



RAPID RISK ASSESSMENT

Enterovirus detections associated with severe neurological symptoms in children and adults in European countries

8 August 2016

Main conclusions and options for response

Since April 2016, Denmark, France, the Netherlands, Spain, Sweden and United Kingdom (Wales) have reported severe enterovirus infections associated with a variety of different strains. Compared with previous years, the Netherlands and Germany also reported increased detection of enterovirus-D68 and other enteroviruses.

In addition, Ireland reported an increasing number in enterovirus-associated viral meningitis cases.

The timing of the current epidemics closely follows the usual increase in summer, but reports suggest that seasonal enterovirus (EV) activity in the EU/EEA Member States started earlier than in previous years. Some Member States also report an increased frequency of severe disease associated with EV infection.

While it is difficult to interpret these observations in the absence of robust historical data, Member States should consider raising awareness of the importance of including EV infection in the differential diagnosis of neurological and severe respiratory illness in order to identify cases and initiate appropriate precautions, as well as to provide more robust epidemiological information. Reporting of enterovirus clusters and outbreaks through the Early Warning and Response System (EWRS) in EU/EEA countries is encouraged.

The full molecular and biological characterisation of the isolates from the current outbreaks will possibly enhance the understanding of the pattern of enterovirus epidemiology in Europe, including trends in subgenotypes associated with more severe clinical disease and molecular epidemiological links to strains between countries and from outside Europe.

Increased numbers of EV-A71 and EV-D68 detections reinforce the need for vigilance for enterovirus infections, especially cases that present with more severe clinical syndromes. Clinicians should be encouraged to obtain stool and respiratory specimens for enterovirus detection and characterisation from all patients presenting with symptoms suggestive of meningitis; encephalitis; hand, foot and mouth disease (HFMD); acute flaccid myelitis (AFM) or acute flaccid paralysis (AFP). In respiratory disease, respiratory specimens are critical. In addition to non-polio enterovirus laboratory surveillance, AFP surveillance for purposes of polio surveillance or surveillance of meningoencephalitis are likely to be the most sensitive clinical surveillance systems to pick up such signals. The feasibility and benefits of European-level non-polio enterovirus surveillance data collection need to be explored and discussed.

Source and date of request

ECDC internal decision, 1 August 2016.

Public health issue

To assess the risk for EU/EEA countries related to severe enterovirus infections. On 29 July 2016, France reported through the Early Warning and Response System (EWRS) a recent increase of severe acute neurological conditions, probably associated with enterovirus infection, reported by one of the main academic paediatric hospitals in Paris.

Consulted experts

ECDC authors (in alphabetical order): Eeva Broberg, Mike Catchpole, Denis Coulombier, Alastair Donachie, Josep Jansa and Otilia Mardh.

External reviewers: Bruno Lina (CHU Lyon, France), Denise Antona (Santé publique France, France), Kim Benschop and Adam Meijer (RIVM, Netherlands), Sabine Diedrich (Robert Koch Institute, Germany), Stefano Fiore (Istituto Superiore di Sanità, Italy), Brendan Mason (Public Health Wales, UK), Lucía García San Miguel (Ministerio de Sanidad, Servicios Sociales e Igualdad, Spain), Mireia Jané and Ana Martínez (Public Health Agency of Catalonia), Dina Pfeifer (WHO).

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Disease background information

Enteroviruses

Enteroviruses (EV) comprise a large and diverse group of non-enveloped RNA viruses within the genus Enterovirus in the family Picornaviridae [1]. The currently known 116 enteroviruses identified from humans are classified based on their RNA sequence and their order of identification into four enterovirus species EV-A to EV-D and rhinovirus A-C [2].

