Influenza-Associated Pediatric Deaths (Laboratory-Confirmed)

PROTOCOL CHECKLIST

☐ Establish communication channels with Medical Examiners (prior to event) to ensure effective communication during case investigations; communicate information about what to report and when to report

☐ Enter available information into Merlin upon receipt of initial report

☐ Notify the Bureau of Epidemiology regarding the case investigation

☐ Review information on the disease and its epidemiology (see page 3), surveillance case definition (see page 6), and laboratory testing (see page 7)

☐ Prioritize reported cases for follow up, and investigate and interview as appropriate (see page 9)

☐ Contact provider, if necessary, to gather more information

☐ Interview reporting physician

☐ Review disease facts (see page 3)

☐ Modes of transmission

☐ Incubation period

☐ Symptoms

☐ Ask about exposure to relevant risk factors (see page 9)

☐ Identify symptomatic contacts

☐ Determine if an infected patient or symptomatic contact was in a sensitive situation (see page 12)

☐ Recommend exclusions for those infected or symptomatic contacts (see page 12)

☐ Provide education on controlling further spread for symptomatic patients (see page 10)

☐ Address family’s questions or concerns

☐ Follow-up on special situations, including outbreaks or infected persons in relevant sensitive situations (see page 12)

☐ Complete EpiCom post(s)

☐ Complete death certificate review

☐ Enter additional data obtained from interview into Merlin (see page 11)
Influenza-Associated Pediatric Deaths

1. DISEASE REPORTING

A. Purpose of reporting and surveillance

1. To identify severe or unusual influenza strains capable of causing severe outcomes; these can either be novel or seasonal strains with higher pathogenicity or changes in pathogenicity;

2. To document influenza-associated pediatric mortality and associated risk factors for influenza mortality;

3. To determine pediatric mortality rates for laboratory-confirmed influenza (including type of influenza virus infection associated with mortality);

4. To detect possible influenza outbreaks and mitigate further influenza transmission;

5. To mitigate influenza transmission through public health, medical, and behavioral interventions;

6. To create evidence-based primary influenza prevention;

7. To provide data used to monitor influenza vaccine effectiveness.

B. Legal reporting requirements

Laboratories, physicians, and hospitals are required to report deaths of persons under the age of 18 infected with influenza to the county health department (CHD) immediately (24 hours a day, seven days a week) by phone. If there is suspicion of an influenza-associated death in a person under the age of 18, please report even in the absence of laboratory confirmation of influenza. Health departments should also communicate pediatric influenza mortality reporting requirements prior to events to local health care partners such as:

- Medical Examiners
  - Medical examiners often review cases of influenza-associated pediatric deaths and as such are an important reporting resource

- Laboratories
- Physicians
- Hospitals

Prior notification of reporting requirements to local healthcare partners will ensure effective communication and response during a case investigation.

C. County health department investigation responsibilities

Pediatric influenza mortality investigations are often complex requiring coordination with the Bureau of Epidemiology (DCBE) and Bureau of Public Health Laboratories (BPHL) and medical examiners. Additionally, interviews of grieving family members can be challenging. Much of the case investigation can often be completed through
review of medical records, interviews with medical personnel (infection preventionists, nurses, physicians), and medical examiners.

1. Prioritize reported cases for follow-up (see Section 5 for more information)
   a. Group 1: pediatric mortality cases that are part of an outbreak or are in a sensitive situation.
   b. Group 2: pediatric mortality cases that could be due to infection from a novel strain (see Guide to Surveillance and Investigation chapter on novel or pandemic influenza); suspected novel influenza infection at the time of initial report would likely be due to identified travel history or animal exposure.
   c. Group 3: cases occurring in previously vaccinated individuals and those treated with antivirals where antiviral resistance is suspected.
   d. Group 4: all other reported influenza-associated pediatric mortality cases.

2. Follow up with prioritized cases and administer appropriate measures to control further spread of influenza, as appropriate. See Section 6 for recommendations on controlling further spread of influenza.

3. Notify the DCBE at the initiation of the case investigation.

4. Locate all available respiratory pre-mortem specimens or isolates; facilitate collection of post-mortem specimens. Facilitate specimen collection and submission to the BPHL.


