Pediatric Influenza-Associated Mortality

Influenza (flu) is a contagious respiratory illness that occurs worldwide and can cause mild to severe illness[1–4]. Each year between 7,000 and 26,000 children under the age of five years are hospitalized because of influenza complications nationwide[2]. From 2011–2012 to 2019–2020 anywhere from 37 to 199 pediatric deaths associated with laboratory-confirmed influenza were reported to the Centers for Disease Control and Prevention (CDC) each season[2].

Severe influenza complications are most common in children younger than two years old, but children with chronic health problems are also at high risk of developing serious complications[3,5]. Nationwide, most influenza-associated pediatric deaths are attributable to influenza A, occur in children <5 years of age and approximately 50% do not report high-risk conditions [1].

In Arizona, 26 influenza-associated pediatric deaths were identified during the ten seasons from 2011–2012 through 2020–2021[6]. Zero to five deaths have been identified each season[6]. Five (19%) of the 26 cases were the A/H1 influenza strain; 7 (27%) were influenza A/H3; 7 (27%) were influenza A viruses with no subtype identified; 7 (27%) were influenza B[6].

A. Agent:
Influenza viruses are orthomyxoviruses of either A, B or C type (type C is very rare compared to type A and type B). Annual epidemics are caused by influenza virus types A and B, and both influenza A and B virus antigens are included in seasonal influenza vaccines. Type C influenza viruses can cause sporadic mild influenza-like illness in children. Type C antigens are not included in influenza vaccines[1].

B. Clinical Description:
Influenza is a respiratory illness characterized by fever, headache, myalgia, coryza, sore throat, and cough[3]. Influenza-like illness (ILI) is defined as a fever of 100°F or greater, accompanied by cough or sore throat[2]. Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) may be reported in children; however these symptoms are uncommon in adults[3].

- Differential Diagnosis:
  Influenza may be clinically indistinguishable from other diseases caused by respiratory viruses such as rhinovirus, RSV, parainfluenza and adenovirus[3]. Syndromes consistent with influenza include upper respiratory illness, croup, bronchiolitis, febrile seizures and pneumonia[3].
- Secondary infections and co-infections may include bacterial and viral pneumonia, sinusitis, otitis media, febrile seizures, encephalitis/encephalopathy, myositis and worsening of underlying conditions[3].

C. Reservoirs:
Aquatic birds are the primary reservoir for influenza A; however influenza A circulates among other animals, including humans[3]. Humans are the primary reservoir for influenza B[3–4].

D. Mode of Transmission:
Transmission occurs primarily through person-to-person transmission, via respiratory tract droplets produced when an infected person coughs or sneezes[1–2,4,6]. The virus also can spread when a person touches a surface or object contaminated with infectious respiratory tract droplets and then touches his or her mouth, nose, or eye(s)[1,4].

E. Incubation Period:
From exposure to symptom onset ranges from 1 to 4 days, with a mean of 2 days[1].

F. Period of Communicability:
Individuals with influenza are usually considered infectious one day before symptom onset and up to seven days after onset[1–2,4,6]; however young children and immunocompromised patients may pass the virus for greater than seven days[1–3]. Viral shedding and probable communicability from nasal secretions usually peak within the first three days of illness[1,3]. Recommended infection control practices include standard and droplet precautions for the duration of the illness[1].

G. Susceptibility and Resistance:
Influenza immunization should occur annually (all people older than 6 months of age) as soon as the vaccine becomes available[2]. Children 6 months through 8 years who have not previously been immunized against influenza should receive two doses of vaccine at least one month apart to produce a satisfactory antibody response needed for significant protection[1,4–5].

Immunization is recommended annually because after one year, due to the waning of vaccine-induced antibodies and antigenic drift of circulating influenza viruses, populations may become susceptible again[1–2]. Influenza infection and vaccines produce serological responses specific to the infective or vaccine strains; however, it can also provide some cross-protection against similar strains[2].

H. Treatment[1]:
Antivirals may be effective at treating influenza, especially if given within 48 to 72 hours of onset[1,2]. Antiviral treatment should not be delayed pending laboratory testing[1]. Control of fever with acetaminophen, or other appropriate antipyretic agents, may be important especially in young children[1].

