RAPID RISK ASSESSMENT

# Enterovirus 68 detections in the USA and Canada

26 September 2014

## Main conclusions

From mid-August to 24 September 2014, a total of 220 people from 32 US states were confirmed to have respiratory illness caused by EV-D68. Canada has also experienced an increase in severe respiratory illness associated with EV-D68 cases since mid-August 2014.

- An epidemiological link across the clusters reported in several US states has not yet been established, and it cannot be ruled out that the virus is circulating independently in several locations.
- To date, EU/EEA countries have not reported a growing number of acute respiratory infections or an increased number of hospital admissions.
- Sporadic cases of EV-D68 have been documented in several EU/EEA countries in recent years. In 2014, EV-D68 was detected in at least four EU/EEA countries but no epidemic clusters of severe disease have been reported; none of the Member States has so far issued an Early Warning and Response System (EWRS) notification.
- The likelihood for cases to be laboratory-confirmed in EU/EEA countries is low because most countries do not routinely screen for EV-D68, and the disease is not notifiable.
- If all other respiratory pathogen detections were negative, or if rhino-/enterovirus was detected initially, EV-D68 should be considered the causative pathogen of the disease. More systematic testing of severe respiratory illness cases for EV-D68 could be considered in EU/EEA countries to better document the circulation of this virus.
- EU/EEA countries need to remain vigilant and consider strengthening respiratory sample screening for enteroviruses and enterovirus typing.
- Based on the current information, EU/EEA countries have a moderate risk of EV-D68 transmission because the circulation of this strain in the population is low.

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# Public health issue

Outbreak of severe respiratory illness caused by enterovirus 68 (EV-D68) in the USA and Canada.

This rapid risk assessment focuses on the following topics:

- Is the EV-D68 strain currently circulating in the USA and Canada already circulating in the EU?
- What is the current state of knowledge on EV-D68, and how likely it is for this virus to be detected in the EU?
- Should this virus become established in the EU, are there specific groups at an increased risk of infection and severe disease, and what options exist to mitigate this risk?

# Consulted experts

**ECDC internal response team** involved in the production of the risk assessment: Eeva Broberg, Tarik Derrough, Josep Jansa, Pasi Penttinen, René Snacken

**External reviewers**

Denise Antona, Institut de Veille Sanitaire (InVS), St Maurice, France

Susan Gerber, Centers for Disease Control and Prevention (CDC), Atlanta, USA

Bruno Lina, Enterovirus National Reference Centre, Lyon, France

Adam Meijer, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands

Richard Pebody, Public Health England, London, United Kingdom

# Disease background information

Human enterovirus 68 (EV-D68, EV-D68, HEV-D68 or HEV-D68; in this document EV-D68) is one of more than hundred enteroviruses and belongs to the viruses of the family Picornaviridae genus Enterovirus. The genus is further divided to different species of enterovirus A-J and rhinovirus A-C. EV-D68 belongs to the enterovirus species D with three other enterovirus types (EV-D70, EV-D94 and EV-D111). The subtypes were originally numbered in the order of discovery. The current classification is based on viral genome sequence [1]. Enteroviruses have a positive single-stranded RNA genome.

EV-D68 is acid-labile and has genetic and antigenic characteristics related to rhinoviruses. Like rhinoviruses, EV-D68 causes respiratory tract infections, and it was earlier named human rhinovirus 87 [2].

EV-D68 has been detected in respiratory tract and stool specimens and has been associated with mainly respiratory disease since its discovery in 1962 [3], unlike other enterovirus subtypes in the enterovirus D species which can cause acute haemorrhagic conjunctivitis (EV70) or even acute flaccid paralysis (EV94). Some of the rhinovirus respiratory infections present with severe illness [4]. The spectrum of disease caused by EV-D68 ranges from asymptomatic to acute respiratory infection (with significantly more shortness of breath compared to common colds typically caused by rhinoviruses) to hospitalisation with severe respiratory disease to, sporadically, neurological symptoms and death [5] [6] [7] [8].

