RAPID RISK ASSESSMENT

Outbreak of enterovirus A71 with severe neurological symptoms among children in Catalonia, Spain

14 June 2016

Main conclusions and options for response

This localised outbreak of neurological symptoms associated with enterovirus A71 (EV-A71) is notable in terms of its magnitude and the severity of symptoms of the reported cases. As part of this assessment it was determined that no similar outbreaks have been detected in the rest of Spain. Other EU Member States have not reported concomitant enterovirus outbreaks and ECDC is not aware of signals of other unusual enterovirus outbreaks in the EU. Reporting of such clusters and outbreaks through the Early Warning and Response System (EWRS) is encouraged.

There is evidence to suggest that the epidemiological pattern of EV-A71 in Europe is going through a change, both due to virus molecular evolution, as well as an increasing likelihood of importation of new virus strains from outside the EU. The full characterisation of the isolates from the Spanish outbreak, with complete specification of subgenotypes and detailed genomic analysis, and comparison of these to virus sequences from other countries and continents, should contribute to a better understanding of the changing pattern of EV-A71 epidemiology in Europe, including trends in subgenotypes associated with more severe clinical disease.

This outbreak of EV-A71 together with the previously reported clusters of EV-D68 reinforces the need for vigilance for enterovirus infections presenting with hand, foot and mouth disease (HFMD) and more severe clinical syndromes. Paediatricians should be encouraged to obtain specimens for enterovirus detection and characterisation from all patients presenting with symptoms suggestive of meningitis, encephalitis or acute flaccid paralysis (AFP), as well as HFMD. 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.

As a general precaution, children residing in or traveling to Catalonia should be encouraged to avoid contact with symptomatically ill children and follow strict hygiene in personal contacts. Please see the ECDC factsheet on Hand Foot and Mouth disease for more information.

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Public health issue

To assess the risk for EU/EEA countries related to the ongoing outbreak of enterovirus A71 with neurological complications among children in Catalonia, Spain.

Consulted experts

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Disease background information

Enterovirus A71

Enterovirus 71 (EV-A71), one of more than one hundred enteroviruses, belongs to the Human Enterovirus A species of the genus Enterovirus within the family Picornaviridae [1]. Enterovirus A species consists of 25 serotypes, including EV-A71 and coxsackievirus A16 (CV-A16) [2]. EV-A71 was first discovered in California (USA) in association with an outbreak of central nervous system (CNS) disease that occurred between 1969 and 1972 [3]. The current classification of enteroviruses is based on viral genome sequence and order of identification. Enteroviruses have a positive-stranded RNA genome and undergo constant evolutionary changes, like other RNA viruses. EV-A71 viruses 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 and the subgenogroups B4, B5 and C4 are mainly restricted to Asian countries while C1 and C2 circulate mainly in Europe [5]. However, EV-A71 B5 has been reported. in France [6] and Denmark [7]. EV-A71 is antigenically related to CV-A16 [1]. Cross-immunity between EV-A71 genotype A and C4 has been demonstrated *in vitro* [8]. Enteroviruses are cytopathic, and tissue-specific cell destruction occurs during the infection. This causes much of the associated disease together with the infection-induced host immune response [1].

EV-A71 is transmitted primarily through the faecal-oral route but also by oral secretions, respiratory droplets, vesicular fluid or fomites [1]. The incubation period is one to three days [1]. In general, EV-A71 transmission in Europe is associated with limited local spread. An exceptional instance of wider geographical spread to other European countries occurred in relation to an outbreak in the Netherlands in 2007 [9]. European countries may experience several virus introduction events within a year. Sustained circulation in Europe depends on the proportion of susceptible hosts. Long-term survival depends on transmission across larger geographical areas such as Russia and Asia [9]. A study demonstrated that a transmission chain extended from Asia to five different EU countries and from there on to Canada in 2003–2005 [9].