DRUG	VIRUS	ADMINISTRATION	TREATMENT INDICATIONS	PROPHYLAXIS INDICATIONS	ADVERSE EVENTS
Oseltamivir (available as a generic version or as Tamiflu®)[1,2]	A and B	Oral twice daily for 5 days	Any age	≥ 3 months of age	Nausea, vomiting, headache; skin reactions
Zanamivir (Relenza®)[1,2]	A and B	Inhalation twice daily for 5 days	≥ 7 years of age	≥ 5 years of age	Bronchospasm, skin reactions
Peramivir (Rapivab®)[1,2]	A and B	Intravenous as a single dose	≥ 2 years of age	Not recommended	Diarrhea, skin reactions
Baloxavir marboxil (Xofluza®)[2]	A and B	Oral as a single dose	≥ 12 years of age	Not recommended	Nausea, vomiting, diarrhea

I. Clinical Case Definition[7]:

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:

- 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.

J. Laboratory Criteria for Diagnosis:

Laboratory testing for influenza virus infection may be done on the following pre- or post-mortem clinical specimens[7]:

- Isolation of influenza virus in tissue cell culture from respiratory specimens; OR
- Positive reverse-transcriptase polymerase chain reaction (RT-PCR) from respiratory specimens; OR
- Positive immunofluorescent antibody staining (direct or indirect) of respiratory specimens; OR
- Positive rapid influenza diagnostic test of respiratory specimens; OR
- Demonstration of immunohistochemical (IHC) staining for influenza viral antigens in respiratory tract tissue from autopsy specimens; OR
- Four-fold rise in influenza hemagglutination inhibition (HI) antibody titer in paired acute and convalescent sera.

Case Classification[7]	
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.

K. Classification of Import Status:

Import status reflects where the influenza infection was acquired: in county, in state, international, out of county but in Arizona, out of state but in U.S., or location of infection is unknown.

L. Laboratory Testing:

Laboratory testing from any laboratory is considered in the classification of an influenza-associated pediatric death, if it meets the Laboratory Criteria for Diagnosis described above. During the case investigation, any previously collected respiratory specimens and autopsy specimens should be sent to ASPHL for additional testing by RT-PCR and viral isolation, after consultation with the local and state health department. After consultation, clinical material, viral isolates, and tissue collected during autopsy may also be sent to CDC where further testing may be performed, such as immunohistochemical and antiviral susceptibility assays or antigenic characterization.

Influenza Testing Types[2,13]						
Influenza Diagnostic Test	**Method**	**Specimen & Transport**	**Availability**	**Test Time**	**Sensitivity**	**Types Detected**
Rapid influenza diagnostic tests (RIDTs)[a]	Antigen detection	NP swab, aspirate or wash, nasal swab, aspirate or wash, throat swab	Wide	<15 min	10%–70%	A and B
Rapid molecular assays[b]	RNA or nucleic acid detection	NP swab, nasal swab	Wide	15–30 min	86%–100%	A and B
Nucleic acid amplification (RT-PCR and other molecular assays)[c]	RNA or nucleic acid detection	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Limited	1–8 h	86%–100%	A and B
Immunofluorescence, direct (DFA) or indirect (IFA) florescent antibody assays[c]	Antigen detection	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	Wide	1–4 h	70%–100%	A and B
Rapid cell culture (shell vials and cell mixtures)[c]	Virus isolation	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum (specimens placed in VTM)	Limited	1–3 days	100%	A and B
Tissue cell culture[c]	Virus isolation	NP swab, throat swab, NP or bronchial wash, nasal or	Limited	3–10 days	100%	A and B

		endotracheal aspirate, sputum (specimens placed in VTM)				

[a]*Most rapid influenza diagnostic tests are Clinical Laboratory Improvement Amendments (CLIA) waived.*

[b]*Some rapid influenza molecular assays are CLIA waived, depending on the specimen.*

[c]*Not CLIA waived. Requires laboratory expertise.*

M. Assessing Laboratory Results:

Positive influenza results at a commercial laboratory should be sent to the state laboratory for confirmatory testing and potential forwarding to CDC.

N. Outbreak Definition:

An increase in cases in time or place that is greater than expected.

Investigation Guidelines

O. Time Frame[10]:

Providers must submit a report to the Local Health Department within 1 working day after a case or suspect case is diagnosed, treated, or detected. Laboratories must submit a report to ADHS within 5 working days after obtaining a positive test result. Laboratories must submit an isolate or specimen, as applicable, only by request. Local health agencies must notify ADHS within 1 working day after receiving a report. Local health agencies must submit an epidemiologic investigation report to ADHS within 30 calendar days after receiving a report.

