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PERSPECTIVE

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Beyond polio: Exploring non-polio enteroviruses, global health preparedness, and the "Disease X" paradigm

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Abstract

Background and Aims: Disease X represents the possibility that an unidentified infection may spread globally and start a pandemic. This study explored various aspects of emerging non-polio enteroviruses (NPEVs) as a possible source of "Disease X," an enigmatic agent declared by the World Health Organization, and discussed the potential impact of NPEVs on global public health.

Methods: In this perspective article, we collected information from publicly available sources such as Google Scholar, PubMed, and Scopus. We used NPEVs, viral diseases, pandemics, and zoonotic diseases as keywords. We extracted information from the most relevant articles.

Results: Notable outbreaks caused by NPEVs include enterovirus D68 (EV-D68) and enterovirus A71 (EV-A71), among many others. With a focus on therapeutic and preventative components, alternate modes of therapy, and the development of broad-spectrum antivirals, this analysis looks at the origin, epidemiology, genetic alterations, transmission dynamics, and disease pathophysiology of NPEVs. The information presented in the review indicates the current risk assessment of NPEVs, taking into account the following factors: the need for research and therapeutic interventions, the diversity of clinical manifestations, the impact of genetic variability on virulence, the persistence of emergence despite vaccination efforts, recurrent outbreaks, and the global impact of these viruses.

Conclusion: There is a possibility that NPEVs could trigger global pandemics based on their zoonotic origins and urges for complete readiness, continuous research, cooperation, and a comprehensive strategy to combat emerging infectious diseases in a constantly changing global environment. It is peak time to acknowledge how important it is to abide by safety and health laws to prevent these illnesses.

KEYWORDS

disease X, enterovirus, epidemiology, non-polio enterovirus, pandemics, viral diseases, zoonotic disease

1 | BACKGROUND

The World Health Organization (WHO) released the Research and Development Blueprint list of priority illnesses on February 9, 2018, indicating the potential to eventually spark a worldwide pandemic in the future.[1] Along with COVID-19, Ebola, Marburg virus disease, Middle East respiratory syndrome coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome (SARS), and other illnesses that have experienced epidemics recently, the list also contains "Diseases X."[1,2] This hypothesis, "Diseases X," is predicated on the idea that a pathogen that is now unidentified as the cause of human sickness might be the origin of a major worldwide pandemic. The poliovirus, coxsackieviruses, echoviruses, numbered enteroviruses, and rhinoviruses are all members of the genus Enterovirus (EV), which is a member of the family Picornaviridae. Among the non-polio enteroviruses (NPEVs) are enterovirus A71 (EV-A71), enterovirus D68 (EV-D68), enterovirus D70 (EV-D70), coxsackievirus A16 (CVA16), coxsackievirus A24 (CVA24), and echovirus 30 (EV-C30). Several NPEVs have become major public health problems in recent years.[3] NPEVs, such as EV-D68 has sparked a major alarm of severe lower respiratory tract illness in North America, additionally, EV-A71 has caused an outbreak of hand, foot, and mouth disease (HFMD) in Southeast Asia.[4,5] According to the WHO 2018 declaration, the Wuhan pneumonia that had an unidentified cause needs to be acknowledged as the inaugural instance of Disease X. Subsequently, the pathogen was discovered to be a new coronavirus known as 2019-nCoV. Its possible bat origin is suggested by the fact that its complete genome sequence matches SARS-CoV and bat SARS-related coronavirus (SARSr-CoV-RaTG13) by 79.5% and 96%, respectively.[2] Beginning with a conference that took on November 18, WHO is bringing together more than 300 experts to examine the data on more than 25 families of viruses, bacteria, and "Disease X."[6] This study aims to underscore the potential contribution of NPEVs as triggers for the next pandemic. It considers recent epidemiological outbreaks, the zoonotic characteristics of these viruses, genetic mutations, pathogenesis, and transmission modes, and emphasizes recent therapeutic advancements along with potential recommendations for further enhancements.

