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Perspective

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Human enteroviruses and the long road to acute flacid paralysis eradication

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Abstract

Enteroviruses (EVs) are a highly diverse group of viruses multiplying primarily in the gastrointestinal tract and/or the upper respiratory tract, initially distributed in two separate genera: *Enterovirus* and *Rhinovirus*, respectively. According to the similarities in genome organization and particle structure, rhinovirus species were later reclassified as also belonging to genus *Enterovirus*. Human EV infections are usually asymptomatic or causing mild clinical manifestations. Nevertheless, some EV infections may derive in severe neural complications, including acute flaccid paralysis (AFP) such as poliomyelitis, whose etiological agent is poliovirus, a member of the *Enterovirus C* species. The inactivated polio vaccine (IPV) and particularly the oral attenuated polio vaccine (OPV) have contributed to the virtual eradication of the disease. However, sustained global circulation of vaccine-derived poliovirus 2 (cVDPV2), originated from the genetic instability of OPV strain 2 and intertypic recombination between Sabin OPV strains and members of the *Enterovirus C* species, still causes outbreaks of AFP worldwide. In addition, humanitarian crises, in particular armed conflicts, hamper polio vaccination campaigns and facilitate the occurrence of cases. Additionally, besides poliovirus, other EV may also cause AFP, among them EV A71 or EV D68, and it is highly advisable to implement wastewater surveillance to elucidate the occurrence of not only polioviruses, but also of other EV susceptible to derive in serious neural complications, since the screening of viral RNA in cerebrospinal fluid samples in patients suffering from AFP is not a reliable diagnostic tool.

Impact Statement

Global eradication of poliovirus unfortunately remains an arduous task, mainly due to the worldwide occurrence of cases related with cVDPV (mostly cVDPV2). In addition, humanitarian crises, in particular armed conflicts, hamper polio vaccination campaigns and facilitate the occurrence of cases. The continuous war or post-war situation in areas of Afghanistan and Pakistan contributes to the presence of wild-type polio. Nonpolio EV may also contribute to the AFP toll, and it is imperative to apply wastewater-based epidemiology to elucidate the cir- culation of viruses able to cause neurological complications in order to complement the surveillance of AFP cases through the screening of clinical cases, particularly having in mind the infrequent detection of viral RNA in cerebrospinal fluid samples in patients suffering from AFP.

Keywords: poliovirus; polio; poliomyelitis; EV A71; EV D68; IPV; OPV; cVDPV

Introduction: *Picornavirales*, *Picornaviridae*, and *Enterovirus*

Members of order *Picornavirales*, proposed in 2008 (Le Gall et al. 2008), share similar properties: a positive-sense single-stranded RNA genome with a VPg protein (viral protein genome linked) and a poly-A tail (long chain of adenine nucleotides) at its 5′ and 3′ ends, respectively; the genome is "infectious" since it is directly translated into autoproteolytically processed polyproteins; the particles are icosahedral, nonenveloped of around 30 nm in diameter, with a pseudo T = 3 symmetry; and replication occurs through a common three-domain replication block with a Helicase-Protease-Polymerase domain consisting of a superfamily III helicase, a proteinase with a chymotrypsin-like structure, and a superfamily I RNA-dependent RNA polymerase (RdRp).

In order *Picornavirales*, family *Picornaviridae* is one of the largest known viral families, with 63 genera containing 147 species, and still growing with many viruses yet awaiting classification (Zell et al. 2017). In addition, this family is medically and economically important, since it includes human and animal viral pathogens that may cause subclinical infections, but also conditions ranging from mild febrile illness to severe diseases affecting heart, liver, and the central nervous system.

Within the *Picornaviridae* family, genus *Enterovirus* constitutes a large and highly diverse group of viruses, with human enteroviruses (EVs) multiplying primarily in the gastrointestinal tract and/or the upper respiratory tract, although they may also multiply in tissues such as heart, nerve, muscle, etc. (Tapparel et al. 2013).