P. Forms:

- Influenza-Associated Pediatric Mortality Case Report Form

Q. Investigation Steps:

For a local health agency[8]:

A.A.C. R9-6-348. Influenza-Associated Mortality in a Child

Case control measures: A local health agency shall:

1. Upon receiving a report under R9-6-202 of a case or suspect case of an influenza-associated death of a child, notify the Department within one working day after receiving the report and provide to the Department the information contained in the report;
2. Conduct an epidemiologic investigation of each reported case or suspect case of influenza-associated mortality in a child; and
3. 3. For each case of influenza-associated mortality in a child, submit to the Department, as specified in Table 2.4, the information required under R9-6-206(D).

a. Confirm Diagnosis

i. Identify any influenza testing that has already been conducted, and find the results.

ii. If respiratory specimens have not already been submitted to ASPHL, identify pre- or post-mortem specimens that may be available for testing at ASPHL. Specimens collected by the hospital or health care provider may still be at the hospital or commercial laboratory, or the medical examiner may be able to collect appropriate specimens if an autopsy is being conducted.

- Refer to the ASPHL Guide to Laboratory Services and information provided by CDC for information on specimens that are acceptable for submission to either agency (including media, storage, and shipping requirements)[11].

iii. Even if specimens have already been submitted to ASPHL, discuss the option of obtaining additional pre- or post-mortem respiratory specimens for additional testing, using guidelines provided by CDC and in consultation with ADHS.

iv. All specimens to be sent to CDC should be submitted through ASPHL to ensure proper packaging and shipping and coordination of results.

1. The ADHS investigator will coordinate with ASPHL to ensure that influenza specimens are shipped to CDC in accordance with CDC guidance, and will notify CDC that the specimens are available and will be shipped.

b. Conduct Case Investigation

i. The local health department investigator is responsible for coordinating with and collecting information from the medical examiner, the health care facilities, and the case's family, as needed.

- Obtain medical records and complete the CDC influenza-associated pediatric mortality case report form.

ii. The ADHS investigator is responsible for coordinating communications between the local health department, ASPHL, and CDC.

- Submit influenza-associated pediatric mortality case report form to CDC.

c. Initiate Control and Prevention Measures

i. Annual vaccination is the most important method of prevention of influenza infection[2,12]. Annual influenza vaccination is recommended for all individuals 6 months old and older and specifically for individuals at increased risk for influenza-associated complications and their close contacts, including health care workers[1–2,4–6,12].

ii. Non-pharmacologic interventions (e.g., frequent handwashing, improved respiratory hygiene and staying at home when sick) are reasonable and inexpensive ways that have been demonstrated to reduce the overall incidence of respiratory diseases, but they should not replace annual vaccination as the most important method to prevent influenza infection[12].

iii. Standard cleaning and disinfecting should be done for any potentially contaminated surfaces where persons with influenza may have been present. In addition, surfaces touched often should be cleaned and disinfected frequently in public areas during influenza season and in a household with a suspect influenza case. For additional information regarding environmental cleaning and disinfecting see the CDC website.

d. Isolation, Work and Child Care Restrictions

Not applicable for an influenza-associated pediatric death.

e. Case Management

Not applicable for an influenza-associated pediatric death.

f. Contact Management, including Susceptible Contacts

i. Symptomatic contacts at high risk for influenza complications should contact their provider immediately to discuss the need for treatment. All contacts with influenza-like illness should avoid work, school, child care, and other public settings until 24 hours after fever has resolved without the use of fever reducing medication.

ii. Asymptomatic contacts at high risk for influenza complications should contact their provider immediately to discuss the need for chemoprophylaxis. Post-exposure chemoprophylaxis generally is not recommended if more than 48 hours have elapsed since the last exposure to an infectious person.

g.Notifications

i. ADHS is responsible for notifying CDC upon identification of a confirmed case.

ii. ADHS is responsible for submitting information from the investigation form to CDC.

iii. ADHS and the local health department will jointly decide whether to send a health alert notice to providers, create a press release, or provide other public notifications.

iv. ADHS will report that a confirmed influenza-associated pediatric death has been identified and will include brief information about the case in the weekly influenza reports.

R. Outbreak Guidelines:

Refer to the Outbreak Section of the Disease Investigation Manual.

Special Situations

S. Special Situation:

The following situations may call for an expedited investigation:

- The child lives in or spends a significant amount of time in a group setting for individuals at high risk for complications of influenza;
- A cluster of influenza-associated pediatric deaths;
- An influenza-associated pediatric death and multiple epidemiologically-linked hospitalized influenza cases (of any age);
- Case meets the definition for a novel influenza A virus “under investigation”;
- Swine or avian exposure in the two weeks before illness onset; or
- Any other situation in which it seems likely that public health intervention may prevent further severe influenza cases, or that the death may be associated with a novel virus.

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