Clinical symptoms

Most EV infections, including EV-A71, result in asymptomatic infection. Most symptomatic EV-A71 infections manifest as a self-limiting hand, foot and mouth disease (HFMD) and only a very small proportion of patients develop severe and life-threatening disease [10,11]. During HFMD, usually a mild febrile illness develops with papulovesicular rash on the palms and soles as well as oral ulcers [12]. EV-A71 infection can present also as herpangina which is characterised by febrile illness and multiple oral ulcers in the posterior oral cavity, anterior pharyngeal folds, uvula, tonsils and soft palate [12]. Children younger than 2 years of age may experience a more widespread rash. Alternatively, EV-A71 can present as respiratory tract infection, gastroenteritis, non-specific rash, exacerbation of bronchial asthma, bronchiolitis and pneumonia [12]. Although EV-A71 often causes HFMD, some epidemics of EV-A71 have shown only very few cases of HFMD as was the case in Hungary in 1978 where the patients presented with aseptic meningitis, encephalitis or acute flaccid paralysis [13].

Some outbreaks of HFMD caused by EV-A71 have been associated with fatal brainstem encephalitis, restricted largely to young children [14,15]. Severe HFMD can develop within 2–3 days after initially mild disease [16]. Median time from illness onset to death for severe HFMD cases mostly caused by EV-A71 was 3.5 days and from diagnosis to death 0.5 days [16]. Encephalitis is typically a brainstem encephalitis and is often accompanied by severe cardiorespiratory symptoms [12]. Febrile seizures with good recovery of consciousness are typically seen in patients younger than 2 years of age [12]. In Asia, brainstem encephalitis has been associated often with pulmonary oedema [12], which develops after 3-5 days of fever with acute and rapidly progressing cardiorespiratory failure and presents as shock, pulmonary oedema or haemorrhages requiring intensive care to prevent death [12], which is most commonly due to neurogenic pulmonary oedema [17]. In Asia, most of the severe outbreaks have been associated with the genotype B4, B5 and C4 [18].

EV-A71 can be shed a long time after recovery, in the throat up to 2 weeks after recovery from HFMD or herpangina and in stools up to 11 weeks [19].

Long-term sequelae

Severe EV-A71 infection can cause long-term cognitive and motor deficits [20]. In a study of 63 children following outbreaks in Taiwan over the last decade, 51 recovered without deficits , while out of the 12 children who were left with deficits, three died, and of the remaining nine, two had severe motor and respiratory failure [20]. A study in Australia reported that brainstem or motor dysfunction had resolved in 77% of the cases at two months and in 90% at 12 months, but focal paresis persisted at 12 months in five out of six patients with one patient requiring invasive ventilation; the patients seen initially with AFP or pulmonary oedema a had 15 times higher risk of developing motor dysfunction than patients with other symptoms [21].

Severe nervous system-related symptoms can be confirmed by magnetic resonance imaging (MRI) which will reveal inflammation, particularly in the anterior horns of the spinal cord, the dorsal pons and the medulla [12,21]. In the current Catalonian outbreak, magnetic resonance imaging (MRI) changes have been included as part of the case definition. Using a computerised tomography (CT) scan usually shows normal images [12].

Laboratory diagnosis

Real-time reverse-transcription PCR (RT-PCR) based diagnosis of EV-A71 is the most sensitive and rapid diagnostic method available and has become the standard method over virus isolation. Virus isolation is labour-intensive and time-consuming and not practical for clinical decision-making [22]. EV-A71-specific primers 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 [12,23]. In an Australian study, it was found that EV-A71 RNA was more commonly detected in faeces, rectal swabs and throat swabs than in CSF [21]. Hence, a negative CSF does not rule out an EV-A71 infection.

For reverse transcription-seminested PCR (RT-snPCR) assay from clinical specimens, universal detection of enteroviruses by targeting the conserved 5' untranslated region (UTR) can be used, especially with consensus-degenerate hybrid oligonucleotide primers [24]. An EV-A71-specific RT-PCR can also be set up [25]. Specific attention needs to be paid to the sequence of the recently circulating strains and to sequences of related enteroviruses, e.g. CV-A16 strains, to optimise the PCR primers.

For molecular epidemiology purposes, sequencing of the VP1 gene should be performed [22]. 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. EV-A71 can also be detected by a neutralisation test following virus isolation in cultured cells. That requires a qualified type-specific antiserum which is not commercially or otherwise readily available [22]. The neutralisation assay also requires 5–7 days to be completed and is therefore not recommended for routine diagnosis of EV-A71 [22].