The EV taxonomy dramatically changed when rhinoviruses, the most frequent etiological agents of common cold were included in genus *Enterovirus*, with the removal of genus *Rhinovirus* from the picornavirus taxonomy. The terms EV and rhinovirus come from Greek: *enteron*, "intestine," and *Rhino*, "nose." The reclassification of the rhinovirus species within genus *Enterovirus* was based in the similarities in genome organization and particle structure between EV and rhinoviruses (Zell et al. 2017) https://ictv.global/report/chapter/picornaviridae/picornaviridae). However, EV and rhinoviruses differ in their primal replication site, i.e. the enteric

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or respiratory tract, respectively, which influences their acid stability; virions of most EV are stable at pH 3.0, while those of rhinoviruses are unstable below pH 5–6 (Giranda et al. 1992).

EV were previously subdivided into three groups: polioviruses, echoviruses, and coxsackieviruses. Newer isolated EVs were later assigned numbers (e.g. EV 71 or EV A71). Presently, species in genus *Enterovirus* are nominated *Enterovirus A* to *Enterovirus I* (skipping *Enterovirus I* since it could be confused with number 1, and with *Enterovirus A* to *D* infecting humans), and *Rhinovirus A* to *Rhinovirus C* (all infecting humans) (Simmonds et al. 2020; https://ictv.global/report/chapter/picornaviridae/picornaviridae/enterovirus). Nevertheless, the genus taxonomy shows incongruences, contributing to add confusion. Certain viruses initially reported as novel echoviruses were later shown to have been misplaced; for example, echovirus 8 is the same serotype as echovirus 1, echovirus 10 is now reovirus 1, echovirus 28 is now human rhinovirus A1A, and so on.

Genome organization and variability

The EV genome (Fig. 1) is a positive-sense, single-stranded RNA molecule of around 7 100–7 450 nt, with a type I IRES (internal ribosome entry site) in the 5′ end untranslated region (UTR) and no poly(C) tract at the 3′ end UTR (Kitamura et al. 1981). A VPg protein is covalently linked to the 5′ end of the genome and a poly-A tail is located at its 3′ end. The genome encodes a large open reading frame (ORF) that is directly translated into a polyprotein, which is subsequently cleaved by the viral proteases 2A, 3C, and 3CD, yielding the structural proteins VP1-VP4 and the nonstructural proteins, including the proteases and the RdRp 3D, that are involved in the viral multiplication in the host cell. Nevertheless, in most EV, a second ORF, has been described, overlapping the 3′ of the UTR and the VP4 coding region, and coding for a single protein involved in EV growth in gut epithelial cells (Lulla et al. 2019).

RNA viruses exhibit a great variability resulting from two genetic mechanisms: mutation and recombination. The absence of a 3′ to 5′ exonuclease proofreading activity in viral RdRp and reverse transcriptases, together with lack of postreplicative repair mechanisms, acting on DNA but not on RNA, results in a high mutation rate and in the generation of a complex dynamic mutant distributions termed viral quasispecies (Domingo et al. 2012). The second major driving force underlying the genetic variability of RNA viruses is genomic recombination; a process through which genome fragments from different strands combine, creating a new genome (Muslin et al. 2019). Rapidly evolving RNA viruses represent a challenge for the development of effective control measures based on vaccines or antiviral drug treatments.

Diseases caused by human EVs. Poliomyelitis

Human EV infections (reviewed in Tapparel et al. 2013) may frequently be asymptomatic. Nevertheless, there is a wide variety of clinical manifestations (Table 1) that include respiratory illness, mostly mild common cold caused by rhinoviruses, and childhood diseases such as pleurodynia (a pleuritic pain usually accompanied by fever, sore throat, and malaise), herpangina (a mild disease characterized by the onset of lesions on the tonsillar pillars, soft palate, tonsils, uvula, or tongue), and hand-foot-and-mouth disease (a febrile disorder causing vesicular eruptions on hands, feet, and oral mucosa) (de Crom et al. 2016). There is also the controversial association of type 1 diabetes with some human EV (Tapparel et al. 2013).

Myopericarditis may result from EV infection at any age, but most patients are between 20 and 40 years old. Patients may suffer chest pain, arrhythmias, heart failure, or even sudden death. Recovery tends to be complete, but some patients develop dilated cardiomyopathy (Hugron et al. 2022).

