Enterovirus D68 Severe Respiratory Syndrome - (EV-D68) Infection

1. DISEASE REPORTING

A. Purpose of Reporting and Surveillance

1. To identify infections due to Enterovirus D68 (EV-D68) and better understand the spectrum of illness, populations at-risk and modes of transmission.
2. To prevent the spread of EV-D68.

B. Legal Reporting Requirements

1. There are no legal reporting requirements for EV-D68.
2. While there are no legal reporting requirements for individual cases of enterovirus, please report severe cases and clusters.

C. Guidance for Health Care Providers

1. Be aware of EV-D68 as a potential cause of clusters of severe respiratory illness* (see section 3.A. for definition), particularly in young children.
2. Consider laboratory testing of respiratory specimens for enteroviruses when the cause of infection in patients with severe respiratory illness is unclear.
3. Report cases of severe respiratory illnesses that test positive for rhinovirus or enterovirus to your local health department to arrange further testing.
4. Report any increases in cases or clusters of severe respiratory illnesses to your local health departments for further guidance.

D. Local Health Jurisdiction Investigation Responsibilities

1. Contact CDE regarding suspected EV-D68 infections. Facilitate the transport of specimens from suspected cases to the Washington State Public Health Laboratories for submission for typing at CDC picornovirus laboratory.
2. Complete the DOH EV-D68 infection case report form for confirmed EV-D68 cases and fax the completed form to CDE.
3. Since by definition suspected cases are hospitalized, consider tracking suspected cases in your jurisdiction by number of suspected cases at each facility.

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic Agent

Enteroviruses are very common viruses. There are more than 100 types of enteroviruses. It is estimated that 10 to 15 million enterovirus infections occur in the United States each year. Most people infected with enteroviruses have no symptoms or only mild symptoms, but some infections can be serious. Most enterovirus infections in the U.S. occur seasonally during the summer and fall, and outbreaks tend to occur in several-year cycles.

EV-D68 infections are thought to occur less commonly than those with other enteroviruses. EV-D68, like other enteroviruses, appears to spread through close contact with infected people. This virus was first isolated in California in 1962 from four children

with bronchiolitis and pneumonia, and has been reported rarely since that time. Unlike the majority of enteroviruses that cause a clinical disease manifesting as a mild upper respiratory illness, febrile rash illness, or neurologic illness (such as aseptic meningitis and encephalitis), EV-D68 has been associated almost exclusively with respiratory disease[1]. Though EV-D68 usually causes mild to severe respiratory illness, the full spectrum of EV-D68 illness is not well-defined.

On September 8, 2014 an MMWR Early release described Severe Respiratory Illness Associated with Enterovirus D68 – Missouri and Illinois, 2014. Clusters of respiratory illness associated with EV-D68 in Asia, Europe, and the U.S. during 2008-2010 have been described previously. EV-D68 infection was associated with respiratory illness ranging from relatively mild illness to severe illness requiring intensive care and mechanical ventilation. These clusters confirmed that EV-D68 is associated with outbreaks of respiratory illness severe enough to require hospitalization, and in some cases, might contribute to patient death. New-onset wheezing or asthma exacerbation were notable symptoms. However, in each cluster, respiratory specimens typically were collected from persons who had sought medical care or were hospitalized, which would have biased these reports toward more severe disease. No data is currently available regarding the overall burden of morbidity or mortality from EV-D68 in the U.S. The U.S. seems to be experiencing a nationwide outbreak of EV-D68 at this time.

Additionally, a cluster of nine pediatric patients hospitalized with acute neurologic illness characterized by focal limb weakness and abnormalities of the spinal cord gray matter on MRI were identified in Colorado from August 9 – September 17, 2014. Most of the children reported having fever and symptoms of respiratory illness in the 2 weeks before onset of neurologic symptoms. CSF testing to date was negative for West Nile virus and enteroviruses, including polio. Respiratory specimens from eight of the children were tested for rhinovirus/enterovirus. Four were positive for EV-D68, and investigation is ongoing to determine whether this cluster of neurologic illness in Colorado is linked to the current nationwide outbreak of EV-D68. A health alert regarding this situation was sent out on September 26, 2014.

