WETENSCHAPPELIJK INSTITUUT VOLKSGEZONDHEID
INSTITUT SCIENTIFIQUE DE SANTÉ PUBLIQUE

Dienst Epidemiologie van Infectieziekten

Service Epidemiologie Maladies Infectieuses

Risk Assessment Group

PRIMARY RISK ASSESSMENT

Enterovirus detections associated with severe neurological symptoms in Europe

Date of the signal	Date of the PRA	Signal provider	Experts consultation	Method
29/07/2016	**10/08/2016**	EWRS	**Permanent experts:** S. Quoilin, D. Reynders, V. Laisnez, C. Schirvel, J-M Trémérie, P. Demol, M. Thomas **Specific experts:** M. Van Ranst, NRC Enterovirus, UZ Leuven E. Padalko, Virology, UZ Gent P. Schelstraete, paediatrician, UZ Gent MC. Nassogne, neuro-paediatrician, UCL N. Bossuyt, WIV-ISP M. Sabbe, WIV-ISP	**Email consultation**
Date of update	**Closing date**			

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RAPID RISK ASSESSMENT OF POTENTIAL PUBLIC HEALTH EVENT

Signal	On 29 July 2016, France reported an increase of severe acute neurological conditions in an academic paediatric hospital in Paris, associated with a range of enterovirus (EV) infections (EV-A71 subgenotype C1 (n=3), EV-D68 (n=2), Coxsackievirus A10 (n=1) and Coxsackievirus A2/EV68 co-infection). Retrospectively, several European countries observed severe enterovirus (EV) infections associated with a variety of different strains since April 2016. The Netherlands and Germany have reported increased detection of enterovirus-D68 (in respiratory specimens) and all enteroviruses (in aseptic meningitis cases) respectively, compared to previous years. Ireland has reported an increased trend in EV-associated viral meningitis cases and in Catalonia, Spain, an outbreak of EV-A71 associated with neurological complications is ongoing since mid-April 2016. Link to RA from ECDC: http://ecdc.europa.eu/en/publications/Publications/01-08-2016-RRA-Enterovirus%2071-Spain,%20France,%20Netherlands.pdf

	Description	**Score**	**Description / arguments**
1	Cause known?	Yes	Enteroviruses (EV) comprise a large and diverse group of non-enveloped RNA viruses within the genus Enterovirus in the family Picornaviridae. The currently known 116 enteroviruses identified from humans are classified into four enterovirus species, EV-A to EV-D and rhinovirus A-C. EV are further divided into genogroups and subgenogroups within the serotypes. The viruses can be transmitted by both faecal-oral and respiratory routes. Most infections are asymptomatic. When symptomatic, EV can cause a diverse spectrum of clinical symptoms 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). A single enterovirus type can cause a variety of clinical manifestations and many enterovirus types can cause similar symptoms. Large outbreaks of EV infections have been described.
2	Unexpected/unusual	Unusual	Although an increase of EV infections is usually observed in summer, reports suggest that this year the seasonal EV activity in the EU/EEA Member States started earlier than in previous years. Some countries also report an increased frequency of severe disease associated with EV infection.
3	Severity	Possibly high	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. 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.
4	Dissemination (Low/Medium/High)	Medium	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 and therefore

			outbreaks are difficult to control. The EV-A71 virus can be shed in faeces for several weeks after patient's recovery, making the transmission among close contacts possible even when no symptoms in the primary case are visible.
5	Risk of (inter)national spread	Medium	Increase of enterovirus infections and occurrence of severe infections is observed in several countries, including France, Germany and The Netherlands. The VP1 sequence of the EV-A71/C1 isolated in Paris in 2016 displayed close genetic relationships with available sequences of EV-A71/C1 strains collected in Germany in 2015. Epidemics of EV can be local, regional, national or even international.