Despite all the laboratory methods for diagnosis, diagnosing an EV infection can be challenging. As asymptomatic EV infections are common, an identification of an EV in a patient sample does not prove disease causation. EV infections can also cause a wide variety of unspecific symptoms and therefore specimens may not be collected in the early phases of the symptoms for laboratory confirmation. 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 with stool specimens regardless of clinical presentation.

Antiviral treatment and vaccines

There is no antiviral treatment for EV-A71 infections. Due to large outbreaks of EV71 in South-East Asia in the last decades, causing severe disease, several vaccine candidates have been developed in China, Singapore and Taiwan and tested in phase 1–3 clinical trials [26-28] . One vaccine candidate, a formaldehyde inactivated EV-A71 C4 subgenotype initially isolated and produced in Vero cells by China CDC and adsorbed to $Al(OH)_3$ as adjuvant, has been tested by Sinovac Biotech Co. Ltd, China, in a phase III clinical trial in a 2-dose schedule in children 6–35 months of age (n=10 245). Cross-reactivity to other EV-A71 geno- and subgenotypes needs to be investigated and confirmed as the evidence generated to date is limited. The phase III trial showed promising safety, immunogenicity and efficacy and the vaccine candidate was authorised for use in children by the Chinese Medical Product Agency December 30, 2015. The Chinese vaccine is currently not pre-qualified by WHO and no EV-A71 vaccine is licensed in the EU/EEA.

Risk factors for EV-A71 infection

An increased risk of a severe outcome has been associated with those of a younger age [29]. Furthermore, a study showed that patients who had two of the following three symptoms: peak temperature of 38.5°C or more, fever for three days or longer and a history of lethargy, experienced more severe outcomes [30]. Clinical screening for abnormal heart rate variability has been proposed as a predictor of impending cardiorespiratory failure [12]. A study from Thailand identified the following risk factors for severe outcome: age less than 1 year, absence of oral lesions, and drowsiness/lethargy [31]. Each extra day of symptoms since symptom onset and living in a rural area has been associated with a higher risk of mortality [16]. The risk for cardiopulmonary failure increased if patients had brainstem encephalitis and more CNS-regions involved [32].

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 [33], although this study focused on non-polio enterovirus infected neonatal intensive care unit (ICU) cases. In Norway, 14.5% of children below two years of age had an EV-A71 infection based on a serial stool sampling of healthy infants in 2001–2003 [34]. In the USA, incidence varies from 3.2% in January to 50% in August and October in children below 90 days of age [35]. In China, based on a systematic review and meta-analysis of seroprevalence studies, 78% of neonates were seropositive to EV-A71, but the maternal antibodies waned by five months of age. Twenty-six percent of the one-year olds and 70% of the 5-year olds were positive for EV-A71 antibodies [36]. Comparison of seroprevalence of enteroviruses should take into account location, time and age, and therefore data from different years and locations cannot be compared [1]. A 7.2 million HFMD case surveillance registry study in China in 2010-2012, estimated the incidence of HFMD at 1.2 per 1 000 person-years. Every year, 500 to 900 reported deaths, mainly in young children have been reported with predominance of EV71 in severe cases [16]. The case-fatality rate was 0.03%, the case-severity rate 1.1% and the severe case-fatality rate 3.0% with highest incidence and mortality in children aged 12–23 months (38.2 cases per 1 000 person-years and 1.5 deaths per 100 000 person-years in 2012) [16].

EV-A71 has caused large epidemics in Asia and the Pacific region (China, Taiwan and Australia) where it is characterised by a high prevalence and severe outcomes often associated with the type C2 and C4 subgenogroups [37-40].

In temperate climates, enterovirus infections (EV) follow a seasonal pattern with highest incidence in the summer and autumn although outbreaks can extend to winters [1,35]. EV-A71 circulation shows a marked seasonal pattern from spring to fall in the northern hemisphere while this pattern is not observed in tropical areas were the seasonal distribution is homogenous [41,42]. The seasonal pattern of EV infection in Spain and in particular in Catalonia shows the highest incidence in spring, mid-April to the beginning of July, and with a second much smaller increase in November. Although the magnitude of the current outbreak is yet to be quantified, the time distribution of cases follows the usual pattern.