EV-D68 can be detected by a rhino-enterovirus polymeric chain reaction (PCR) of the 5'untranslated region of the viral genome [9]. However, the specific EV-D68 diagnosis requires at least partial genotyping of the viral protein 1 (VP1) genome area, but other genome areas and whole genome sequencing are suitable as well [10]. Genotyping is used for distinguishing the different enterovirus species and subtypes [1]. It is to be noted that the EV-D68 genome evolves continuously and has a substitution rate comparable to other enteroviruses, e.g. enterovirus 71 genotype B (4.2x10-3 substitutions/site/year) [10], which corresponds to the rapid evolutionary rate of avian influenza [11]. Currently, three major genetic groups of EV-D68 circulate in the world on the basis of the VP1 gene sequence [8].

Since EV-D68 causes respiratory illness, the virus can be found in an infected person's upper or lower respiratory tract secretions (saliva, nasal mucus or sputum). EV-D68 likely spreads from person to person when an infected person coughs, sneezes, or touches contaminated surfaces. Although the acid-labile rhino-/enteroviruses do not mainly transmit through the faecal-oral route, some rhinoviruses can be detected in stool samples in a severe infection [4].

Incubation period for EV-D68 is not known but it is likely to be similar to rhinovirus incubation period of 1.9 days (95% CI 1.4-2.4) [12].

A study with rhinoviruses shows that within families, rhinoviruses transmit efficiently within 2 to 16 days to all siblings and half of the parents [13]. Nasal samples can be positive for rhinovirus for up to five weeks after a symptomatic infection [10].

Recent research has suggested a change in the antigenicity and receptor properties of EV-D68, which now preferably binds to upper respiratory tract sialic acid receptors as opposed to the earlier lower respiratory tract binding [14].

There is no specific treatment for people with respiratory illness caused by EV-D68, and in severe cases the treatment is supportive.

# Event background information

**Current epidemiological situation in the USA**

From mid-August to 24 September 2014, 220 persons from 32 states were confirmed to have respiratory illness caused by EV-D68. The 30 states are Alabama, Arkansas, California, Colorado, Connecticut, District of Columbia, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Jersey, New York, North Carolina, North Dakota, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Utah, Virginia, Washington, and West Virginia. The cases of EV-D68 infection were confirmed by the CDC or state public health laboratories, which then notified CDC. This represents an increase in the number of confirmed and suspected cases associated with this viral strain in comparison to reports from previous years. In the period 2009–2013, the CDC's National Enterovirus Surveillance System (NESS) received only 79 reports of EV-D68. Small clusters were also reported in 2009–2010 [15].

The initial signal for this event was recorded on 30 August 2014 and later (8 September 2014) confirmed when the Centers for Disease Control and Prevention (CDC) reported that:

- on 19 August 2014, a paediatric hospital in Kansas City (Missouri) notified CDC of an increase in patients admitted with severe respiratory illness compared to historical data. In addition, an increase of detections of rhino-/enterovirus by PCR in nasopharyngeal specimens was reported, starting on 5 August 2014;
- on 23 August, a paediatric hospital in Chicago (Illinois) notified CDC of an increase in patients with similar symptoms as the ones in Kansas City. This was also confirmed by the Illinois Department of Public Health.

EV-D68 was identified in 19 of 22 specimens from Kansas City (Missouri) and in 11 of 14 specimens from Chicago (Illinois). Of the 19 laboratory-confirmed cases from Kansas City, the age ranged from 6 weeks to 16 years (median = 4 years). Thirteen patients (68%) had a previous history of asthma or wheezing, and six patients (32%) had no underlying respiratory illness. All patients had respiratory symptoms and hypoxemia, and four (21%) had wheezing but only five patients (26%) were febrile. All patients were admitted to the paediatric intensive care unit.