Preparedness and response			
6	Preparedness	High	Diagnostic capacity exists in Belgium at the National Reference Center, UZ Leuven. Surveillance of EV is in place but should be reinforced.
7	Specific control measures (surveillance, control, communication)		Many clinical laboratories perform routine EV testing in Belgium, without genotyping. Epidemiological surveillance of enteroviruses with typing is performed by the NRC, and aims to support poliovirus eradication by detection of poliovirus circulation (if any), to identify potential EV outbreaks, to identify emergence of EV (new types, or new strains of old types) and to monitor epidemiology. Laboratories are invited to send EV-positive specimens for typing in presence of neurological symptoms (i.e. AFP, meningitis) or suspected infection with EV-D68. All cerebrospinal fluid (CSF) samples sent to the NRC are typed as well as a proportion of other samples (blood, stool, respiratory specimens…). The NRC receives samples from about 20 laboratories, accounting for a total of 100 to 200 specimens a year. In addition to surveillance done by the NRC, the sentinel network of laboratories also reports weekly number of positive EV tests (PCR mainly) in CSF, but the number of laboratories reporting data is limited.
a			
A	Public health impact in Belgium (Low/Medium/high)	Low	In Belgium, the NRC observes an increase of positive EV isolates in 2016, with a wide range of genotypes (analyses ongoing). However, up to now, there is no increase of EV-A71 or EV-D68. More detailed data are presented in annex. No unusual increase has been reported by the sentinel laboratories in 2016 so far (see annex). Surveillance of AFP through the network of paediatricians (Pedisurv) did not identify an unusual number of AFP cases neither up to now, but reporting is estimated to be incomplete (2-3 cases reported every year, instead of the 19 expected

			according to WHO estimations).
B	Recommendations (surveillance, control, communication)		Although an increase in positive EV isolates has also been observed in Belgium, no EV-A71 or EV-D68 genotypes were isolated at this stage. Based on the epidemiological information currently available, there is no indication that there is unusual increase of EV-infections associated with severe disease in our country. Recommended actions: - As most EU Member States are experiencing seasonal transmission of EV in summer and early autumn, vigilance for increased disease rates and new recombinant viruses should be kept high in Belgium in the coming months. - Discussions to enhance EV surveillance, in parallel with AFP surveillance, are already ongoing and will continue. - Microbiologist should be encouraged to send EV-positive CSF specimens for typing to the NRC. - It remains important to share information on circulating genotypes within European countries to enhance the understanding of the pattern of EV 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.
C	Actions		- Update on genotypes isolated in 2016 by the NRC, and on clinical manifestations associated with the most frequent types. - Enhance surveillance of EV in Belgium in the coming months: 1) set criteria for sampling/testing in case of outbreaks of EV infection (including HFMD) and severe clinical manifestations; 2) send letter to paediatricians, neurologists and neuro-paediatricians to inform them on the surveillance; 3) send letter to microbiologists to increase the representatives of data available at the NRC. - Provide information on the increase in Europe in the next (monthly) Newsflash. - Further follow-up of reported EV clusters and outbreaks in other European countries through the Early Warning and Response System (EWRS).