In recent years, severe sporadic cases of meningoencephalitis with EV-A71 were observed in France [41,43-45]. In the United Kingdom, a proportion of C1 and C2 strains (49% and 42%, respectively) [41] different from those reported between 1998 and 2006 (78% and 12 %) was observed [46], which confirms the changing pattern of EV-A71 subgenotypes coherent with their rapid genomic evolution. This was later confirmed by others [4,47]. Moreover, the EV-A71 circulation in Europe is being influenced by the importation of EV-A71 subgenotypes that have been infrequently detected in Europe [48,49]. As the population is largely immunologically naïve to these new subgenotypes, the infection can possibly present with a more aggressive clinical pattern.

A different epidemiological pattern has been observed in Europe (Table1). After the large outbreaks in Bulgaria and Hungary in the 1970s [50,51], the circulation of EV-A71 has not been associated with epidemics, but rather with sporadic, often mild cases, presenting mainly with HFMD [7,46,52,53] (Table 1). Similar genotypes of C and B to the ones detected in Asia were observed in Europe (Annex 1).

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

ECDC reviewed the capacities in EU/EEA countries for enterovirus surveillance and detection of non-polio enteroviruses in the spring of 2016. The results are still pending full analysis. Based on preliminary analysis, most EU/EEA countries have good capacity to detect non-polio enteroviruses, as was shown in connection with the 2014 outbreak of enterovirus D68 [54]. Spain has surveillance for AFP and HFMD as well as enterovirus surveillance for respiratory specimens. The latter is a voluntary surveillance system.

Event background information

An outbreak with neurological complications caused by enterovirus has been ongoing in Catalonia since mid-April 2016, affecting children up to ten years of age. As of 7 June, 87 cases of enterovirus infection with neurological complications have been reported, most of which have evolved favourably, but 22 of the cases remain in hospital, including seven in intensive care units. According to the information received from regional authorities, there are no deaths related to this outbreak. The cases are widespread in Catalonia. No cases have been identified from other areas in Spain [55].

As of 7 June, the onset of symptoms for the 87 documented cases ranged from 7 April to 6 June, with a peak around mid-May. The age of the cases ranges between three months and ten years (57 % between 1 and 2 years and 22% between 3 and 4 years). Fifty-eight per cent of cases are male and 42% are female, 26% of cases are classified as probable (encephalitis, in particular rhomboencephalitis, or AFP plus altered MRI) and 74% are confirmed (probable case plus positive sample for enterovirus) [56]. The main clinical symptoms associated with the cases are seizures, drowsiness and myoclonia. Twelve (14%) of the 87 cases required admission in ICU. Follow-up of cases will be carried out according to local clinical protocols.

Stool and respiratory specimens have tested positive for EV-A71 in this outbreak. Until 10 June, 11 cases were tested positive for both stool and nasopharyngeal swab specimens. Eight additional tested positive either in stool or nasopharyngeal specimen. This finding is consistent with the predominant circulation of EV-A71 in Spain this year according to the information obtained from the EV surveillance system in Spain.

ECDC threat assessment for the EU

There are only four larger outbreaks of EV-A71 in Europe documented in the published literature. The last epidemics of EV-A71 infection in Europe occurred in Bulgaria in 1975 with over 705 cases, of which 149 developed paralysis and 44 died. Hungary had an outbreak of EV-A71 in 1978 with 323 cases (13 poliomyelitis-like paralysis, 145 encephalitis, 161 aseptic meningitis, 4 HFMD). The current case definition used in Catalonia is highly specific and does not include cases with neurological symptoms without MRI confirmation or EV-71 cases without neurological symptoms. It is likely that there is ongoing transmission of EV-A71 in the population in Catalonia and these detected and reported cases represent only the severe end of the clinical picture. Thus far in Europe, EV-A71 has caused mostly asymptomatic infections and has been only occasionally associated with severe infection of the extent seen currently in Catalonia.

EV-A71 infection is transmitted from person to person by direct contact with nose and throat discharges, saliva, fluid from blisters, or the faeces of infected persons and therefore outbreaks are difficult to control. The virus can be shed up to 11 weeks after recovery in faeces, making the transmission within close contacts possible even when no symptoms in the primary case are visible. 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 patients in Catalonia presenting with severe illness requiring admission to intensive care, the epidemic causes considerable burden on paediatric intensive care units.