Of the 11 laboratory-confirmed cases from Chicago, the age ranged from 20 months to 15 years (median = 5 years). Eight patients (73%) had a previous history of asthma or wheezing. Ten patients were admitted to the paediatric intensive care unit for respiratory distress.

Admissions for severe respiratory illness have continued at both locations at rates higher than expected for this time of year. As of 3 September 2014, Kansas City has treated 500 children, 15% of whom were admitted to ICU. No fatalities were reported. The number of daily admissions has decreased by 50%, from 30 per day to 15 per day. The increase in respiratory illness is likely due to other viruses as well, and the role of EV-D68 is still being investigated.

On 10 September, the Kansas Health Institute reported a decrease in the number of suspected cases, probably due to the communication of preventive measures and early recognition and management of symptoms.

CDC provides regular updates on the number of cases and on the US states that report confirmed EV-D68 infections.

**Current epidemiological situation in Canada**

From 1 to 11 September 2014, laboratory tests confirmed ten EV-D68 cases in Calgary (Alberta), five in Edmonton (Alberta) and three additional cases in central and northern Alberta. The CEO of Windsor Regional Hospital (Ontario) reported more than ten children treated due to a severe respiratory illness since 11 September 2014. Among children hospitalised in Calgary, nine cases had confirmed EV-D68 infection. The ages of the patients ranged from 22 months to 12 years. Four of the nine are female. Health authorities conduct laboratory tests to confirm whether the strain is the same strain as the on currently circulating in the US. Further studies are ongoing to determine when the virus first appeared in Canada. Studies are also being carried out on the diversity of the circulating strains and the clinical presentation associated with EV-D68.

The increase in cases has also been acknowledged by Public Health Canada.

**Epidemiological background – EV-D68 infections**

Since the original isolation of EV-D68 in four children with respiratory illness in California in 1962 [3], EV-D68, which is not a reportable disease, has been reported rarely: ten publications which reported similar symptoms during 2006–2011 in

Asia, Europe and the United States were retrieved from the scientific literature [16] (Table 1). Table 1 provides an overview of publications on EV-D68 epidemiology with regard to reports of acute respiratory illness worldwide between 2006 and 2011.

No fatalities were reported from the recent clusters in the USA, while five deaths were reported in previous reports [14]. A retrospective study (1994–2010) in the Netherlands has found 71 positive specimens in a sample collected for acute respiratory infections; 67 (94%) of which were from symptomatic patients [8]. Following the 2010 outbreak, no cases were detected in 2011, 10 in 2012, 3 in 2013, and 8 in 2014 so far, all in respiratory specimens from patients with respiratory symptoms (personal communication).

Since 2008, 60 cases have been reported in France through the National Enterovirus Network (personal communication), 63% of which with respiratory symptoms. To date, one respiratory case was notified in a baby (personal communication).

In the United Kingdom, seven cases from young children were reported in 2012, three in 2013, and two in 2014. Nine of twelve cases were diagnosed from respiratory samples (personal communication).

In Finland, several different enteroviruses have been circulating in 2014, and one EV-D68 detection has been confirmed in one diagnostic laboratory (data not covering the whole country; personal communication).