Available commercial, multi-pathogen detection systems can detect enteroviruses, and are approved by the Food and Drug Administration for use in clinical settings (Luminex xTAG RVP, Idaho Technologies FilmArray Respiratory Panel). But, these systems use broadly reactive primers that amplify RNA from either human rhinoviruses (HRVs) or enteroviruses, and results are reported as “entero-rhinovirus” or “human rhinovirus/enterovirus”. Most hospitals are not able to perform enterovirus typing to identify specific enterovirus. The gold standard test for EV-D68 detection is partial sequencing of the structural protein genes, VP4-VP2 or VP1.

There is no specific treatment for EV-D68 infections; specifically there are no anti-viral medications currently available for this purpose. Many infections will be mild and self-limited, requiring only symptomatic treatment. Some people with severe respiratory illness caused by EV-D68 may need to be hospitalized and receive intensive supportive therapy.

Vaccines for preventing EV-D68 infections currently are not available.

For updates on recently reported cases of infection with EV-D68 in the United States, see http://www.cdc.gov/non-polio-enterovirus/about/EV-D68.html

B. Description of Illness

Enteroviruses are associated with various clinical symptoms, including mild respiratory illness, febrile rash illness, and neurologic illness, such as aseptic meningitis and encephalitis. EV-D68, however, primarily causes respiratory illness[1], although the full spectrum of disease is not well-defined.

In August 2014, CDC was notified by a hospital in Missouri, of an increase (relative to the same period in previous years) in patients hospitalized with severe respiratory illness, including some admitted to the pediatric intensive care unit. An increase also was noted in detections of rhinovirus/enterovirus by a multiplex polymerase chain reaction assay in nasopharyngeal specimens obtained during August. CDC was also notified by a hospital in Illinois of an increase in patients similar to those seen in Missouri. To further characterize these two geographically distinct observations, nasopharyngeal specimens from most of the patients with recent onset of severe symptoms from both facilities were sequenced by the CDC Picornavirus Laboratory. Enterovirus D68 (EV-D68) was identified in 19 of 22 specimens from Missouri and in 11 of 14 specimens from Illinois. Following the initial reports, admissions for severe respiratory illness have continued at both facilities at rates higher than expected for the time of year. Investigations into suspected clusters in other jurisdictions are ongoing. Details of the Illinois and Missouri clusters can be found in MMWR September 12, 2014 / 63(36);798-799.

Investigation is also ongoing to determine if a cluster neurologic illness with focal weakness of limbs in nine Colorado children may be associated with EV-D68.

C. EV-D68 Infection in Washington

As of September 26, 2014, 36 specimens from children with respiratory illness that screened positive for enterovirus/rhinovirus were submitted to CDC for testing. EV-D68 was identified from 3 (20%) of 15 specimens submitted from Washington for whom results have been received

For the most recent information about EV-D68 in the United States, please see the CDC EV-D68 website at: http://www.cdc.gov/non-polio-enterovirus/about/EV-D68.html

D. Reservoirs

Humans are the only known reservoir for members of the Human Enterovirus group of viruses. These viruses are generally shed for longer periods of time in stools than in secretions from the upper alimentary tract like gastrointestinal tract and mouth where food first enters mouth. Specific reservoirs for EV-D68 are less well defined.

E. Modes of Transmission

EV-D68 is not frequently identified, so it is less studied and the ways it spreads are not as well-understood as other enteroviruses. EV-D68 causes respiratory illness, and the virus can be found in respiratory secretions such as saliva, nasal mucus, or sputum. The virus likely spreads from person to person when an infected person coughs, sneezes, or touches contaminated surfaces.

F. Incubation Period

Because many enterovirus infections are asymptomatic or only cause mild illness the incubation period is not well defined.

G. Period of Communicability

The period of communicability for EV-D68 is unknown at this time. The illness is likely contagious during the acute stage and perhaps longer. A person is likely most contagious during the initial stages of the illness but the contagious period is not well defined.

Follow droplet precautions in addition to the standard and contact precautions usually recommended for enteroviruses; persons with EV-D68 should avoid public settings (for example, by not going to work or to school) until 10 days after onset or until respiratory symptoms have resolved. Good hand washing and respiratory etiquette should be continued thereafter.

See Appendix A in 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings available at: http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf.

H. Treatment

There is no specific treatment. Medical care is supportive.