EV infections may spread to neural compartments, often resulting in meningitis (meningeal inflammation), without progressing to encephalitis (parenchyma inflammation) or myelitis (spinal cord inflammation). Acute flaccid paralysis (AFP) occurs when the infection reaches the gray matter in the spinal cord (Kincaid and Lipton 2006, Tapparel et al. 2013). EV infections account for over 90% of all viral meningitis, yet only 3% of neural complications from EV infections result in encephalitis (Irani 2008).

Poliovirus, a member of the *Enterovirus C* species, is the etiological agent of poliomyelitis, whose manifestations include meningitis, myelitis, and, fortunately less often, AFP. Humans are the sole natural host of poliovirus.

Why polio is not yet eradicated?

Poliomyelitis was once one of the most feared diseases, and through extensive vaccination programs, the disease is almost eradicated worldwide. There are three serotypes of polioviruses, being type 1 the most pathogenic and responsible nowadays for most cases of wild-type polio, which is concentrated in two countries: Afghanistan and, particularly, Pakistan (https://polioeradication.org/polio-today/).

Two existing vaccines have contributed to the virtual eradication of poliomyelitis: the inactivated polio vaccine (IPV) developed in 1955 by Jonas Salk, administered by intradermal or intramuscular injection, and the oral attenuated polio vaccine (OPV), developed by Albert Sabin and widely administered since 1959 (https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-polio-vaccination).

In 1988, the World Health Assembly lead an initiative to achieve the complete polio eradication, and, simultaneously, the Global Polio Eradication Initiative (GPEI) was launched, being OPV the most effective and widely employed vaccine at that stage of global polio eradication. Polio-free countries switched to employ the IPV in routine immunization schedules; nevertheless, this vaccine is not adequate for routine use in polio-endemic countries or in developing countries at risk of poliovirus importations since it does not stop transmission of the virus, as OPV does, and in addition it is more complex to administer, as well as pricey (https://polioeradication.org/polio-today/polio-now/).

The polio endgame strategy (2019–2023) of the GPEI (https://polioeradication.org/wp-content/uploads/2019/06/english-polio-endgame-strategy.pdf) achieved remarkable accomplishments: the global eradication of wild-type poliovirus 2, the cessation of global circulation of wild-type poliovirus 3, and the overall reduction of wild-type poliovirus 1, restricted at that time to three countries: Afghanistan, Pakistan, and Nigeria—being this latter country declared polio-free in 2015, despite that polio eradication efforts were hampered by Boko Haram extremists (Webster 2017).

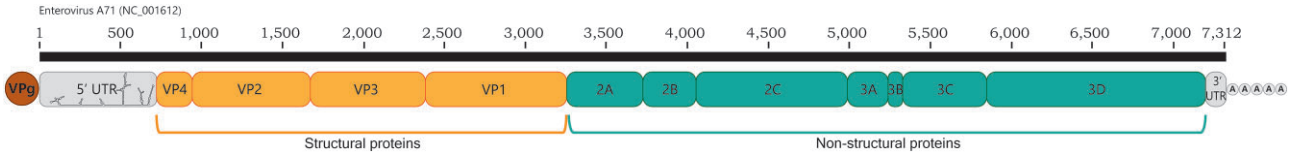

Figure 1. Genome of EV A71 (Adapted from Noisumdaeng et al. 2018). A VPg protein is covalently linked to the 5′ end of the genome and a poly-A tail is located at its 3′ end. A type I IRES is located in the 5′ end UTR (depicted). VP1-VP4 are the structural proteins and nonstructural proteins, include the proteases and the RdRp 3D (Kitamura et al. 1981).

Table 1. Main clinical manifestations associated with human EV infections.