**Table 1: Clusters of acute respiratory illness (EV-D68 epidemiology, 2006–2011)**

| Date/time period | Country/region | Number of cases and/or positive samples for EV-D68 | Common signs and symptoms upon presentation | Demographics | Underlying illness | Comment | Ref. |
|---|---|---|---|---|---|---|---|
| Aug–Dec 2006 and Jan–Dec 2008 | China | 11 in 2006; 2 in 2008 out of 130 human enterovirus-positive cases | Pharyngeal congestion, myalgia, headache, chills, sore throat, rhinorrhoea, sneezing, cough | Adults with acute respiratory tract infection | | A large follow-up of respiratory illness in >15-year-olds over the period August 2006 through April 2010 | [17] |
| May 2008–May 2009 | Philippines (eastern Region) | 21 (2.6%) out of 816 samples collected from patients hospitalised with pneumonia | Cough, difficulty breathing, wheezing and retractions | 17 (81%) out of 21 were aged 0–4 years | Not specified | 2 fatalities.<br>Sampling done only among paediatric patients | [7] |
| Sep 2009 to Jun 2010 | France (north-east) | Of the 16 HEV strains, 10 (63%) were identified as the EV-D68 genotype | Acute wheezing or bronchitis | 651 consecutive paediatric patients tested.<br>The 10 EV-D68 positive patient were 6 months to 10 year old (median: 3.8 years) with a male–female of 1:1.5. | 8 out of 10 EV-D68-positive patients had underlying pathologies (not specified) | Sampling among hospitalised paediatric patients.<br>None of the 10 EV-D68-positives required admission to ICU. | [18] |
| Jul–Oct 2010 | Japan (reports from local public health authorities)* | >120 cases | * Asthmatic bronchitis, pneumonia, febrile convulsions (1 case) | * 10 out 11 paediatric patients were aged 0–4 years (the study did not include patients aged 20 years and over | Not specified | * clinical and demographic information assessed only in 11 paediatric patients only.<br>One fatality (boy aged 4 years) | [16] |
| Aug–Oct 2009 | Pennsylvania, USA | 28 (42%) out of 66 children who tested positive for rhinovirus were EV-D68 positive | - | 15 (54%) out of 28 patients who were EV-D68 positive were aged 0–4 years. No information on the age distribution of the other patients. | - | 15 (54%) out of 28 admitted to ICU.<br>No fatalities.<br>Mean stay in hospital: 5 days | [16] |
| Aug–Sept 2010 | Arizona, USA | 18 patients with respiratory illness. EV-D68 isolated in 5 of 7 specimens sent to CDC | Cough and tachypnea or hypoxemia, wheezing, abnormal lung examination | Not specified | Not specified | Increase in paediatric cases triggered investigation | [16] |
| 1994–2010 | The Netherlands (nationwide) | Biobank of GP surveillance for ARI: 240 (2.4%) of 9979 specimens were EV positive and 57 (24% of all EV) were EV-D68.<br>Children cohort study: 76 (2.7%) of 2764 specimens were EV positive and 13 (12% of all EV) were EV-D68 | GP surveillance:<br>EV-D68-positive patients had significantly more dyspnoea, cough, and bronchitis when compared to EV-D68-negative patients<br>Children cohort study: mild symptoms, cough | GP surveillance:<br>Highest prevalence of EV-D68-positive patients was in those aged 50–59 years.<br>Highest prevalence of EV-D68-negative patients in those aged 10 years or less. | - | Samples collected as part of general practice sentinel ARI surveillance (1994–2010) and three children cohort studies (2004–2009).<br>Highest number of EV-D68-positive patients in 2010 over a 6-week period | [8] |
| Oct 2008–Oct 2009 | Italy (Pavia) | 12 out of 1500 samples collected | Adult and paediatric patients admitted with acute respiratory illness | - | - | - | [19] |
| Aug–Nov 2010 | The Netherlands (Groningen) | 24 patients with EV-D68 out of 231 admitted with respiratory illness | Exacerbation: asthma/wheezing (10 patients), pneumonia (6), upper respiratory tract infection (8) | 1 month to 72 years of age (median: 14 years)<br>10 patients were under 10 years (42%) | 14 with underlying pulmonary disease; 5 with unspecified underlying chronic illness | 5 patients admitted to ICU.<br>No fatalities | [5] |
| 2006–2011 | Thailand | 25 EV-D68 cases of Thai children<br>with respiratory illnesses from 2006–2011 (n=1810) | Fever, cough, dyspnoea, and wheezing | Majority of cases were children aged >5 years (64%) | | 36% required hospitalisation | [10] |

# ECDC threat assessment for the EU

**Is the increase number of cases in the USA and Canada unexpected?**

The increasing trend in detections of the EV-D68 in the recent years has been unexpected in comparison to historical data [16]. In the USA and Canada, the authorities have reported that the upsurge in severe respiratory illness cases, particularly in the paediatric hospitals, has been unexpectedly high in comparison to previous years.