3. CASE DEFINITIONS

A. Case Classification

Severe respiratory illness* (for purpose of considering EV-D68 testing, please use the following definition for "severe respiratory illness"):

*Patient presented with

- Cough, and/or
- Shortness of breath, and/or
- Difficulty breathing

That was severe enough to require hospitalization

AND

Also requires some type of respiratory support, e.g.:

- Continuous oxygen
- CPAP or BiPAP
- Ventilator

Suspected EV-D68 Case

A suspected case is meeting the severe respiratory illness* case definition above AND for whom testing of respiratory specimens has confirmed the presence of enterovirus or rhinovirus.

Note: Commercially available assays for rhinovirus often detect enterovirus and vice-versa.

Confirmed EV-D68 Case

A confirmed case is a person with laboratory confirmation of EV-D68 infection. Confirmatory laboratory testing requires typing at specialized laboratories such as the CDC's polio and picornavirus laboratory.

Neurologic illness with limb weakness of unknown cause

If EV-D68 is being considered in the differential diagnosis for children hospitalized for neurologic illness that includes limb weakness of unknown cause, please use the following case definition:

- Patients ≤21 years of age with
- Acute onset of focal limb weakness occurring on or after August 1, 2014
  AND
- An MRI showing a spinal cord lesion largely restricted to gray matter

4. LABORATORY DIAGNOSIS AND SERVICES

A. Laboratory Diagnosis

All typing for EV-D68 testing must be discussed with and approved by local health before submission to PHL

PHL does not conduct enterovirus testing, but will facilitate submission of specimens to CDC's polio and picornovirus laboratory which does typing to confirm EV-D68.

Testing to screen for enterovirus/rhinovirus should be considered for patients hospitalized with severe respiratory illness* (see section 3.A.).

Please note:

1. When submitting specimens to PHL for enterovirus typing at CDC, priority should be given to patients requiring admission to ICU.
2. Specimens will only be submitted for typing at CDC on patients with severe respiratory illness* (see section 3.A.) that have been screened for enterovirus/rhinovirus and for whom results of that testing were positive.
3. Health care providers should consult with the local health jurisdiction (LHJ) about whether specimens should be submitted to PHL for enterovirus typing at CDC. Only specimens approved by the LHJ will be accepted.
4. A CDC-required patient summary form must accompany each specimen sent to PHL for submission to CDC for typing. LHJ's can ask health care providers to complete the form, then fax a copy of the form to DOH CDEpi. (Form is also attached to this guideline as Appendix A).
5. A different form must accompany the specimens submitted for children under 21 with neurologic illness that includes focal limb weakness. The form can be downloaded at

Acute Neurological Illness with Limb Weakness in Children: Patient Summary Form or accessed at http://www.cdc.gov/ncird/investigation/viral/sep2014.html.

B. Specimen Collection and Shipping

1. **For severe respiratory illness:**

Refrigerate all respiratory specimens at 2-8ºC up to 72 hours and ship cold; if 72 hours holding time will exceed 72 hours, freeze at -70ºC and ship on dry ice. Specimens that will arrive on Saturday must arrive frozen and special arrangements must be made. Nasopharyngeal and oropharyngeal specimens are the preferred specimens as they have optimal yield for detection of EV-D68.

Nasopharyngeal and oropharyngeal swabs (NP/OP swabs)

Use only synthetic fiber swabs with plastic shafts. Calcium alginate swabs or wooden shafted swabs may inhibit PCR tests. Place swabs immediately into sterile tube containing 2-3 mL viral transport media. NP/OP specimens should be combined, placing both swabs in the same vial.

- **Nasopharyngeal swabs –** Insert a swab in the nostril parallel to the palate. Leave in place for a few seconds to absorb secretions. Swab both nasal areas.
- **Oropharyngeal swab –** Swab the posterior pharynx, avoiding the tongue.

Note: While EV-D68 has been detected in stool in the past, it is unknown if stool specimens would be adequate for detection of EV-D68 in persons with severe respiratory illness. Submission of stool specimens is not recommended at this time and CSF specimens are believed to be insensitive for detection of EV-D68 in persons with severe respiratory illness.