Syndrome	Main implicated EV types
Respiratory disease	Echovirus 4, 8, 9, 11, 20, Coxsackievirus A21, A24, B1, B3, B5, EV D68, Rhinoviruses, Others
Pleurodynia (Bornholm disease)	Coxsackievirus B1, B2, B3, B4, B5, B6
Herpangina	Coxsackievirus A2, B3, B4, B6, B8, B10, Others
Hand-foot-and-mouth disease	EV A71Coxsackievirus A6, A9, A16, Coxsackievirus B2, B3, B4, B5, Others
Myopericarditis	Coxsackievirus A4, A16, B1, B2, B3, B4, B5, Echovirus 9
Meningitis or encephalitis	Coxsackievirus A9, B4, Echovirus 4, 16, EV, A71
Paralysis or myelitis	Poliovirus 1, 2, 3, EV A71, C99, D68, D70, Coxsackievirus A7, Echovirus 4, 6, 9, Others
Conjunctivitis	EV A70, Coxsackievirus A24
Rash	Coxsackievirus A9, B1, B3, B4, B5, Echovirus 9, 16, Others
Type 1 diabetes?	EV A71, D70, Coxsackievirus A9, B1, B2, B3, B4, B5, B6, Echovirus 3, 4, 5,6,9,11,16, 18, 24, 25, 30, Others

A major problem with polio eradication at present is the emergence of pathogenic circulating vaccine-derived polioviruses (cVDPV), originated from the genetic instability of OPV strains due to the low fidelity of the RdRp, and the intertypic recombination between Sabin OPV strains and members of the *Enterovirus C* species, which have caused numerous outbreaks of paralytic poliomyelitis worldwide (Muslin et al. 2019). While in 2022, wild-type poliovirus 1 was only circulating in 2 countries (two cases in Afghanistan and 20 cases in Pakistan), cVDPV cases, mostly related with type 2, occurred in other 31 countries, including USA, UK, Israel, Malawi, Chad, the Democratic Republic of the Congo, and Yemen (https://polioeradication.org/?s=vaccine±derived±polio).

Concern is caused at present by the sustained global circulation of cVDPV2 (circulating vaccine-derived poliovirus 2). cVDPV2 was consistently detected during the second half of 2022 in wastewater samples from North and East London boroughs, suggesting the spread of this virus between individuals in these areas, although no associated cases of paralysis were reported (Klapsa et al. 2022). In July 2022, a cVDPV2-related case of the polio AFP, affecting a nonvaccinated adult, was declared in New York (Link-Gelles et al. 2022). Wastewater surveillance demonstrated the circulation of cVDPV2 in several neighboring New York counties (Ryerson et al. 2022). A few month earlier, in March 2022, an AFP case in a nonvaccinated 4-year-old girl, caused by a cVDPV3 was confirmed in Israel (https://polioeradication.org/news-post/circulating-vaccine-derived-poliovirus-type-3-confirmed-in-israel/).
At the time of writing this manuscript (end of 2024), cVDPV-2 has been detected in wastewater from several parts of Europe, first in Barcelona, Spain, and later in Warsaw, Poland; in Cologne, Bonn, Hamburg, and Munich, Germany; and in Tampere, Finland (https://www.science.org/content/article/poliovirus-keeps-popping-european-wastewater-perplexing-and-worrying-scientists). No associated AFP cases have been reported.

Despite the aforementioned problems caused by OPV-derived strains that could greatly hinder the polio Endgame initiative, a cornerstone of the polio eradication strategy in countries with wild-type poliovirus transmission is to ensure routine oral polio children vaccine coverage of above 80% in the first year of life. Different types of OPV offer protection accordingly against different poliovirus serotypes: e.g. the bivalent OPV, widely used since 2016, protects only versus polioviruses 1 and 3 (Yeh et al. 2023), since wild-type poliovirus 2 was declared eradicated in 1999. In 2019, it was declared the global eradication of wild-type poliovirus 3 (https://www.who.int/news-room/feature-stories/detail/two-out-of-three-wild-poliovirus-strains-eradicated). In addition, a novel type 2 OPV has been proposed to minimize the problems caused by the genetic instability of cVDPV2 (Wahid et al. 2022).