Cross-border transmission of EV-A71 has been clearly documented in the scientific literature. Barcelona and Catalonia in Spain are popular destinations for tourism. Therefore the possibility exists of an infected child transmitting the disease in other EU Member States. However, the seasonal pattern of EV infection in Catalonia and in Spain and the apparent decline of the outbreak are reducing the risk of cross-border transmission. Most EU Member States are experiencing seasonal transmission of enterovirus only in early autumn. Therefore, outbreaks in other EU Member States related to the outbreak in Catalonia could be easier to identify.

The majority of EU/EEA Member States have adequate laboratory capacities to detect these viruses, however, the absence of coordinated EU surveillance for non-polio EV infection is a challenge for interpretation of the epidemiological pattern. The availability of advanced molecular methods for detection offer the possibility to respond in a timely manner and to understand new epidemiological trends and consider adequate response measures.

Conclusions and options for response

This localised outbreak of neurological symptoms associated with enterovirus A71 is notable in terms of its magnitude and the severity of symptoms of the reported cases. As part of this assessment it was determined that no similar outbreaks have been detected in the rest of Spain. Other EU Member States have not reported concomitant enterovirus outbreaks and ECDC is not aware of signals of other unusual enterovirus outbreaks in the EU. Reporting of such clusters and outbreaks through the EWRS is encouraged.

There is evidence to suggest that the epidemiological pattern of EV-A71 in Europe is going through a change, both due to virus molecular evolution, as well as an increasing likelihood of importation of new virus strains from outside the EU. The full characterisation of the isolates from the Spanish outbreak, with complete specification of subgenotypes and detailed genomic analysis, and comparison of these to virus sequences from other countries and continents should contribute to a better understanding of the changing pattern of EV-A71 epidemiology in Europe, including trends in subgenotypes associated with more severe clinical disease.

This outbreak of EV-71 together with the previously reported clusters of EV-D68 reinforces the need for vigilance for enterovirus infections presenting with HFMD and more severe clinical syndromes. Paediatricians should be encouraged to obtain specimens for enterovirus detection and characterisation from all patients presenting with symptoms suggestive of meningitis, encephalitis or AFP, as well as HFMD. 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.

As a general precaution, children residing in or travelling to Catalonia should be encouraged to avoid contact with symptomatically ill children and follow strict hygiene in personal contacts. Please see the ECDC factsheet on Hand Foot and Mouth disease for more information [57].

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Annex 1. Enterovirus A71 outbreaks in Europe, 1975–2015, based on a literature search

Date/time period	Country/region	No. of cases or positive samples for EV-A71	Genotype	Signs and symptoms	Demographics	Type of study	Publication year	Reference
1975	Bulgaria	451	B1	Non-specific febrile illness or neurological disease	Children	Outbreak	1979	[50]
1978	Hungary	323	B1	Aseptic meningitis and encephalitis; flaccid paralysis	Children	Outbreak	1982	[13]
2001–2003	Norway	19	C1	Asymptomatic	Children below 2 years	Prospective study	2007	[34]
1998–2006	The UK	32	C1-C2	Mostly mild infections, including HFMD, but neurological symptoms, including one fatality	Children and adults	Retrospective sample review	2008	[46]
1963–2008; peaks in 1986 and 2007	The Netherlands	198	B-C	Meningoencephalitis, meningitis, gastroenteritis	Children	Retrospective sample review	2009	[52]
1997–2007	Germany	28	C1-C2-C4	Neurological or cutaneous manifestations	Children	Retrospective sample review	2009	[58]
2004	Austria	2	C4	Aseptic meningitis and aseptic meningitis plus diarrhoea	Children	Retrospective lab survey	2009	[59]
2000–2008	Hungary	6	C1,C4	Aseptic meningitis	Children	Retrospective lab survey	2010	[53]
2005–2008	Denmark	29	B5, C1,C2	Meningoencephalitis, meningitis, gastroenteritis	Children below 1 year	Survey	2011	[7]
2000–2009	France	46	C1-C2	Hospitalised cases	Children	Retrospective lab survey	2011	[43]
2013	Russia	78	C4	Meningoencephalitis	Children 1–7 years	Outbreak	2015	[51]