2 | EPIDEMIOLOGY OF NPEVS INFECTION

EVs are small, non-enveloped viruses with a positive-sense, single-stranded RNA genome. They annually afflict millions of humans and other mammals, presenting a notable health risk.[7] Although effective vaccination initiatives have the potential to eliminate the extensively studied poliovirus serotype (EV-C), concerns have arisen over the past few decades due to outbreaks of NPEVs such as EV-A71, EV-D68, and CV-A16 in the United States of America, China, and South-East Asia.[7]As far as clinical conditions go, EVs can cause a wide range of illnesses. These include common colds, HFMD, and nonspecific febrile illnesses; they can also cause more serious outcomes like myocarditis, acute flaccid myelitis, encephalitis, pancreatitis, and paralysis. In individuals with compromised immune systems, these illnesses may persist over time and, in some cases, lead to fatal outcomes.[3] The emerging EV-A71 C1 genotype sparked an outbreak of HFMD in Taiwan (China) from 2018 to early 2019. A recent investigation revealed that a newly identified sublineage, EV-A71 C4, demonstrates greater virulence compared to the B5 lineage responsible for the HFMD outbreak in Vietnam during 2015–2016.[8] Furthermore, illnesses of increased severity have been linked to EV-A71 viruses that bear naturally occurring mutations. Despite the successful global vaccination efforts that have largely eliminated poliovirus, there is a persistent emergence of NPEVs such as EV-A71 and EV-D68, leading to diseases resembling polio-induced paralysis.[9,10] EV-A71 epidemics have affected countries like Malaysia, Taiwan, South Korea, Vietnam, and Thailand between 1997 and 2018, with Vietnam reporting 53,000 total identified cases of EV-A71 outbreaks in 2018, compared to Vietnam's previous record of 174,677 identified cases of EV-A71 outbreaks between 2011 and 2012 (Figure 1).

Extensive outbreaks of EV-D68 occurred not only in the United States but also in various regions globally during the years 2014, 2016, and 2018.[12,13]

During the COVID-19 pandemic in 2020, there were reports of detecting low levels of EV-D68 in the United States.[14] EV-D68 resurfaced in the fall of 2021, notably in Europe and, to a lesser

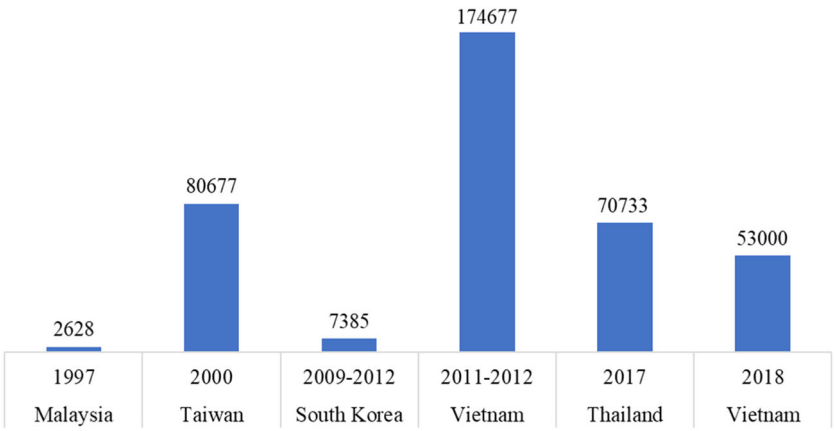

FIGURE 1 Number of identified EV-A71 cases in the countries of the Asia-Pacific region between 1997 and 2018.[11]

extent, in the United States. It reappeared once more in 2022, with reports indicating a significant rise in the prevalence of EV-D68 linked to acute respiratory illnesses, mainly in children in both the United States and Europe.[15–17] Earlier outbreaks of EV-D68 in both Europe and the United States were linked to serious infections in the lower respiratory tract, instances of wheezing illnesses, and, less frequently, occurrences of acute flaccid myelitis or other neurological manifestations in children.[18,19] Furthermore, the emergence and reemergence of NPEVs, like EV-A71 and EV-D68, that cause serious illnesses like acute respiratory infections, myocarditis, and paralysis, point to the urgent need for efficient antiviral therapies, a better comprehension of the genetic factors that contribute to virulence, and research into environmental, host-related, and viral variables that contribute to the persistence and resurgence of these viruses.