6. Complete EpiCom post(s).

7. Review reported cases by street address, reporting source, race, ethnicity, age group, onset or report date, etc. to detect possible clusters of infected individuals.

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic agent

There are two main types of influenza that cause seasonal infections in humans: influenza A and influenza B. Influenza A viruses are divided into subtypes based on the hemagglutinin (H) and neuraminidase (N) proteins on their surfaces. The structure of these surface proteins changes frequently due to antigenic drift, resulting in regular changes in the specific strains of circulating seasonal influenza. The strains included in the influenza vaccine are re-evaluated each year and changed to respond to or anticipate changes in the predominating strains of influenza in the northern and southern hemispheres.

Since 1977, three influenza virus subtypes have been in widespread seasonal circulation: influenza A H3N2, influenza A H1N1, and influenza B. In April 2009, a novel H1N1 virus was identified from several U.S. states and Mexico and caused the first influenza pandemic of the 21st century. This virus is no longer considered “novel” and is circulating as a seasonal strain. Influenza A is typically associated with more severe outcomes (such as mortality) than influenza B. In addition, seasonal
influenza A H3 has previously been found to be more likely to lead to death than influenza A H1.

Note: Human infections due to avian and swine influenza viruses are considered novel virus infections. In recent years, humans have been infected with avian-origin viruses in Asia and Europe such as influenza A (H5N1) and influenza A (H7N9) as well as swine-origin viruses in the United States such as variant influenza A H3N2. Cases under investigation, probable, and confirmed cases of human infection with novel or pandemic strains of influenza A are reportable in Florida for all ages. More information on novel strains of influenza A can be found at http://www.floridahealth.gov/diseases-and-conditions/diseases-from-animals/novel-influenza-viruses.html. Additionally, please refer to the Guide to Surveillance and Investigations Chapter for Novel or Pandemic Influenza.

B. Description of illness

An influenza-associated death is defined, for surveillance purposes, as a 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.

Patients with influenza infection may have symptoms that include fever, chills, cough, headache, sore throat and other upper respiratory tract symptoms (rhinorrhea), myalgias, arthralgias, fatigue, vomiting, and diarrhea. Symptoms can be minimal.

Complications of influenza can include primary viral pneumonia, secondary bacterial pneumonia, ear infections, sinus infections, dehydration, worsening of chronic medical conditions (such as congestive heart failure, asthma, or diabetes), and death.

Generally, those at higher risk for influenza-related complications include: children younger than 5 years of age, adults 65 years and older, pregnant women, and persons with chronic medical conditions such as asthma, chronic obstructive pulmonary disease (COPD), morbid obesity, immunosuppressive therapy or disease, diabetes, hemoglobinopathy, and neuromuscular disease. American Indians and Alaska Natives may also be at higher risk for flu complications. Available at: http://www.cdc.gov/flu/about/disease/high_risk.htm

C. Reservoirs

Reservoirs for influenza A viruses include humans, swine, poultry, woodland birds and other mammals. Humans are the primary reservoir for influenza B.

D. Modes of transmission

Death itself is not transmissible. Influenza viruses are primarily spread person-to-person primarily through large-particle respiratory droplet transmission. Transmission via large-particle droplets requires close proximity between source and recipient persons because droplets do not remain suspended in the air and generally travel only a short distance (< 6 feet). Other possible routes of influenza transmission are mucosal contamination from hands touching contaminated surfaces and airborne
transmission. The relative contribution of each type of transmission has not been fully defined but airborne transmission is thought to be small.

Avian influenza is transmitted from birds to humans directly or through environmental contamination. Only rare cases of person-to-person transmission of avian influenza have been reported and have involved close personal contact.

E. Incubation period

There is no incubation period for death. There should be no period of complete recovery between the illness and death.

The incubation period for influenza is typically 1–4 days, but can range from 1–7 days.

F. Period of communicability

There is very little to no communicability of influenza after death.