It may not seem sound to extend IPV programs in regions of the world where poliomyelitis has been declared eradicated. However, despite routine IPV immunization by itself cannot eradicate the disease, high vaccination coverage contributes to increase herd immunity, thus reducing the incidence of polio and making eradication a reachable goal. In contrast, when

immunization coverage is reduced, the increase in the number of nonimmunized children favors the possibility of continued virus spread and the occurrence of polio outbreaks. It is also imperative to ascertain the complete eradication of the virus, conducting an exhaustive surveillance based not only on the screening of AFP cases, but also on wastewater-based epidemiology data after the surveillance of sewage for poliovirus occurrence, as specified in the WHO Strategic Plan of the Global Polio Eradication Initiative for the biennium 2010–2012 (Hovi et al. 2012), and the 2022 Proposal for a Directive of the European Parliament and of the Council, concerning urban wastewater treatment (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52022PC0541).

Poliovirus may eventually be eradicated, but what about polio-like AFP?

As mentioned above, some nonpolio EV infections may result in the severe neural complications (Table 1) (Schubert et al. 2019). An example is EV A71, usually associated with asymptomatic infections or mild cases of hand-foot-and-mouth disease, but also involved in cases of aseptic meningitis, encephalitis, and even AFP (Ooi et al. 2010). In the spring of 2016, over 200 cases associated with a new recombinant variant belonging to subgenogroup C1 of EV A71 were declared among Spanish children, mostly in Catalonia, in the northeast of the country (González-Sanz et al. 2019). Most severe cases ($n = 140$) were related with brainstem encephalitis, meningoencephalitis, encephalitis, and polio-like AFP (Table 2). EV A71 was mostly detected in stool and/or respiratory samples and, only in a low proportion of patients, in cerebrospinal fluid. Also in 2016, outbreaks caused by subgenogroup C1 of EV A71 were reported in Germany and France, causing a much lower number of severe cases (Antona et al. 2016, Böttcher et al. 2016). This disparity may result from the low circulation of the emerging C1 variant in Spain before 2016, while reports exist on its earlier spread in Germany and France (Hassel et al. 2015).

Another nonpolio EV of concern, mostly associated with small outbreaks of respiratory infections of the variable severity in children is EV D68, formerly rhinovirus D68. Additionally, this virus may cause larger outbreaks resulting in high morbidity and even some casualties. Cases of children with focal limb weakness and AFP after the respiratory illness are also observed (Messacar et al. 2015). In a widespread outbreak of severe respiratory disease in the US caused by EV D68, with sporadic cases of AFP (Greninger et al. 2015), the virus was detected in respiratory specimens and in the blood of one child during the progression of the disease to AFP. Sequences from the isolated viruses were very close to those of polioviruses and other EV associated with AFP, supporting the potential causal role of EV-D68 in this latter syndrome.

The US Centers for Disease Control and Prevention (CDC) reported outbreaks of AFP in 2014, 2016, and 2018 with 120, 153, and 238 cases reported to CDC each year, respectively (Fig. 2, https://www.cdc.gov/acute-flaccid-myelitis/cases/index.html). Peaks in AFP cases coincided with periods of increased EV D68 detection in the outbreak-affected areas.

Almost two decades ago, Jiang and coworkers (Jiang et al. 2007) pointed to the potential emergence, in an eventually poliovirus-free world, of new EV strains resulting from intertypic recombination between *Enterovirus* C species, capa-

Table 2. Neurological disorders among EV-A71 patients in the 2016 outbreak, Spain.

	Severity	Neurological disorders	Number of cases	%	*P*-value	HFMD associated
Patients infected with EV-A71-C1 variant ($n = 217$)	Severe	Brain stem encephalitis	53	64.5	Not applicable	4
		Meningoencephalitis	47			-
		Encephalitis	18			1
		AFP/myelitis	12			-
		Other motor disorders	10			3
	Mild	Aseptic meningitis	25	12.4	<0.001	4
Patients infected with EV-A71-C1 or C2 ($n = 16$)	Severe	Brain stem encephalitis	2	31.2	Not applicable	-
		Meningoencephalitis	3			
	Mild	Aseptic meningitis	5	31.2	0.069	1

AFP: acute flaccid paralysis; EV: enterovirus; HFMD: hand-foot-and-mouth disease.
Significant variations between groups were evaluated by chi-squared test; *P* values comparing the number of cases with severe neurological disorders with the remaining clinical manifestations are shown.
Adapted from González-Sanz *et al.* (2019).