3 | GENETIC MUTATION OF NPEVs

Genetic mutation is a crucial evolutionary process in EVs. Mutation in RNA viruses has been well-documented since its discovery. It is known that recombination can happen across distinct EV serotypes or within a single serotype. Within a species, naturally occurring EVs recombine every few years, and the genome area that codes for capsids develops almost separately from the genome region that codes for nonstructural proteins. Most likely, the last century saw the emergence of every known variety of EV kinds.[20] Recombination between CVs and EV-A71 is important in the development of EV-A71 genotypes, according to analysis of the EV-A71 genome. Since Hirst (1962) initially reported the first instance of RNA recombination in a poliovirus, more research has shown that recombination occurs frequently and significantly in enteroviruses.[21] Alternatively, nucleotide deletions in the 5' untranslated region would have increased the virulence of EV-D68.[22] There may be evidence of genetic drift in a few kinds, but the relative stability of types throughout time indicates that they correlate with fitness peaks, implying that genetic changes are required to form a new lineage.[20] According to one explanation, the increase in transmission is caused by immune escape-associated mutations that allow for the evasion of preexisting population immunity or by evolutionary selection for increased replication fitness. Comprehending the principles behind EV development is essential for forecasting the emergence of new EV types with modified virulence.[20]

4 | TRANSMISSION AND SPREAD OF NPEVS TO CAUSE INFECTION

We might speculate that the emergence of a disastrous "Disease X," epidemic is probably due to the zoonotic spread of a very pathogenic RNA virus.[23] With a few notable exceptions, the majority of human enteroviruses enter the body through the alimentary or respiratory tract and are disseminated by both fecal-oral and respiratory paths.[22] NPEVs can be spread via direct contact, touching infected surfaces, changing diapers, or drinking contaminated water. They are found in feces, eye, nose, and mouth secretions, as well as blister fluid. Even in the absence of symptoms, infected people might secrete the virus for weeks at a time. Breastfeeding moms should see their doctors if they suspect an infection, as pregnant women may pass the virus to their unborn children if they become infected close to birth.[24] The primary route of EV-A71 transmission in humans is through the fecal-oral pathway. The gastrointestinal tract's epithelial cells are where the virus first replicates. After that, the virus travels throughout the body, causing HFMD. Fortunately, most patients recover, and the infection is eradicated. Occasionally, though, the virus penetrates the central nervous system (CNS) by some unidentified method. The CNS's neurons are the places where viruses replicate. In fatal instances, there are severe lesions in the CNS but not in other organs.[25] Saliva, nasal mucus, or sputum-mucus-like discharges from the lungs are examples of respiratory secretions from an infected individual that contain the EV-D68 virus, which causes respiratory disease. It is most likely that EV-D68 transmits from person to person by coughing, sneezing, or touching a surface that is subsequently touched by other people.[26]

5 | DISEASE PATHOGENESIS OF NPEVs INFECTION

Surprisingly, over 10% of children in good physical health have EVs in their stools.[27] The majority of individuals who contact NPEVs either remain asymptomatic or experience only mild symptoms, similar to a typical cold.[28] When present, EV infections usually result in nonlife-threatening symptoms that do not necessitate hospitalization.[28] Severe instances of specific EV infections may manifest with various symptoms such as acute flaccid paralysis (AFP), herpangina, hepatitis, pleurodynia, diarrhea, fever, upper and lower respiratory infections, pericarditis, conjunctivitis, meningitis, encephalitis, pancreatitis, and potentially, diabetes.[27,28] EV-D68 has been identified as a key linked agent of these biannual AFM epidemics based on accumulating clinical, immunological, and epidemiological data.[29] For instance, EV-B forms have also been detected through HFMD, despite EV-A types being more frequently linked to HFMD.[30,31] A prospective epidemiological survey in Rochester, New York, revealed a noteworthy incidence rate of EV infections, which are common in the newborn period. As per the survey, during the usual EV season (June to October), 12.8% of neonates tested positive for EV in stool or throat cultures. Remarkably, 79% of these infections didn't cause any symptoms. The remaining 21% had signs, including fever and lethargy, which resulted in hospitalization for every neonate afflicted. This highlights the clinical significance of EV in neonates by showing a hospitalization incidence of at least seven per 1000 live births as a result of symptomatic EV infections.[32] According to a more recent examination of the molecular epidemiology and clinical aspects of EV-D68 infections by analyzing cases at a hospital in Barcelona, Spain, from 2014 to 2021. Respiratory samples were collected from hospitalized or outpatient individuals exhibiting symptoms of acute