Enteroviruses have a positive-stranded RNA genome and undergo constant evolutionary changes, like other RNA viruses. Within the EV species, several serotypes exist, e.g. enterovirus A species consists of 25 serotypes, including EV-A71 and Coxsackievirus A16 (CV-A16) [3]. EV are further divided into genogroups and subgenogroups within the serotypes. EV-A71 viruses, for example, are divided into six genogroups (A to F) [4], with only B and C known to be associated with outbreaks. Within the genogroups, subgenogroups exist. Subgenogroups B4, B5 and C4 are mainly restricted to Asian countries while C1 and C2 circulate mainly in Europe [5]. Similarly, EV-D68 is divided into genetic clades A, B and C, with subclades A1 and A2 and B1 and B2. Most acute flaccid paralysis (AFP) cases associated with EV-D68 are infected with EV-D68 subclade B1 [6].

Most EV infections result in asymptomatic infection. Nevertheless, enteroviruses can cause a diverse spectrum of clinical symptoms in humans, ranging from mild febrile illness and viral exanthema to respiratory infections; hand, foot and mouth disease (HFMD); myocarditis; meningitis; encephalitis; and rare but severe acute flaccid paralysis (AFP) or acute flaccid myelitis (AFM). Enteroviruses are cytopathic, and tissue-specific cell destruction occurs during the infection [1]. A single enterovirus type can cause a variety of clinical manifestations and many enterovirus types can cause similar symptoms. Enteroviruses can cause large outbreaks, as was seen with EV-D68 in the USA and Canada in 2014 [7] and with EV-A71 in the Asia-Pacific region [8].

EV can be transmitted by both faecal-oral and respiratory routes. Faecal-oral transmission may predominate in areas with poor sanitary conditions, whereas respiratory transmission may be important in areas with good sanitation and hygiene systems. In addition, transmission of acid-sensitive EV, such as EV-D68, is considered most likely to be through the respiratory route, as it almost exclusively infects and replicates in the respiratory tract. EV that cause vesicular exanthema can presumably be spread by direct or indirect contact with vesicular fluid. EV are transmitted by hand contact with secretions and autoinoculation to the mouth, nose or eyes. Young children generally introduce EV into the family [1]. Infections in different family members can result in different clinical manifestations. Community transmission also occurs under circumstances of close mixing, when EV can be rapidly transmitted, and therefore social-distancing measures have been used during outbreaks [9].

Nosocomial transmission of various Coxsackie viruses A and B and Echoviruses has been documented, especially in nurseries for newborns. Although no known non-human reservoir for EV exists, EV can survive for months in environmental conditions with neutral pH, moisture and low temperatures when embedded in organic

material [1]. EV has been isolated from swimming and wading pools, but there is no evidence that recreational swimming in chlorinated water is associated with a risk for transmission [1].

The incubation period for enteroviruses is usually three to ten days, although some enteroviruses can give rise to symptoms in one to three days [1]. Epidemics of EV can be local, regional, national or even international [1].

Some outbreaks of HFMD caused by EV-A71 have been associated with fatal brainstem encephalitis, restricted largely to young children [10,11]. In severe HFMD, death can occur 1–3 days after onset [12]. Encephalitis is typically a brainstem encephalitis and is often accompanied by severe cardiorespiratory symptoms [13].

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), hospitalisation with severe respiratory disease and sporadically to neurological symptoms and death [14-17]. In a retrospective paediatric pneumonia study from a 3.9 million population in the Philippines, 21 of 816 pneumonia patients had EV-D68 infection and two (9.5%) of these died. Among all pneumonia-related deaths, EV-D68 accounted for 2.9% (2 out of 70 deaths) [16]. In three separate Dutch children cohort studies conducted between 2004 and 2009, none of a total of twelve EV-D68-positive patients developed complications. All respiratory symptoms did clear up within four weeks following detection of EV-D68 [17]. During the US outbreak in 2014, the odds of having EV-D68 infection for children with AFM were 10.3 times higher than for those tested for acute respiratory infection [18]. The CDC case definition for EV-D68 associated with neurological illness included acute onset of limb weakness occurring in a person ≤ 21 years of age and with spinal MRI lesions largely restricted to spinal grey matter [19]. However, EV-C105 infection has also been associated with the American AFM cases [20].