The change in the antigenicity and receptor properties of EV-D68 to bind now to upper respiratory tract sialic acid receptors in comparison to the earlier lower respiratory tract binding [14] would suggest a greater adaptation for human infection and transmission between humans. However, it would not explain the more severe outcomes of the EV-D68 infection. It cannot be ruled out that the increased number of confirmed cases in 2014 in the USA and Canada are a surveillance artefact related to increased laboratory testing of acute respiratory illnesses with improved assays. Several European countries have reported EV-D68 cases for a number of years both in hospitals and the community (Table 1). It is likely that EV-D68 is circulating in other countries as well, but is not detected/reported because of the current diagnostics.

In temperate countries, enteroviruses typically circulate with summer–autumn seasonality. In addition, the apparent severity of EV-D68 may be an artefact and relate to the fact that the severe cases are more likely to be investigated. There are only few community-based studies assessing the incidence of EV-D68 infection in the general population.

**Is the EV-D68 strain currently circulating in the USA and Canada already circulating in the EU?**

Canada is currently investigating whether the clusters of EV-D68 seen in Alberta and Ontario are caused by the same virus strain currently affecting the USA. To date, this has not yet been confirmed.

EV-D68 is currently circulating in the EU/EEA Member States and has been detected in Finland, France, the Netherlands, and the United Kingdom in 2014 (personal communication). Not all characteristics of those viruses are known, but the viruses in the Dutch cluster are in the same major genetic group as the viruses currently circulating in the US (personal communication). There are, however, also viruses of a different genetic group that have been detected (personal communication). There is no broader evidence that viruses identified in Europe are related to the current viruses circulating in the USA and Canada.

**What is the current status of non-polio enterovirus surveillance in Europe?**

Respiratory infections of rhinoviruses or non-polio enteroviruses are not notifiable infections in the EU/EEA. Only Belgium, Romania and the Slovak Republic conduct syndromic surveillance of severe acute respiratory infections (SARI). Additionally, Finland, France, Ireland, Spain, Sweden and the United Kingdom report laboratory-confirmed influenza infections of ICU patients to The European Surveillance System (TESSy) and may possibly use the same system to report also other pathogens like EV-D68.

Only a few EU/EEA countries conduct enterovirus surveillance, and ECDC does not have information which countries have established surveillance schemes for respiratory specimens (screening for enteroviruses) or have other schemes for testing for rhino-/enteroviruses, e.g. using acute respiratory infection sentinel sampling, which is part of influenza surveillance, to focus on rhino-/enteroviruses during the summer and autumn months.

ECDC does not have a good overview of activities in Member States aimed at the detection of non-polio enteroviruses, and it is likely that the involved processes vary considerably.

**What is the laboratory capacity to detect EV-D68 in Europe?**

Some laboratories based in hospitals or the community may encounter EC-D68 samples, but they will not necessarily pass on their findings to the national reference centres for enteroviruses, which reduces the overall awareness of EV-D68 infections. When receiving samples from severely ill patients with respiratory symptoms, clinical and hospital laboratories should be aware of the possibility that EV-D68 could be the cause of the infection.

Earlier data show that some detection assays, e.g. multiplex assays, may not be sensitive enough to detect EV-D68. Alternatively, the assays may falsely detect EV-D68 as a rhinovirus [9]. Therefore, it is important that the laboratories compare their primer sets (also from commercial assays) to the publically available EV-D68 sequences and make all necessary adjustments to their detection algorithms. However, even perfectly tuned algorithms and associated assays would detect EV-D68 only as an enterovirus. In order to identify enterovirus 68, sequence typing is necessary, which is usually not performed in clinical laboratories.