respiratory tract infection or suggestive of EV infection. EV-D68 primarily affected children (86%) and exhibited a biennial pattern of occurrence (2016, 2018, 2021). Lower respiratory tract infection was the most common sign/symptom in patients under 16 years old, with 11.8% requiring admission to the pediatric intensive care unit and 2.3% needing invasive mechanical ventilation.[33] Although factors such as alterations in viral fitness and human immunity probably contribute, the precise mechanisms behind the emergence and transmission dynamics of NPEV are not well-defined. Our comprehension of the full spectrum of illnesses attributed to specific NPEV serotypes is continually developing. For instance, EV-D68, traditionally linked to respiratory problems, is now thought to be implicated in the occurrence of acute flaccid myelitis.

6 | THERAPEUTIC AND PREVENTIVE MEASURES OF NPEVs INFECTION

While there aren't any vaccinations for EV-D68 at the moment. [34] By focusing on both viral proteins and host variables, antivirals against EV-A71 have had significant success.[35] As of right now, China has approved three EV71-targeting vaccines that make use of C4 genogroup strains. There are ongoing trials underway abroad for potential EV vaccines containing the B4 and B5 genogroups. Additionally, research into the creation of EV vaccines against Coxsackie A16, A6, and A10 is still underway, with a focus on the possibility of developing combination or multivalent vaccinations.[36] As per the recommended approach, administering intravenous immunoglobulin (IVIg) treatment early in the onset of the illness may yield optimal effectiveness. Occasionally, intravenous steroids and plasma exchange are employed due to their potential immune-modulating properties. In mouse models simulating EV D68 nervous system infection, the timely application of IVIg therapy resulted in reduced paralysis. Conversely, steroid treatment elevated spinal cord viral titers and worsened outcomes.[37] The incidence and mortality from EVA71 in Taiwan declined dramatically between 1998 and 2020 when proactive EV surveillance and preventative measures were put in place.[38] To accelerate the development of medical countermeasures against potentially extremely virulent RNA viruses, the strategy concentrates on universal features of product development, highlighting low-risk, pathogen-agnostic prospects for the best possible near-term readiness. The research found A cell-intrinsic antiviral effector called E3 ubiquitin ligase TRIM7 targets viral 2BC, a membrane remodeling protein, for ubiquitination and proteasome-dependent destruction, therefore limiting the growth of several human enteroviruses.[39] The international research community should persist and enhance its endeavors in various domains to prepare for forthcoming pandemics. This involves documenting the landscapes and animal sources of viruses affecting humans through vigilant monitoring and metagenomics, establishing animal models for potentially pandemic-causing viruses, delving into fundamental research to deepen our comprehension of the molecular virology of such viruses, creating early-stage vaccines and subjecting them to testing in animal models, and crafting comprehensive antivirals as a primary defensive measure.[40] However, vaccines containing B4 and B5 genogroups are still in progress and have not reached the licensing phase. Research could focus on expediting the development and approval of vaccines for these genogroups, addressing potential challenges, and ensuring a comprehensive protection strategy. While progress has been made with C4 genogroup EV vaccines, the gap lies in exploring and advancing various vaccine types (recombinant vaccines, subunit vaccines, vectored vaccines, and virus-like particle vaccines). A comparative study of these vaccine types in terms of efficacy, safety, and scalability could help identify the most promising candidates. While the incidence and mortality from EV A71 in Taiwan declined between 1998 and 2020, there is a need for ongoing research to understand the factors contributing to this decline. Additionally, research could focus on refining and expanding surveillance and preventative measures to maintain and further improve the control of EV71 and related viruses. The global research community must continue and bolster its efforts in several areas to be ready for future pandemics by (i) cataloging the terrain and animal reservoirs of viruses that infect humans through surveillance and metagenomics; (ii) developing animal models for viruses that could start pandemics; (iii) researching for better understand the molecular virology of these viruses; (iv) developing early-stage vaccines and testing them in animal models; and (v) developing broad antivirals as a first line of defense.

