

Influenza-Related Pediatric Mortality Investigation and Reporting: Guidance for Medical Examiners, Pathologists and Healthcare Providers

Michigan Department of Health and Human Services (MDHHS) Division of Communicable Disease

Immediately contact the MDHHS Division of Communicable Disease (517-335-8165; after hours 517-335-9030) or your local health department to report suspect or confirmed cases.

Reporting Rationale

- Reporting of pediatric deaths due to influenza is **required** in Michigan (*Communicable Disease Rules 325.171-325*)
- The Centers for Disease Control and Prevention (CDC) and the Council of State and Territorial Epidemiologists (CSTE) list pediatric mortality associated with influenza infection as a nationally reportable condition
- Nationally, over 1,700 influenza-associated pediatric mortalities have been reported since 2004
- MDHHS also requests that any unexplained pediatric death with evidence of an infectious process be reported. These cases are of public health interest and investigations lead to a better understanding of fatal disease agents and processes.

Case Definitions

Lab-confirmed: Death in a patient <18 years of age associated with a laboratory-confirmed influenza infection via one of the following test methods:

- Rapid antigen
- Polymerase chain reaction (RT-PCR or multiplex panel)
- Viral culture
- Direct or indirect fluorescence assay (DFA/IFA)
- 4-fold antibody titer rise in acute and convalescent sera

Suspect: Death in a patient <18 years of age with an influenza-like illness (fever >100°F with cough and/or sore throat) or other symptoms consistent with a viral respiratory illness, without a recovery to baseline health between illness and death

- A negative influenza test should not preclude further case investigation
- Attention should be paid to cases presenting as secondary bacterial co-infection due to a preceding primary influenza-like illness
- MDHHS encourages inquiries on cases that do not fit the above definitions but have noteworthy clinical presentation, lab results or pathology

Reporting and Investigation Procedures

1. To report a suspect or confirmed influenza-associated pediatric mortality, or an unexplained pediatric mortality with clinical suspicion of infection, immediately contact the MDHHS Division of Communicable Disease 517-335-8165 (after hours 517-335-9030) or your local health department.
2. **Consider Multisystem Inflammatory Syndrome in Children (MIS-C) in any pediatric death with evidence of SARS CoV-2 infection** <https://www.cdc.gov/mis-c/hcp/>
3. MDHHS and/or the local health department will request relevant medical and laboratory records for review. This documentation will most often include hospital records and autopsy reports from the medical examiner/pathologist and other medical staff.
4. MDHHS and the local health department will work with healthcare providers, laboratories, and the medical examiner/pathologist to coordinate submission of representative premortem and postmortem samples to the MDHHS Bureau of Laboratories (see Specimen Collection/Submission section - pg 2)
5. Specimens will be tested at MDHHS and/or forwarded to the CDC. CDC testing may take several weeks to obtain final results. Results will be sent to both the medical examiner/pathologist and the local health department. There is no charge for MDHHS or CDC influenza testing services.

Specimen Collection/Submission

All specimens should be sent directly to MDHHS Bureau of Laboratories*

1. Premortem and Postmortem specimens for PCR or viral culture confirmation at MDHHS

- Premortem clinical influenza specimens (e.g. rapid test and/or PCR specimens in viral transport media, viral cultures)
- Non-fixed postmortem specimens (e.g. nasopharyngeal, tracheal swabs or fresh lung tissue)
- Shipping these specimens requires refrigeration, or freezing at -70°C and shipment on dry ice

2. Postmortem specimens for testing by PCR or immunohistochemistry (IHC) at CDC

Viral antigens may be focal and sparsely distributed in patients with influenza. Larger airways have the highest yield for detection of influenza viruses by CDC testing methods. Additional representative tissues, especially those showing significant pathology that may be related to influenza infection (e.g. myocarditis, encephalitis, rhabdomyolysis) should also be submitted.

Optimal tissues to collect for all cases are:

- Central (hilar) lung with segmental bronchi
- Right and left primary bronchi
- Trachea (proximal and distal)
- Representative pulmonary parenchyma from right and left lung

Additional tissues may include:

- Myocardium from the right and left ventricle
- CNS including cerebral cortex, basal ganglia, pons, medulla, and cerebellum
- Skeletal muscle or other organs showing gross or microscopic pathology

A minimum of 8 tissues blocks or fixed tissue samples representing the above sites should be submitted if available. Tissues can be submitted in the following preparations:

- **Paraffin-embedded tissue blocks (preferred)** - This is the preferred specimen and is especially important when tissues have been in formalin for a significant time
- **Wet tissue** - If available, unprocessed tissue in 10% neutral buffered formalin should be submitted with paraffin blocks
- **Unstained slides** - If paraffin blocks are unavailable, unstained sections cut at 3-5 microns (10 slides per block) may be tested by IHC staining
- **Fresh-frozen tissue** - Requires submission on dry ice
- **Electron microscopy (EM) specimens** - Samples fixed in glutaraldehyde and held in phosphate buffer (containers should be filled to the top with phosphate and sent on wet ice). Epoxy-embedded tissues are also accepted.

3. Unexplained pediatric deaths with no evidence of influenza infection may require different samples, which will be determined on a case-by-case basis.

4. Additional materials to include with specimen shipment to MDHHS:

- Autopsy report (preliminary or final if available)
- Cover letter – include the following items:
 - Brief patient clinical history
 - Patient lab results (viral and bacterial testing), influenza vaccination status and travel history
 - Your name, title, mailing address, phone and fax numbers, and email address

*All shipping must be done in consultation with the MDHHS Division of Communicable Disease. Please contact MDHHS for assistance with identifying shipping services.

Contact the MDHHS Division of Communicable Disease (517-335-8165; after hours 517-335-9030) or your local health department for any questions, case consultation, or investigation coordination.