Laboratory diagnosis

The diagnosis of EV based on real-time reverse-transcription PCR (RT-PCR) is a sensitive and rapid diagnostic method which has become the standard method over virus isolation. Virus isolation is labour-intensive and time-consuming and not practical for clinical decision-making [21]. EV-specific primers targeting the conserved 5' untranslated region (UTR) are used to perform real-time RT-PCR directly from clinical specimens, on respiratory or rectal swabs, vesicle fluid, stool sample, cerebrospinal fluid (CSF), blood or urine [13,22].

An Australian study found that EV-A71 RNA was more commonly detected in faeces, rectal swabs and throat swabs than in CSF [23]. Hence, a negative CSF does not rule-out an EV-A71 infection. Specific RT-PCR assays have been developed for EV-A71 [24] and for EV-D68 [25].

For typing and molecular epidemiology purposes, sequencing of the VP1 gene should be performed [21]. For typing from clinical specimens, a reverse transcription-semi-nested PCR (RT-snPCR) assay can be used, especially with consensus-degenerate hybrid oligonucleotide primers [26]. Attention needs to be paid to the sequence of the recently circulating strains, recombinants, and sequences of related enteroviruses, in order to optimise the PCR primers. Genotyping provides more information than serotyping, and the nucleotide sequence of VP1 can function as a surrogate for antigenic typing in order to distinguish EV serotypes [1]. Many EV serotypes share some antigenicity, e.g. EV-A71 and CV-A16, and are therefore difficult to distinguish by neutralisation assays.

Diagnosing an EV infection remains challenging. As asymptomatic EV infections are common, an identification of an EV in a specimen does not prove disease causation. EV infections can also cause a wide variety of unspecific symptoms and therefore specimens for laboratory confirmation should not be collected in the early phases of the symptoms. Central nervous system (CNS) specimens have limited sensitivity for detection of EV, and it is uncommon to find virus in the CSF from encephalitis cases [1]. The highest sensitivity for EV detection is usually found with stool specimens regardless of clinical presentation, except for respiratory disease, for which a respiratory specimen has highest sensitivity and should be the preferred specimen.

Treatment

There is no antiviral treatment for EV infections. However, efforts are being made to develop broad spectrum antivirals [27,28]. Patients with severe neurological disease should be treated following routine clinical management standards [19]. According to the US CDC, no concrete evidence has been found for the benefit of corticosteroids, intravenous immunoglobulin, plasmapheresis, interferon, antivirals, or other immunomodulatory agents in the treatment of AFM [19]. Moreover, US CDC guidance discourages the use of plasmapheresis and immunosuppressive biologic modifiers, including corticosteroids, in the management of AFM [19].

Due to large outbreaks of EV71 in south-east Asia causing severe disease, several vaccine candidates were developed in China, Singapore and Taiwan, and tested in phase 1–3 clinical trials [29–31]. No EV-A71 or other enterovirus vaccine other than polio vaccine is licensed in the EU/EEA.

Incidence and earlier outbreaks

The incidence of non-polio enterovirus infections in EU/EEA countries is unknown. In the Netherlands, an incidence of 26 per 100 000 neonates (age ≤ 30 days) has been estimated [32], although the study focused on non-polio enterovirus infections in neonatal intensive care units.

The epidemiological pattern observed in Europe differs from Asia. In temperate climates, EV infections follow a seasonal pattern, with the highest incidence in summer and autumn – although outbreaks can extend to winter [1,33].

We have summarised earlier outbreaks of EV-A71 and EV-D68 in previous risk assessments [34–37]. In short, after the large outbreaks in Bulgaria and Hungary in the 1970s [38,39], the circulation of EV-A71 has not been associated with epidemics, but rather with sporadic, often mild cases, presenting mainly with HFMD [40–43]. In Norway, 14.5% of children below two years of age have had an EV-A71 infection, based on a serial stool sampling of healthy infants in 2001–2003 [44]. In Germany, from 2006–2014, approximately 2 500 faecal or CSF specimens from national enterovirus surveillance of hospitalised patients were tested annually for EV: 25–30% of all samples were positive. In 0.8–12.7% of the positive sample, EV-A71 was identified, with increased detection rates in more recent years and with C2 as the predominating subgenogroup [45]. In addition, a new recombinant variant C1 strain was identified in Germany in 2015 [45]. Besides characteristic symptoms for EV-A71 (including nuchal rigidity, headache, fever, and vomiting), cerebral seizures, myoclonia, ataxia, petechiae, and stomatitis were also mentioned for some patients who tested positive for the new variant C1-like strains [45].