The likelihood for individual cases of EV-D68 to remain undetected in the EU/EEA is high because, for example, many of the rhinovirus-positive specimens would not be further characterised through sequencing. However, if a larger severe respiratory outbreak would take place in any of the Member States, the causative pathogen would be characterised. The European Polio Laboratory network in the EU/EEA offers enterovirus typing. Furthermore, some diagnostic and public health laboratories have can characterise a large variety of viruses and also work on rhino- and enteroviruses.

It is important that the laboratories which detect and typing EV-D68 publish the sequences of those viruses on open-access sequence databases such as GenBank to ensure the possibility of comparing the viruses from other countries.

**Should this virus become established in the EU, are there specific groups at increased risk of infection and severe disease, and what options exist to mitigate this risk?**

Based on the age profiles of the earlier outbreaks, children under 10 years of age are in risk for severe EV-D68 infection, especially if they are affected by an underlying illness in the respiratory tract such as asthma. However, EV-D68 can also infect adults. It is possible that respiratory enterovirus subtypes are more pathogenic than rhinovirus strains which could lead to more severe respiratory symptoms in acute cases [18] [5].

It is important that the management of underlying respiratory illnesses of children, such as asthma, is optimised according to national and European guidelines.

Clinicians should be made aware of the current reports of EV-D68 in North America and remain vigilant for possible increases in unexpected infections causing respiratory illness, especially among children returning from North America. In general, enteroviruses circulate and peak in summer and autumn, so it is not unusual to see additional cases caused by enteroviruses at this time of year.

Enteroviruses, such as EV-D68, are related to the common cold virus and can spread from person to person through coughing and sneezing, by close contact with infected persons, or by touching a contaminated surface. Therefore reminding ill people of the most basic hygiene measures (including hand washing, avoiding contacts and staying home if sick) to control transmission between people remains effective.

ECDC is closely monitoring the situation and will continue to inform Member States if additional EV-68 cases are confirmed in the USA, Canada and EU/EEA Member States.

# Conclusions

- Since mid-August 2014, some regions in the USA and Canada have been experiencing an increase in reports of severe respiratory illness associated with EV-D68 infection. Paediatric admissions for severe respiratory illness have increased for some hospitals as compared to historical data. As of 19 September 2014, EV-D68 has been detected in 22 US states and two provinces in Canada.
- It remains unclear if increased testing or improved sensitivity of the surveillance has contributed to the current increase in EV-D68 infections in the USA and Canada, or if a change in the pattern of the disease caused by EV-D68 is the underlying cause of the current epidemic. There is no detailed description of the clinical picture of EV-D68 cases in the USA and Canada.
- An epidemiological link across the clusters reported in several US States has not yet been established, and it cannot be ruled out that the virus is circulating independently in several locations.
- Initial contacts with several EU/EEA countries have not indicated a growing number of acute respiratory infections or an increased number of hospital admissions.
- However, sporadic cases of EV-D68 have been documented in several EU/EEA countries in recent years. In 2014, EV-D68 was detected in at least four EU/EEA countries but no epidemic clusters of severe disease were reported; none of the Member States has so far issued an Early Warning and Response System (EWRS) notification.
- Based on the current information, EU/EEA countries have a moderate risk of EV-D68 transmission because the circulation of this strain in the population is low.
- The likelihood for cases to be laboratory-confirmed in EU/EEA countries is low because most countries do not routinely screen for EV-D68, and the disease is not notifiable. If all other respiratory pathogen detections were negative, or if rhino-/enterovirus was detected initially, EV-D68 should be considered the causative pathogen of the disease. More systematic testing of severe respiratory illness cases for EV-D68 could be considered in EU/EEA countries to better document the circulation of this virus.
- EU/EEA countries need to remain vigilant and consider strengthening respiratory sample screening for enteroviruses and enterovirus typing as there has been an apparent upsurge in EV-D68 cases in the USA and Canada.
- Patterns of transmission are thought to be similar to the rhinovirus transmission through direct and respiratory droplet transmission, with an incubation period of a few days.

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