2. **For neurologic illness with focal limb weakness:**

Refrigerate all respiratory specimens at 2-8ºC up to 72 hours and ship cold; if 72 hours holding time will exceed 72 hours, freeze at -70ºC and ship on dry ice. Specimens that will arrive on Saturday must arrive frozen and special arrangements must be made.

All specimens collected as soon as possible after onset/presentation, and for thorough analysis of paralysis, it is important that all three types of specimen are collected if at all possible.

- **CSF** – 2-3 ml
  and
- **NP or oropharyngeal swab** (collect as described above)
  and
- **Stool –** Stool should be collected as soon as possible, but within 14 days of onset at the latest. Stool should be sent undiluted, either in the original specimen cup or at least 1 gram transferred to a separate vial. All specimens will be tested by molecular assays. In order to rule out polio (which is standard for a domestic paralysis workup) stool will also be inoculated into culture.

CDC requires that these specimens be accompanied by a 5-page patient summary form which can be downloaded at: Acute Neurological Illness with Limb Weakness in Children: Patient Summary Form

C. Shipping

- Specimens should be stored and shipped at the temperatures indicated above.
- When shipping frozen specimens use a combination of dry ice and frozen gel ice-packs, not wet ice, to maintain temperatures over several days.

Avoid shipping problems:

- Do not place any dry ice in the primary container" or secondary container, foam envelopes, ziplock bags, cryovial boxes, or hermetically sealed containers.
- Do not place primary containers sideways or upside down in zip-sealing bags.
- Do not place any paperwork in the zip-sealing bags, so as not to damage the paperwork.
- Do not use biohazard autoclave bags to prepack your materials due their inadequate sealing.

Note that PHL require all clinical specimens have **two** patient identifiers, a name **and** a second identifier (e.g., date of birth) both on the specimen label and on the submission form. Due to laboratory accreditation standards, specimens will be rejected for testing if not properly identified. Also include specimen source and collection date.

Each specimen sent to PHL must be accompanied by a completed PHL virology form: http://www.doh.wa.gov/Portals/1/Documents/5230/302-017-SerVirHIV.pdf. Along with the patient and submitter names, include the date of collection and date of illness onset on the form.

5. CONTROLLING FURTHER SPREAD

A. Infection Control Recommendations in Healthcare Settings

EV-D68 is not frequently identified, so it is less studied and the ways it spreads are not as well-understood as other enteroviruses. Implementation of droplet as well as standard and contact precautions is recommended for persons with confirmed or suspected EV-D68.

For full details of these precautions, see the 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings.

B. Contact Management

No specific recommendations for management of contacts are available.

C. Environmental Measures

No specific recommendations.

6. ROUTINE PREVENTION

A. Immunization Recommendations

There are no vaccines for preventing EV-D68 infections.

B. Prevention Recommendations

1. **Asthmatics seem to be at greater risk for severe disease and should maintain optimal control of their asthma condition in consultation with their primary health care provider.**
2. **Persons should practice "respiratory etiquette" or good health manners to stop the spread of respiratory pathogens.**

   Persons can keep respiratory pathogens to themselves by:

   - Covering the nose and mouth with a tissue when sneezing, coughing or blowing the nose.
   - Throwing out used tissues in the trash as soon as possible.
   - Always washing hands after sneezing, blowing the nose, or coughing, and after touching used tissues or handkerchiefs.
   - Washing hands often when sick.
   - Using warm water and soap to wash hands (note: alcohol-based hand sanitizers are NOT effective against enteroviruses).
   - Staying home if sick.
   - Seeing a healthcare provider if you have an acute onset of difficulty breathing is prolonged, and following their instructions.
   - If requested, using face masks provided in medical offices or clinic waiting rooms.

   Persons can keep pathogens away by:

   - Washing hands before eating, or touching eyes, nose or mouth.
   - Washing hands after touching anyone else who is sneezing, coughing, blowing their nose, or whose nose is running.
   - Washing hands after changing diapers.
   - Disinfecting frequently touched surfaces, such as toys and doorknobs, especially if someone is sick. Bleach is preferred for disinfecting surfaces.
   - Not sharing things like cigarettes, towels, lipstick, toys, or anything else that might be contaminated with respiratory germs.
   - Not sharing food, utensils or beverage containers with others.

ACKNOWLEDGEMENTS

This document was created from information from the Centers for Disease Control and Prevention.