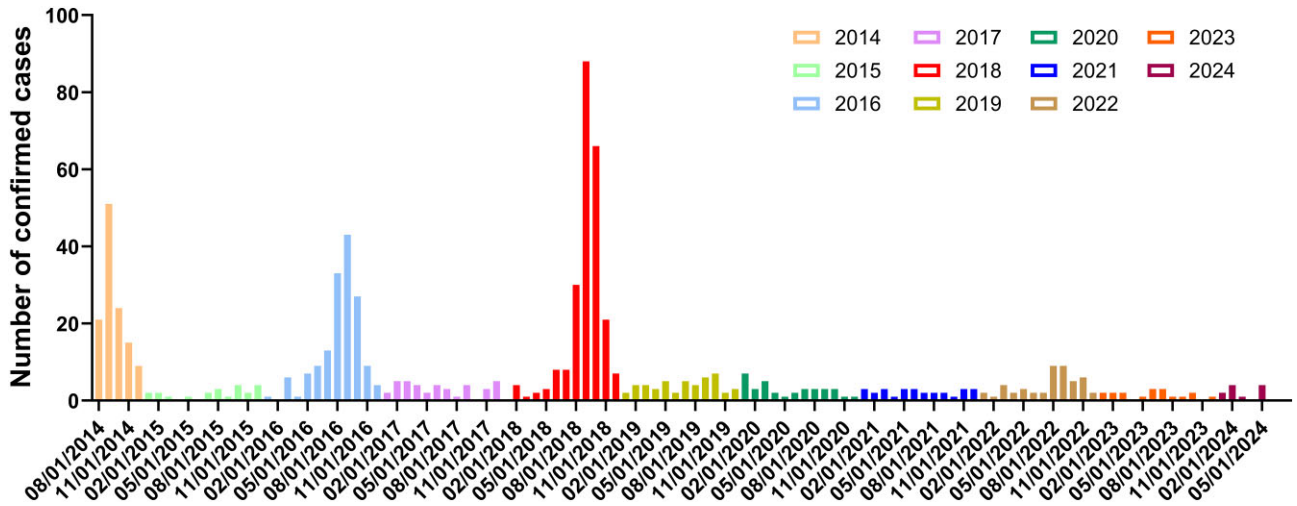

Figure 2. AFP cases by month, USA 2014–2023 (adapted from https://www.cdc.gov/acute-flaccid-myelitis/cases/index.html). Most patients developed AFP between August and November, with increases in AFP cases in 2014, 2016, and 2018. Among other viruses, EVs were circulating at this same time of year, and were likely responsible for the increase in AFP.

ble to cause polio-like AFP. Genome characterization of the cVDPV2 isolated from London wastewater in 2022 showed the loss of two mutations, through recombination with other *Enterovirus C* species, that are key in the attenuation of OPV strains (Klapsa et al. 2022). There is the growing concern that new polio-like EV may emerge through recombination events among OPV strains and several other EV species, most likely, but not exclusively, those belonging to *Enterovirus C* species.

Conclusive remarks

Nowadays, global eradication of poliovirus remains an arduous task, mainly due to the worldwide occurrence of cases related with cVDPV (mostly cVDPV2). In addition, humanitarian crises, in particular armed conflicts, hamper polio vaccination campaigns and facilitate the occurrence of cases. The continuous war or post-war situation in areas of Afghanistan and Pakistan contributes to the presence of wild-type polio, and very recently the first case of poliomyelitis in 25 years has just been declared in Gaza on August 16, 2024, within the framework of the ongoing Israel-Hamas war.

Another cause of concern derives from the fact that nonpolio EV may also contribute to the AFP toll, and it is imperative to apply wastewater-based epidemiology to elucidate the circulation of viruses able to cause neurological complications in order to complement the syndromic surveillance of AFP cases through the screening of clinical cases, particularly having in mind the infrequent detection of viral RNA in cerebrospinal fluid samples in patients suffering from AFP.