The period of communicability for currently identified pandemic influenza viruses has been found as long as three weeks after initial infection. Viral shedding generally occurs from one day prior up to 5–10 days following initial illness onset, although communicability decreases rapidly 24 hours after fever resolves (without fever reducing medication). Communicability prior to illness onset and early in illness makes control challenging. This is due to the fact that people are infectious to others before they feel sick and are likely to continue to move about in the population spreading the virus without recognizing their role in infecting others. Persons who continue to be ill longer than 7 days after illness onset should be considered potentially contagious until symptoms have resolved. Children, especially younger children, can shed influenza virus for 10 or more days. Immunocompromised persons may shed virus for weeks or months.

G. Treatment

N/A

While cases are often reported to the CHD following death, if severe cases are reported prior to death, antiviral medication should be initiated as early as possible for patients with suspected or confirmed influenza who: 1) have severe or progressive illness or 2) are at higher risk for influenza complications. Antiviral treatment is most effective when started within 48 hours of illness onset and treatment should not be delayed while laboratory results are pending.

Centers for Disease Control and Prevention (CDC) provides recommendations for antiviral medications: http://www.cdc.gov/flu/professionals/antivirals/index.htm. In addition, CDC’s Flu View provides weekly data on antiviral resistance patterns for circulating strains, which are available at http://www.cdc.gov/flu/weekly/.

Additional therapy such as antibiotics should be used at the discretion of the provider based on the patient’s clinical presentation. Secondary bacterial pneumonia infections can be caused by *Staphylococcus aureus* (both methicillin-sensitive and
methicillin-resistant) and Streptococcus pneumoniae. These secondary infections can be very serious including leading to death. Clinical guidance for community-acquired pneumonia should be followed and can be accessed on the American Thoracic Society website at: http://www.thoracic.org/statements/index.php.

H. Prophylaxis

N/A

Seasonal influenza vaccination has been found to lessen severe outcomes (such as death) even if influenza infection occurs. Annual, seasonal influenza vaccination prior to the start of influenza season is recommended for individuals who may be at risk of severe influenza complications.

Vaccination:
Routine annual influenza vaccination is recommended for all persons 6 months and older. Annual vaccination is particularly important for persons at increased risk of complications and for persons in contact with those at high-risk for complications including (http://www.cdc.gov/flu/protect/vaccine/index.htm):
1. Children less than 5 years old, but particularly those under 2 years old;
2. Pregnant women;
3. People 50 years of age and older;
4. People of any age with certain chronic health conditions such as asthma and other pulmonary disease, diabetes, hepatic disease, hematologic abnormalities, neurologic or neuromuscular abnormality, immunosuppressive disease or therapy, cancer in the past year, or cardiovascular disease;
5. Persons who live in nursing homes and other long-term care facilities;
6. Children receiving long-term aspirin therapy;
7. American Indians/Alaska Natives;
8. People who are morbidly obese;
9. Household contacts of person at high-risk for complications from influenza;
10. Household contacts and out-of-home caregivers of children < 5 years old and adults > 50 years old, but particularly contacts of children under 6 months of age;
11. Health care workers.

Chemoprophylaxis:
In general, post-exposure chemoprophylaxis should not be started more than 48 hours after the last exposure. Inform asymptomatic contacts to stay home if they develop symptoms of early influenza-like illness.

3. CASE DEFINITION

A. Clinical description

An influenza-associated death is defined for surveillance purposes as a 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 persons aged < 18 years should be reported.
A death should not be reported if:
1. There is no laboratory confirmation of influenza virus infection;
2. The influenza illness is followed by full recovery to baseline health status prior to death;
3. The death occurs in a person 18 years or older;
4. After review and consultation, there is an alternative agreed-upon cause of death.

B. Case classification

Confirmed: A laboratory-confirmed influenza-associated death is defined as a death resulting in directly or indirectly from a clinically compatible illness that was confirmed to be influenza by an appropriate laboratory test. There should be no period of complete recovery between the illness and death. Laboratory criteria for diagnosis include:
1. Influenza virus isolation in tissue cell culture from respiratory specimens;
2. Reverse-transcriptase polymerase chain reaction (RT-PCR) testing of respiratory specimens;
3. Immunofluorescent antibody staining (direct or indirect) of respiratory specimens;
4. Rapid influenza diagnostic testing of respiratory specimens;
5. Immunohistochemical (IHC) staining for influenza viral antigens in respiratory tract tissue from autopsy specimens;
6. Fourfold rise in influenza hemagglutination inhibition (HI) antibody titer in paired acute and convalescent sera.