In recent years, severe sporadic cases of meningoencephalitis with EV-A71 were observed in France [46–49] and the United Kingdom [40,46]. In Italy, a cluster of EV-A71 subgenogroup C2 was detected in a nursery school; the children presented with fever, vomiting, drowsiness, neck stiffness and headache [50]. As the population is largely immunologically naïve to these new subgenotypes, the infections could become more frequent and also cause more severe clinical presentations.

In Europe, only limited information is available on the earlier and current circulation of EV-D68. This is in part because clinicians do not usually request enterovirus diagnostics for patients with respiratory disease, but also because many in-house and commercial molecular detection assays do not distinguish between rhinoviruses and enteroviruses, which is problematic when trying to determine enteroviruses as the cause of a respiratory disease.

There is, however, evidence that cases of EV-D68 infection appear to be sporadic in general, and no large outbreaks were seen, even if several severe infections were reported [14,17,51–54]. In the United Kingdom (Wales), a cluster of atypical adult Guillain–Barré syndrome was temporally related to a cluster of four children with AFP (two with EV-D68 and one with echovirus 25 detection) in 2015–2016 [55].

Enterovirus surveillance and capacities to detect enteroviruses in EU/EEA countries

ECDC reviewed the capacities for enterovirus surveillance and detection of non-polio enteroviruses in EU/EEA countries in the spring of 2016. The results are still pending full analysis. Based on a preliminary analysis, most EU/EEA countries have good capacities to detect non-polio enteroviruses, as was demonstrated in connection with the 2014 outbreak of enterovirus D68 [54].

Event background information

Reporting through the Early Warning and Response System on 29 July 2016, France informed the Member States about an increase of severe acute neurological conditions, probably associated with enterovirus infection, reported by one of the main academic paediatric hospitals in Paris. Upon being alerted, on 6 July 2016, the authorities initiated a retrospective case review that identified 22 children since April 2016, 18 with rhombencephalitis, encephalitis, cerebellitis or myelitis, and four with facial nerves radiculitis. The patients' ages ranged from three months to 15 years, with a median age of three years. As of 28 July, enterovirus infection was

confirmed in eight of these patients. The types of enterovirus detected were EV-A71 belonging to the subgenotype C1 (n=3), EV-D68 (n=2), Coxsackievirus A10 (n=1), and Coxsackievirus A2/EV68 co-infection (n=1). The VP1 sequence of the EV-A71/C1 displayed a close genetic relationship with the sequences of EV-A71/C1 strains collected in Germany in 2015 [45]. Further investigations are ongoing.

In the Netherlands, an increase in the number of paediatric pneumonia cases with positive EV-D68 respiratory specimens was reported in July 2016 (n=32) through the national enterovirus molecular surveillance network (VIRO-TypeNed) [56]. As during the outbreaks in 2010 and 2014 [17], the current outbreak is associated with an increased detection of EV-D68 cases (n=5) across the country in the course of surveillance of influenza-like illness (ILI) and acute respiratory infection (ARI). All EV-D68 cases detected in 2016 for which the VP1 was sequenced belonged to subclade B1. In addition to EV-D68, two cases each of EV-C105 and CV-A6 – causing a family cluster of HFMD – were detected through the ILI/ARI surveillance system. VIRO-TypeNed reported that so far this season, Echovirus 6 is the dominant EV strain detected in the Netherlands (12% of all reported and typed EV infections), followed by EV-A71 (10%, subgenogroups C1 and C2), EV-D68 (10%), and Echovirus 11 (9%).