Author contributions

Albert Bosch (Conceptualization, Supervision, Writing – original draft), Albert Carcereny (Writing – original draft, Writing – review & editing), David García-Pedemonte (Writing – review & editing), Cristina Fuentes (Writing – review & editing), Maria I. Costafreda (Writing – review & editing), Rosa M. Pintó (Conceptualization, Writing – original draft), and Susana Guix (Conceptualization, Writing – review & editing)

Conflict of interest: None declare.

Data availability

There are no new data associated with this article.

References

Antona D, Kossorotoff M, Schuffenecker I *et al*. Severe paediatric conditions linked with EV-A71 and EV-D68, France, May to October 2016. *Euro Surveill* 2016;**21**:30402. https://doi.org/10.2807/1560-7917.ES.2016.21.46.30402

Böttcher S, Obermeier P, Neubauer K *et al*. Recombinant enterovirus A71 subgenogroup C1 strains, Germany, 2015. *Emerg Infect Dis* 2016;**22**:1843. https://doi.org/10.3201/eid2210.160357

de Crom SCM, Rossen JWA, van Furth AM *et al*. Enterovirus and parechovirus infection in children: a brief overview. *Eur J Pediatr* 2016;**175**:1023–9. https://doi.org/10.1007/s00431-016-2725-7

Domingo E, Sheldon J, Perales C. Viral quasispecies evolution. *Microbiol Mol Biol Rev* 2012;**76**:159–216. https://doi.org/10.1128/MMBR.05023-11

Giranda VL, Heinz BA, Oliveira MA *et al*. Acid-induced structural changes in human rhinovirus 14: possible role in uncoating. *Proc Natl Acad Sci USA* 1992;**89**:10213–7. https://doi.org/10.1073/pnas.89.21.10213

González-Sanz R, Casas-Alba D, Launes C *et al*. Molecular epidemiology of an enterovirus A71 outbreak associated with severe neurological disease, Spain, 2016. *Euro Surveill* 2019;**24**:1800089. https://doi.org/10.2807/1560-7917.ES.2019.24.7.1800089

Greninger AL, Naccache SN, Messacar K *et al*. A novel outbreak enterovirus D68 strain associated with acute flaccid myelitis cases in the USA (2012–14): a retrospective cohort study. *Lancet Infect Dis* 2015;**15**:671–82. https://doi.org/10.1016/S1473-3099(15)70093-9

Hassel C, Mirand A, Lukashev A *et al*. Transmission patterns of human enterovirus 71 to, from and among European countries, 2003 to 2013. *Euro Surveill* 2015;**20**:30005. https://doi.org/10.2807/1560-7917.ES.2015.20.34.30005

Hovi T, Shulman LM, Van Der Avoort H *et al*. Role of environmental poliovirus surveillance in global polio eradication and beyond. *Epi-*

demiol Infect 2012;**140**:1–13. https://doi.org/10.1017/S095026881000316X

Hugron A, Houde C, Viel-Thériault I. Myocarditis as a complication of enterovirus infection in infants. *Pediatrics* 2022;**149**:351.

Irani DN. Aseptic meningitis and viral myelitis. *Neurol Clin* 2008;**26**:635–55. https://doi.org/10.1016/j.ncl.2008.03.003

Jiang P, Faase JAJ, Toyoda H *et al*. Evidence for emergence of diverse polioviruses from C-cluster coxsackie a viruses and implications for global poliovirus eradication. *Proc Natl Acad Sci USA* 2007;**104**:9457–62. https://doi.org/10.1073/pnas.0700451104

Kincaid O, Lipton HL. Viral myelitis: an update. *Curr Neurol Neurosci Rep* 2006;**6**:469–74. https://doi.org/10.1007/s11910-006-0048-1

Kitamura N, Semler BL, Rothberg PG *et al*. Primary structure, gene organization and polypeptide expression of poliovirus RNA. *Nature* 1981;**291**:547–53. https://doi.org/10.1038/291547a0

Klapsa D, Wilton T, Zealand A *et al*. Sustained detection of type 2 poliovirus in London sewage between February and July, 2022, by enhanced environmental surveillance. *Lancet* 2022;**400**:1531–8. https://doi.org/10.1016/S0140-6736(22)01804-9