REFERENCES

1. Enterovirus Surveillance – United States, 1970-2005; MMWR, September 15, 2006 / 55(SS08);1-20

UPDATES

APPENDIX A

Enterovirus D68 (EV-D68) Patient Summary Form

*** CDC-required form to be completed by health care providers for all patients for whom specimens are sent to PHL for submission to CDC for EV-D68 typing.**

Enterovirus D68 (EV-D68) Patient Summary Form

To be completed for all patients for whom specimens are being submitted to CDC for EV-D68 typing. As soon as possible, please 1) notify and send completed form to your local/state health department, and 2) include a hard copy of the form along with the 50.34 form for specimen shipment.

Today's Date: _____ **Name of person filling in form:** _____

Phone: _____ **Email:** _____

Hospital / Health Care Facility Name: _____ **STATE:** _____ **COUNTY:** _____

Hospital ID: _____ **State ID:** _____

Specimen ID (as submitted on 50.34 form for specimen shipment):_____
If multiple specimens are submitted per patient, please include additional specimen IDs in table below

Patient Sex: ☐ M ☐F **Age**: _____ ☐Months ☐Years **Patient's State of Residence** _____

Race: ☐Asian ☐Black or African American ☐Native Hawaiian or Other Pacific Islander ☐American Indian or Alaska Native ☐White (More than one box can be checked) **Ethnicity**: ☐Hispanic ☐Non-Hispanic

Date of symptom onset: _____

Symptoms (*mark all that apply*): ☐Fever / Highest recorded temperature _____ (°F / °C) ☐Chills ☐Cough ☐Wheezing ☐Sore throat ☐Runny nose ☐Shortness of breath / difficulty breathing ☐Tachypnea ☐Retractions ☐Cyanosis ☐ Vomiting ☐Diarrhea ☐Rash ☐Lethargy ☐Seizure ☐Other (describe): _____

Does the patient have any comorbid conditions? (*mark all that apply*): ☐None ☐Unknown ☐Asthma ☐Reactive airway disease ☐Bronchopulmonary dysplasia ☐Cardiac disease ☐Immunocompromised ☐Prematurity, if yes gestational age_____ ☐Other (describe): _____

Abnormal Chest radiograph ☐Yes ☐No ☐Unknown **Abnormal Chest CT** ☐Yes ☐No ☐Unknown

	Yes	No	Unknown
Is/Was the patient: Hypoxic (sat <93%) on room air?			
Treated with supplemental oxygen?			
Treated with bronchodilators?			
Treated with antibiotics?			
Hospitalized? If Yes, *admission date*: _____			
If Yes, was the patient admitted to the Intensive Care Unit (ICU)?			
If Yes was the patient placed on non-invasive ventilation (BiPAP/CPAP)			
If Yes, was the patient intubated?			
If Yes, was the patient placed on ECMO?			
Did the patient die? If Yes, *date of death*: _____			

General Pathogen Laboratory Testing (*mark all that apply*)

Pathogen	Pos	Neg	Pending	Not Done	Pathogen	Pos	Neg	Pending	Not Done
Influenza A PCR					Rhinovirus and/or Enterovirus				
Influenza B PCR					Coronavirus (not MERS-CoV)				
Influenza Rapid Test					*Chlamydophila pneumoniae*				
RSV					*Mycoplasma pneumoniae*				
Human metapneumovirus					*Legionella pneumophila*				
Parainfluenzavirus					*Streptococcus pneumoniae*				
Adenovirus					Blood culture ☐Yes ☐No If positive, which bacteria_____				
Other: _____					CSF culture ☐Yes ☐No If positive, which bacteria_____				
Other: _____					Sputum culture ☐Yes ☐No If positive, which bacteria_____				

Enterovirus Typing - Specimen Type	Date Collected	Specimen ID	Enterovirus Typing - Specimen Type	Date Collected	Specimen ID
NP OP NP/OP (*circle one*)			Bronchoalvelolar lavage (BAL)		
Nasal wash / aspirate			Tracheal Aspirate		
Sputum			Stool/Rectal swab		
Other: _____			Other: _____		

To be completed by CDC: ***Patient ID:*** _____ ***CSID:*** _____ ***CSID:*** _____

CSID: _____ ***CSID:*** _____ ***CSID:*** _____