenza type B alone in throat swabs or nasal wash specimens. The specimen must be collected early in the onset of the illness and contain sufficient cellular material and mucous to receive reliable results.

- **Blood** serology may be used for laboratory confirmation of influenza, but is not the recommended procedure for routine diagnosis. If a unique or a new strain (subtype) of influenza virus is suspected, this method may prove valuable. The laboratory diagnosis will be based on a four-fold rise in antibody titer between the acute and convalescent specimens of serum. CDC laboratories do a limited number of specialized serology tests each year. **CALL the District Communicable Disease Coordinator, the District Senior Epidemiology Specialist, or the State Influenza Surveillance Coordinator at the Bureau of Communicable Disease Control and Prevention for direction before collecting serum specimens.** The SPHL will fill out D.A.S.H. lab flow sheets (CDC 50.34) to send with these specimens.

**Reporting Requirements**

**General reporting information:**

- **Influenza cases** are reported in aggregate through WebServ by Local Public Health Agencies. Results by laboratories other than SPHL are part of the aggregate report. Laboratory Confirmed Influenza shall be reported on a weekly basis in aggregate form to the local health authority or to the Missouri Department of Health and Senior Services. Viral cultures from private laboratories will generally not have the detailed antigenic information; the hemagglutinin (H) and neuraminidase (N) antigen results. Therefore, results from private laboratories should be entered into the aggregate system.

- **Cases** confirmed through SPHL are entered into WebServ by the Bureau of Communicable Disease Control and Prevention (BCDCP). The SPHL is the primary source of culture confirmed testing, therefore positive influenza isolates from the SPHL will be entered into WebServ by name along with other information contained on the lab slip to include hemagglutinin (H) and neuraminidase (N) antigen results (e.g. H3N2).
  
  - When additional information is available from the CDC, these results will also be entered. All positive influenza results from the SPHL are reported to the BCDCP, where the cases will be entered.
  
  - The cases will be entered with a “confirmed” status and a “closed” resolution. No further follow-up is required and paper lab slips will not be sent to the Districts for dissemination to the LPHAs. These cases will appear, and are available for review, when the LPHA uses the notify function in WebServ. (The 2009 H1N1 virus is currently the circulating influenza virus and should be entered in WebSurv as discussed above for influenza cases.)
PCR tests can be performed more rapidly with results available earlier than the culture results. As soon as the culture information is available from the SPHL, BCDCP will update the information in WebServ.

- **Mortality** of children <18 years: For all cases, complete a “Disease Case Report” (CD-1). For all confirmed cases, complete the CDC Influenza-Associated Pediatric Deaths Case Report Form. Laboratory Confirmed Influenza-Associated Pediatric Mortality shall be reported within one (1) day to the local health authority or to the Department of Health and Senior Services.

- **Novel Influenza**: For all confirmed and probable cases, complete a “Disease Case Report” (CD-1). Novel Influenza should be reported within one (1) day to the local health authority or to the Department of Health and Senior Services. (Missouri considers the 2009 H1N1 virus to be the circulating influenza A virus.)

**Outbreak Reporting Information:**

- For **school or child care outbreaks/closures**, complete the “Influenza Outbreak/School Closure Information form” and forward the completed document to District Communicable Disease Coordinator, the District Senior Epidemiology Specialist, or the State Influenza Surveillance Coordinator.

- For **outbreaks in health care facilities**, nursing homes, residential care facilities or rehabilitation facilities, complete the “Institutional Influenza Investigation Report” and forward the completed document to the District Communicable Disease Coordinator, the District Senior Epidemiology Specialist, or the State Influenza Surveillance Coordinator.

- For **outbreaks in all other settings**, complete the Missouri Outbreak Surveillance Form (CD-51) and forward the completed document to the District Communicable Disease Coordinator, the District Senior Epidemiology Specialist, or the State Influenza Surveillance Coordinator.

- An **outbreak summary** should be submitted within 90 days from the conclusion of the outbreak:
  - When the outbreak occurs in health care facilities, nursing homes, residential care facilities, rehabilitation facilities, school, child care center, or
  - When significant resources are applied by either the Local or State Health Department to intervene with the outbreak.

- The outbreak summary may be waived as necessary.

- Submit the final outbreak summary to the District Communicable Disease Coordinator, the District Senior Epidemiology Specialist, or the State Influenza Surveillance Coordinator.

For more detailed reporting information through WebServ click here: [http://dhssnet/ehcdp/FluReptIndex.htm](http://dhssnet/ehcdp/FluReptIndex.htm)

To view the entire reporting rule click here:
References


Other Sources of Information – Web Sites

6. Centers for Disease Control and Prevention, “Interim Guidance on Case Definitions to be Used For Investigations of Novel Influenza A (H1N1) Cases*” http://www.cdc.gov/h1n1flu/casedef.htm (1 June 2009)