C. Criteria for epidemiologic linkage

The patient has had contact with one or more persons who either have or had the disease AND transmission of the agent by the usual modes of transmission is plausible.
OR
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.

4. LABORATORY TESTING

A. Criteria for diagnosis

Diagnostic laboratory tests for influenza include viral culture, serology, rapid antigen testing, polymerase chain reaction (PCR), and immunofluorescence assays.

Information regarding laboratory diagnosis of flu is available at http://www.cdc.gov/flu/professionals/diagnosis/.

Note: Ideally, some specimens will be available from pre-mortem collection. Case investigations should be performed to locate all previous test results conducted for influenza during the course of illness as well as to determine if there are any pre-mortem specimens or isolates available for testing. In addition, post-mortem specimens may need to be collected to confirm illness.
B. Services available at the BPHL

BPHL can culture for influenza and perform an RT-PCR test to detect and subtype influenza in clinical specimens.

Specimens or isolates should be collected and forwarded to BPHL for confirmation typing and strain identification. Specimens may also be forwarded on to CDC for further testing (such as for antiviral resistance, if suspected). Specimen collection and submission will likely require CHD staff to coordinate with hospital staff (infection preventionists) and/or medical examiners.

C. Testing requests

1. Submitting specimens to BPHL
   b. Electronic Laboratory Ordering (ELO) may also be used by entering request into the HMS State Laboratory System, placing bar coded label on the vial, and writing the date collected on the vial.

2. Locate all available respiratory pre-mortem specimens or isolates to forward to BPHL for confirmation.

3. Specimen collection—post mortem:
   a. Collect specimen as soon as possible after death: obtain a nasopharyngeal specimen using swabs with a synthetic tip (such as Dacron or nylon) and a plastic or wire shaft and place in viral transport media. Viral antigens and nucleic acids may be focal and sparsely distributed in patients with influenza. In addition, the degradation of live virus and growth of other contaminating organisms in the respiratory tract following death may reduce the efficacy of viral isolation from respiratory specimens. Extensive sampling of both upper and lower tracts that occurs as soon as possible after death ensures the best chance of detecting the virus.
   b. During autopsy: obtain a tracheal specimen using a swab with a synthetic tip and place in viral transport media. Additionally, collect multiple lung tissue specimens, if possible, and specimens from other organs showing pathology. Place fresh lung tissue in viral transport media. Store fresh-frozen and fixed lung tissue for further testing if needed. Obtain any additional appropriate specimens for culture.
   c. Please label all specimen tubes with specimen source, the decedent’s name, date of birth and date of collection.
   d. Nasopharyngeal specimens should be placed into sterile viral transport media (VTM) and immediately placed into a cool storage container with ice or cold packs or in a refrigerator (4°C) for transport to the laboratory.
   e. All respiratory specimens should be kept at 4°C for no longer than 4 days.
4. Packaging and shipping  
   a. Send specimens for influenza testing to the Jacksonville or Tampa BPHL.
   b. Place the tube of VTM containing the swab in a Ziploc bag with a paper towel to absorb leaks. Please place the Clinical Lab Submission Form 1847 in a plastic Ziploc bag between the inner and outer container. Package according to International Air Transport Association (IATA) regulations, labeling the outer shipping container: UN3373, Biological Substance Category B.
   c. Specimens should be sent in a small cooler with frozen blue ice or gel cold pack with sufficient stuffing to prevent leaking or shifting during transport.
   d. Laboratory specimen packaging flowchart:
   e. Laboratory specimen packaging notes:

5. Contact the regional laboratory with questions:

5. CASE INVESTIGATION

All influenza-associated deaths in persons aged < 18 years, regardless of laboratory testing method, should be investigated and managed as follows.

A. Evaluate the diagnosis

   Collect medical records to review clinical course, secondary infections, co-morbidities, patient health status, antiviral treatment and vaccination history. Identify confirmatory laboratory testing results. Identify existing specimens or isolates and/or request specimen collection and send to BPHL for influenza testing.