Le Gall O, Christian P, Fauquet CM *et al*. Picornavirales, a proposed order of positive-sense single-stranded RNA viruses with a pseudo-T = 3 virion architecture. *Arch Virol* 2008;**153**:715–27. https://doi.org/10.1007/s00705-008-0041-x

Link-Gelles R, Lutterloh E, Ruppert PS *et al*. Public health response to a case of paralytic poliomyelitis in an unvaccinated person and detection of poliovirus in wastewater-New York, June-August 2022. *Am J Transplant* 2022;**22**:2470–4. https://doi.org/10.1111/ajt.16677

Lulla V, Dinan AM, Hosmillo M *et al*. An upstream protein-coding region in enteroviruses modulates virus infection in gut epithelial cells. *Nat Microbiol* 2019;**4**:280–92. https://doi.org/10.1038/s41564-018-0297-1

Messacar K, Schreiner TL, Maloney JA *et al*. A cluster of acute flaccid paralysis and cranial nerve dysfunction temporally associated with an outbreak of enterovirus D68 in children in Colorado, USA. *Lancet* 2015;**385**:1662–71. https://doi.org/10.1016/S0140-6736(14)62457-0

Muslin C, Mac Kain A, Bessaud M *et al*. Recombination in enteroviruses, a multi-step modular evolutionary process. *Viruses* 2019;**11**:859. https://doi.org/10.3390/v11090859

Noisumdaeng P, Sangsiriwut K, Prasertsopon J *et al*. Complete genome analysis demonstrates multiple introductions of enterovirus 71 and coxsackievirus A16 recombinant strains into Thailand during the past decade. *Emerg Microbes Infect* 2018;**7**:214. https://doi.org/10.1038/s41426-018-0215-x

Ooi MH, Wong SC, Lewthwaite P *et al*. Clinical features, diagnosis, and management of enterovirus 71. *Lancet Neurol* 2010;**9**:1097–105. https://doi.org/10.1016/S1474-4422(10)70209-X

Ryerson AB, Lang D, Alazawi MA *et al*. Wastewater testing and detection of poliovirus type 2 genetically linked to virus isolated from a paralytic polio case—New York, March 9-October 11, 2022. *MMWR Morb Mortal Wkly Rep* 2022;**71**:1418–24. https://doi.org/10.15585/mmwr.mm7144e2

Schubert RD, Hawes IA, Ramachandran PS *et al*. Pan-viral serology implicates enteroviruses in acute flaccid myelitis. *Nat Med* 2019;**25**:1748–52. https://doi.org/10.1038/s41591-019-0613-1

Simmonds P, Gorbalenya AE, Harvala H *et al*. Recommendations for the nomenclature of enteroviruses and rhinoviruses. *Arch Virol* 2020;**165**:793–7. https://doi.org/10.1007/s00705-019-04520-6

Tapparel C, Siegrist F, Petty TJ *et al*. Picornavirus and enterovirus diversity with associated human diseases. *Infect Genet Evol* 2013;**14**:282–93. https://doi.org/10.1016/j.meegid.2012.10.016

Wahid R, Mercer L, Gast C *et al*. Evaluating stability of attenuated Sabin and two novel type 2 oral poliovirus vaccines in children. *NPJ Vaccines* 2022;**7**:19. https://doi.org/10.1038/s41541-022-00437-5

Webster P. Nigeria's polio endgame impeded by Boko Haram. *CMAJ* 2017;**189**:E877–8. https://doi.org/10.1503/cmaj.1095433

Yeh MT, Smith M, Carlyle S *et al*. Genetic stabilization of attenuated oral vaccines against poliovirus types 1 and 3. *Nature* 2023;**619**:135–42. https://doi.org/10.1038/s41586-023-06212-3

Zell R, Delwart E, Gorbalenya AE *et al*. ICTV virus taxonomy profile: picornaviridae. *J Gen Virol* 2017;**98**:2421–242. https://doi.org/10.1099/jgv.0.000911

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