While clinical data are reported sparsely in the Netherlands, three cases infected with Echovirus 6 were reported with neurological symptoms. Two other cases with neurological symptoms were found infected with CV-B4 and CV-B3. The EV-A71 subgenogroup C1 viruses (six cases, all identified in July) belonged to the same subgenotype C1 cluster identified in Germany in 2015 [45]. Nevertheless, an increase in the number of neurological enterovirus cases submitted for typing was neither observed nor confirmed in the Netherlands.

Of the 32 EV-D68 cases reported in July 2016, twenty-four patients presenting with severe symptoms, including one case of acute flaccid myelitis (AFM), were reported in the region of Groningen, in the northern part of the Netherlands (personal communication). The eight adults who were hospitalised have recovered. Twelve out of 16 hospitalised children under the age of six required intensive care, and all but one fully recovered; one case remains in a serious condition with paralysis. None of these cases showed identifiable epidemiological links.

In Catalonia, Spain, an outbreak of EV-A71 associated with neurological complications has been ongoing since mid-April 2016, affecting children up to twelve years of age. As of 3 August 2016, 109 cases of enterovirus infection with neurological complications have been reported, most of which have resolved favourably. The latest update from regional health authorities reported that three children remain hospitalised, including one with acute neurological disease who was admitted to intensive care [57]. The age of cases ranges between one month and twelve years of age. All cases were confirmed having at least one sample specimen positive to enterovirus. Up to the beginning of August 2016, 34 children were tested positive for EV-A71.

In Ireland, viral meningitis and encephalitis are notifiable conditions but an enhanced surveillance data collection is not in place. Notifications of viral meningitis increased in 2016: 201 cases were notified during the first six months of 2016 versus 165 for the same period in 2015. Most cases are infants. In both years, the majority of viral meningitis cases were caused by enteroviruses, but complete virus characterisation is pending. An increase in 2016 has also been observed in viral encephalitis: 33 cases this year compared with 47 in total in 2015. None of the viral encephalitis cases had a positive enterovirus detection. In 2016, one case of AFM was notified in a two-year-old child.

In the UK (Wales), EV-D68 activity was detected in the last couple of weeks, with one child in critical care (personal communication).

In Italy, recent surveillance activities do not show an unusual increase of enterovirus infections in children with acute flaccid paralysis (AFP). In 2016, only two cases of AFP were associated with enterovirus infection (personal communication). The serotypes detected were Echovirus 6 and EV-D68 (personal communication).

In Portugal, no increase in severe acute neurological conditions associated with enterovirus infection was detected in 2016. Laboratory notifications of confirmed enterovirus cases with neurological symptoms were reported in December 2015 and January 2016. The serotypes detected were EV-D68 (n=2), EV-A71 (n=2) and Coxsackievirus A6 (n=1).

In Germany, as of 5 August 2016, 173 of 1 221 cases of aseptic meningitis investigated since the beginning of 2016 tested positive for enteroviruses, with an increase observed since mid-June. In 2015 (weeks 1–30), 1 095 reported cases of aseptic meningitis (with 110 enterovirus detections) were reported in Germany. The EV serotypes detected were EV-A71 (n=19), EV-D68 (n=1), Echovirus-6 (n=13), Coxsackievirus A6 (n=7), Coxsackievirus A9 (n=5), Coxsackievirus B4 (n=7), Coxsackievirus B5 (n=5), Echovirus-7 (n=6), Echovirus-30 (n=6), Echovirus-25 (n=4), Echovirus-18 (n=5), and Echovirus-9 (n=7). Typing results are pending for 75 isolates. Of the genotyped EV-A71, 14 were determined as subgenotype C1 and three as C2.

In Denmark, there was no overall increase in enterovirus infections in 2016. There were no cases of EV-D68, but nine cases of EV-A71 were detected. Clinical information was available for seven of these cases. One patient presented with meningitis, one with encephalitis, three patients were described as having enteroviral disease (all three had diarrhoea), one was described as having HFMD, and one patient had a rash as the only symptom.