B. Case management

   Often the CHD is not aware of the case until after death has occurred. This limits the ability to perform certain case management activities (such as recommending isolation), particularly if illness has been prolonged. The case investigation for laboratory-confirmed influenza-associated pediatric deaths involves reviewing medical records and completing the influenza case report form at:

C. Identify potential sources of infection

   Inquire about recent travel or exposure to ill persons who have recently traveled, and about exposure to animals such as poultry and swine.
D. Identify contacts

While many times cases are not reported to CHDs until after death has occurred, contacts should be identified to evaluate if the case is a sporadic occurrence or is part of a cluster or outbreak or if infection is suspected to be due to novel influenza (see http://www.floridahealth.gov/diseases-and-conditions/disease-reporting-and-management/disease-reporting-and-surveillance/#i).

E. Manage contacts

Contact investigations for laboratory-confirmed influenza-associated pediatric deaths should be performed based on whether the case is a sporadic occurrence or part of a cluster or outbreak. Given that many times CHDs are not notified until after death or late in the course of illness, contact management may be limited. Contact investigations should be geared toward identification of other ill persons at risk of severe complications.

Influenza antiviral prescription drugs can be used to treat influenza or to prevent influenza.

Two FDA-approved influenza antiviral medications are recommended for use in the United States during the 2013–2014 influenza season: oseltamivir (Tamiflu®) and zanamivir (Relenza®). Oseltamivir and zanamivir are chemically related antiviral medications known as neuraminidase inhibitors that have activity against both influenza A and B viruses.

More information can be found here: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

1. Symptomatic contacts
Symptomatic contacts at high-risk for influenza complications should contact their provider immediately to discuss the need for treatment. All contacts symptomatic with influenza-like illness should avoid work, school, childcare, and other public settings until 24 hours after fever has resolved.

2. Asymptomatic contacts
Asymptomatic contacts at high-risk for influenza complications should contact their provider immediately to discuss the need for chemoprophylaxis if they are still within the prophylactic window. In general, post-exposure chemoprophylaxis should not be started more than 48 hours after the last exposure. Inform asymptomatic contacts to stay home if they develop symptoms of early influenza-like illness.

F. Investigate and interview

Much of the investigation can be completed through review of medical records and interviews with attending medical staff or infection preventionists. Family member interviews can be difficult following the death of a child and may not be warranted if there is no concern of an outbreak or cluster.
1. The purposes of investigation, interview, and/or counseling are to:
   a. Collect specimens for strain identification,
   b. Determine use of antivirals and vaccination status,
   c. Determine whether close contacts may have put or be putting others at risk in
      a sensitive situation,
   d. Determine whether the suspected influenza-associated pediatric death may
      be part of a recognized or unrecognized outbreak, as a trigger to further
      investigation; and,
   e. Determine if the severe outcome represents a change in the circulating
      influenza virus (novel strain identification or more pathogenic strain).

2. Contact the reporting physician, infection preventionist or medical professional to
   complete an interview as soon as possible after being reported to optimize recall.
   a. Make at least three phone call attempts to reach the reporting physician, if
      still within the prioritization time frame.

3. The case report form for cases of laboratory-confirmed influenza-associated
   pediatric death is available online: http://www.floridahealth.gov/diseases-and-
   conditions/disease-reporting-and-management/disease-reporting-and-
   surveillance/_documents/crf-influenza-ped-deaths.pdf. This form can be used to
   guide the interview and can be completed at that time.

4. Extended Data screen is available in Merlin to enter data from the case report
   form.
   a. Determine if others (e.g., family, friends etc.) are known or thought to be ill
      with symptoms compatible with influenza-like illness. If so, inquire about
      possible common source exposures. Obtain the name, phone number or
      address and clinical information of the other ill people. Anyone meeting the
      probable case definition should be reported and investigated in the same
      manner as a confirmed case.
   b. Determine if any symptomatic household or other close contacts are
      associated with sensitive situations (i.e., an attendee or employee of a
daycare/ childcare setting, or an employee in a health care setting with direct
patient care). Determine the dates and times he/she worked to determine the
risk of transmission to others. See Section 7 for recommended exclusions
for symptomatic persons or contacts in sensitive situations.
   c. Provide basic instruction to potentially exposed contacts about proper
infection control measures. See Section 6 for recommendations on
controlling further spread.