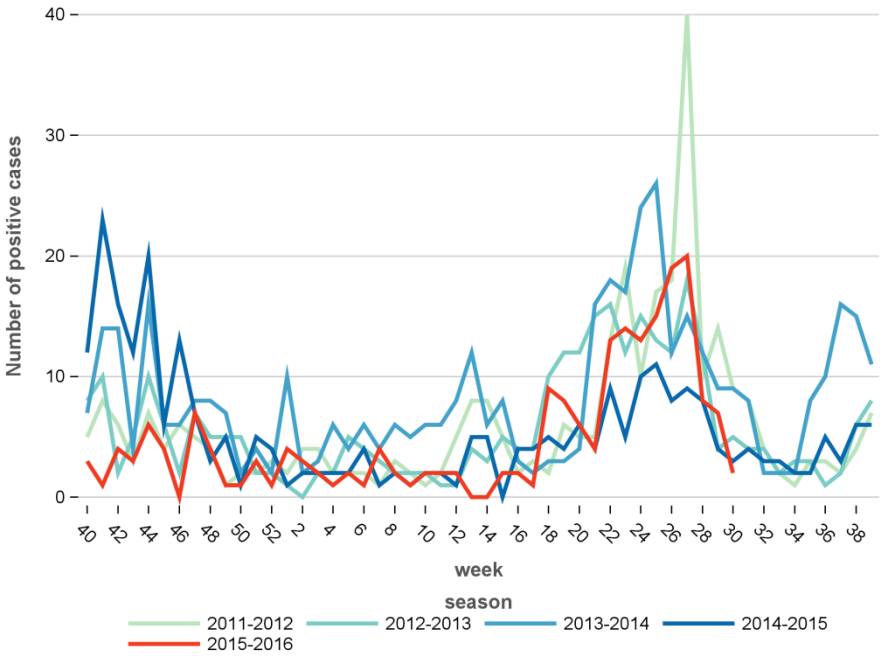
MAIN REFERENCE

- European Center for Disease Prevention and Control (ECDC). Rapid Risk Assessment: Enterovirus detections associated with severe neurological symptoms among children and adults in European countries. http://ecdc.europa.eu/en/publications/Publications/01-08-2016-RRA-Enterovirus%2071-Spain,%20France,%20Netherlands.pdf

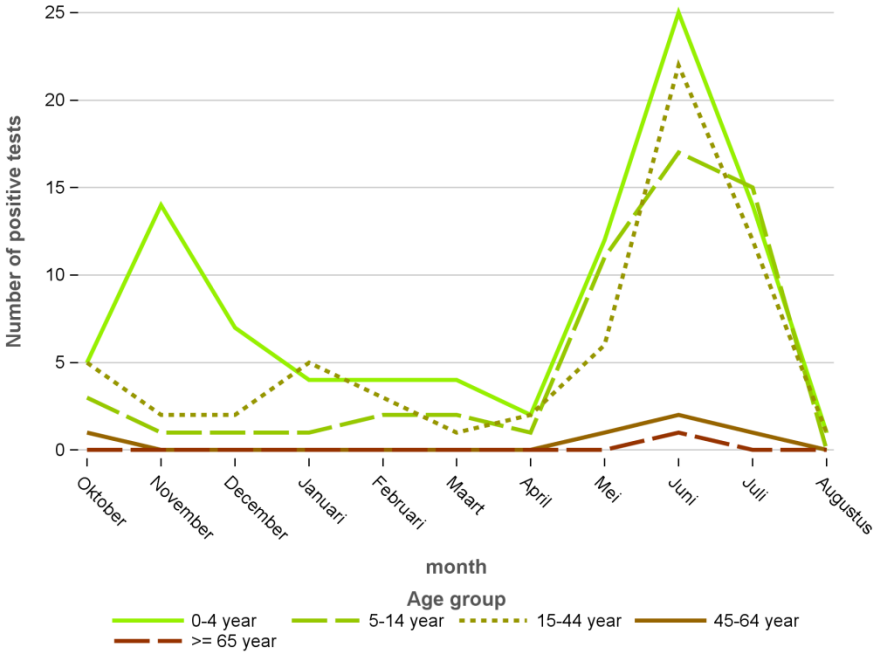
ANNEX: EPIDEMIOLOGICAL SITUATION IN BELGIUM

SENTINEL LABS

Number of positive tests in cerebrospinal fluid, Belgium, 2011-2016



Number of positive tests in cerebrospinal fluid by age group, Belgium, 2016



Number of positive tests by year, Belgium, 2010-2016

Year	Number of positive tests	
	All specimens	CVF specimens
2010	187	
2011	104	
2012	142	
2015	92	51
2016		

Type of specimen, Belgium, 2015

Specimen	Frequency	Percent
BAL	2	2.17
CSF	51	55.43
FAECES	19	20.65
Other	20	21.74

Genotypes isolated by age group, Belgium, 2015

Genotype	Age group							Total
	00-04	05-09	10-14	20-24	25-29	30-34	35-39	
COX A9	2	1	0	0	0	0	0	3
COX B1	5	0	0	0	0	0	0	5
COX B2	1	0	0	0	0	0	0	1
COX B5	1	0	0	0	1	0	0	2
E11	3	1	0	1	0	0	0	5
E13	0	0	0	0	0	1	0	1
E14	0	0	0	0	0	0	1	1
E30	2	1	0	0	1	5	0	9
E5	6	1	0	0	1	0	0	8
E6	2	2	1	0	0	2	1	8
E7	0	0	0	0	1	0	0	1
E9	0	2	0	0	0	0	0	2
EV B	2	2	0	0	0	0	0	4
EVA 71	1	0	0	0	0	0	0	1
Total	25	10	1	1	4	8	2	51