In Sweden, enterovirus surveillance was performed for all viral meningoencephalitis cases. Since April 2016, samples from 40 patients have tested positive for enteroviruses. Sixteen samples from children below 12 years of age were positive for EV-A71 (n=5), Echovirus-30 (n=2), Coxsackievirus B5 (n=2), and one of each

Coxsackievirus A6, B1, Echovirus-3, 5, 9, 11 and 18. The VP1 sequence of the EV-A71 showed a close genetic relationship with the available sequences of EV-A71/C1 strains.

Outside Europe, an unusually intense season of HFMD was reported from Korea in 2016 [58]. In addition, in the USA, during the first half of 2016, 21 AFM cases were reported; in all of 2015, a total of 21 AFM cases were reported from 16 states [59]. As of July, the US CDC is aware of limited sporadic EV-D68 detections in 2016 but there is no indication of unusual activity [60].

ECDC threat assessment for the EU

Since April 2016, several EU/EEA countries have reported severe enterovirus infections. Some countries reported an increased numbers of enterovirus detections compared to previous years. It is likely that there is ongoing widespread transmission of different enterovirus species and serotypes in Europe, including EV-A71 and EV-D68, with the majority of detected and reported cases representing the more severe clinical disease. Before 2016, infections caused by EV-A71 have only occasionally been associated with severe outcomes in Europe, which makes the current situation in Europe unusual.

Enterovirus epidemics in temperate countries tend to occur in summer and autumn, so the current increase in detections of enteroviruses in the EU was expected; what was not expected in 2016 was the unusually early start in April.

Enterovirus infections are transmitted from person to person by direct contact with nose and throat discharges, saliva, fluid from blisters, or the faeces of infected persons. Outbreaks are therefore difficult to control. The EV-A71 virus can be shed in faeces for several weeks after a patient's recovery, making transmission among close contacts possible even if the primary case displays no symptoms.

EV-A71 is the most neuropathogenic non-polio enterovirus in humans, causing a variety of neurological diseases, including aseptic meningitis, encephalitis, brainstem encephalitis and poliomyelitis-like paralysis. Therefore, EV-A71 outbreaks require careful assessment. As illustrated by the number of EV-A71 patients in Spain presenting with severe illness and requiring admission to intensive care, the epidemic causes considerable burden on paediatric intensive care units. At the same time, based on the experiences from EV-D68 US epidemic in 2014, EV-D68 detections and clusters of cases with severe outcomes have to be carefully assessed.

Most EU Member States experience seasonal transmission of enterovirus in summer and early autumn. Vigilance for increased disease rates and new recombinant viruses should be kept high during this period because additional cases are expected in the coming months.

The majority of EU/EEA Member States have adequate laboratory capacities to detect these viruses, but the absence of coordinated EU surveillance for non-polio EV infection makes it difficult to detect and interpret epidemiological patterns. Advanced molecular methods support accurate and timely diagnostics for EV, which can improve the understanding of epidemiological trends and guide the implementation of adequate response measures. In addition, clinicians should be made aware that acute and severe respiratory illness can be caused by enterovirus infection so that they can request appropriate diagnostics.

Previous ECDC risk assessments on enteroviruses

Outbreak of enterovirus A71 with severe neurological symptoms among children in Catalonia, Spain 14 June. 2016. <http://ecdc.europa.eu/en/publications/Publications/07-06-2016-RRA-Enterovirus%2071-Spain.pdf>

Enterovirus D68 detections in the USA, Canada and Europe – Second update 25 November 2014. <http://ecdc.europa.eu/en/publications/Publications/Enterovirus-68-detected-in-the-USA-Canada-Europe-second-update-25-November-2014.pdf>

Enterovirus 68 detected in the USA and Canada. First update, 15 October 2014. <http://ecdc.europa.eu/en/publications/Publications/Enterovirus-D68-United-States-Canada.pdf>

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