G. Environmental evaluation

Standard cleaning and disinfection should be done for any potentially contaminated
surfaces where persons with influenza may have been present. In addition, surfaces
 touched often, such as doorknobs, refrigerator door handles, telephones, keyboards,
and bathroom handles, should be cleaned and disinfected frequently in public areas
during influenza season and in households with a potentially communicable influenza
case.

For additional information regarding environmental cleaning and disinfecting, see
D. Merlin data entry

Create a case in Merlin under disease code INFLUENZA-ASSOCIATED PEDIATRIC MORTALITY—48700. Enter the data collected into Merlin, being sure to include all required fields on the Basic Data screen, complete the Case Symptoms screen, and attach all relevant labs. Please attach ALL labs received via electronic laboratory reporting (ELR) to the case and include specimen information as available.

Note: Please notify DCBE when the case is reported in Merlin. This is because DCBE staff will need to notify CDC the same week of the date of report in Merlin.

6. ROUTINE PREVENTION

A. Vaccine Recommendations:

Routine annual influenza vaccination is recommended for all persons 6 months and older. Annual vaccination is particularly important for persons at increased risk of complications and for persons in contact with those at high-risk for complications including (http://www.cdc.gov/flu/protect/vaccine/index.htm):

1. Children less than 5 years old, but particularly those under 2 years old;
2. Pregnant women;
3. People 50 years of age and older;
4. People of any age with certain chronic health conditions such as asthma and other pulmonary disease, diabetes, hepatic disease, hematologic abnormalities, neurologic or neuromuscular abnormality, immunosuppressive disease or therapy, cancer in the past year, or cardiovascular disease;
5. Persons who live in nursing homes and other long-term care facilities;
6. Children receiving long-term aspirin therapy;
7. American Indians/Alaska Natives;
8. People who are morbidly obese;
9. Household contacts of person at high-risk for complications from influenza;
10. Household contacts and out-of-home caregivers of children < 5 years old and adults > 50 years old, but particularly contacts of children under 6 months of age;
11. Health care workers.

B. Routine Prevention (general guidance):

General respiratory and hand hygiene measures are recommended at all times, and particularly during periods when respiratory viruses are circulating.

1. If you get sick with respiratory symptoms, stay home for the recommended time period and limit contact with others to keep from infecting them.
2. Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it and then clean your hands.
3. Wash your hands with soap and water frequently, especially after you cough or sneeze. Alcohol-based hand cleaners are also effective against influenza viruses.
4. Try to avoid close contact with people ill with respiratory symptoms.
5. Avoid touching your eyes, nose or mouth.
6. Wear a mask when entering a health care facility if you are coughing or sneezing.

7. MANAGING SENSITIVE SITUATIONS

A. Determining a sensitive situation

Section 64-D3-3.037(3) specifically gives CHD directors the authority to decide what is a sensitive situation, and provides broad authority to take necessary action to control disease.

For example, a CHD director may use his/her discretion to designate an elementary school, or the lower grades of an elementary school, as a sensitive situation, but he/she is not required to do so. This decision should be based on evidence of transmission within a particular setting.

B. CDC guidance is available for managing special situations in addition to those listed below. (See http://www.cdc.gov/flu/professionals/infectioncontrol/index.htm)

1. Schools and Childcare Settings
   CDC guidance is available for preventing the spread of influenza in schools and childcare settings: http://www.cdc.gov/flu/school/index.htm.

2. Health Care Facilities
   CDC guidance is available for managing influenza cases in health care settings: http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm.

3. Emergency Shelters
   CDC guidance is available for managing 2009 H1N1 cases in emergency shelters: http://www.cdc.gov/h1n1flu/guidance/emergencyshelters.htm.

8. IMPORTANT LINKS


B. APHA Media Advocacy Manual:
   http://www.apha.org/NR/rdonlyres/A5A9C4ED-1C0C-4D0C-A56C-C33DEC7F5A49/0/Media_Advocacy_Manual.pdf

9. REFERENCES