7 | PREDICTION OF NPEVs INFECTION TO CAUSE GLOBAL PANDEMICS

The next global health crisis most likely stems from a zoonotic event brought on by a virus that was transmitted to humans by animals, such as bats.[41] In 2022, research on EV-A71 in China points to a worrying pattern in the effect and worldwide spread of NPEVs infections, with EV-A71 being a special emphasis, as well as their potential to trigger pandemics.[42] Therefore, it is assumed that the following risk factors will likely lead to the emergence of a pandemic: human activity near wildlife; production of animal source foods with minimal employee supervision and an unclear supply chain; insect vectors; extremely high population density; limited surveillance and laboratory capacity.[43–45] Some countries still do not diagnose some enteroviruses adequately and this may be another risk factor of global spread to cause international public health emergency.[46] The continuous threat and geographic expansion of EV-D68 and EV-A71 viruses are highlighted by the recurrent outbreaks in various places. As demonstrated in the case of poliovirus, the genetic mutation and recombination seen in enteroviruses, such as EV-A71, may result in the creation of new strains with altered virulence.[21] The potential for rapid and widespread dissemination is highlighted by the modes of transmission, which include the respiratory and fecal-oral pathways, as well as the ability of infected persons to shed the virus for weeks, even in the absence of symptoms. Furthermore, the wide range of clinical presentations, which include everything from minor

symptoms to serious illnesses, including myocarditis, encephalitis, and AFP, point to the viruses' adaptability and plasticity. Ultimately, the lack of targeted antiviral medications and vaccines, together with the requirement for continued research across multiple fields, highlights the significance of readiness and observation. To foresee and mitigate the potential appearance of an NPEVs pandemic, it is imperative to monitor the genetic evolution, comprehend transmission dynamics, and create therapeutic and preventive measures. These stages will require global collaboration and ongoing research efforts.

8 | CONCLUSION

In summary, this study highlights the concerning potential of emerging NPEVs to serve as the mysterious "Disease X," as outlined by the WHO. By examining the impact of NPEVs on global public health, particularly through notable outbreaks such as EV-D68 and EV-A71, this research underscores the urgent need to address these viruses. For a thorough risk assessment and efficient management of NPEVs infections, several factors must be taken into consideration. Mapping the viral ecology, introducing animal models, and advancing early-stage vaccine development is crucial. Together, these essential elements demonstrate the need for continued worldwide collaboration and research to ensure future preparedness against viral threats.

AUTHOR CONTRIBUTIONS

Ramisa Anjum: Conceptualization; data curation; writing—original draft. **Md Aminul Haque**: Conceptualization; data curation; writing—original draft. **Raushanara Akter**: Conceptualization; validation; supervision; writing—review and editing. **Md Rabiul Islam**: Validation; writing—review and editing; supervision; conceptualization.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

ETHICS STATEMENT

It was an analysis of online available aggregate data. No ethical approval was needed.

TRANSPARENCY STATEMENT

The lead author Md. Rabiul Islam affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. World Health Organization. Prioritizing diseases for research and development in emergency contexts. WHO. 2023. Accessed November 29, 2023. https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts
2. Jiang S, Shi ZL. The first disease X is caused by a highly transmissible acute respiratory syndrome coronavirus. *Virologica Sinica*. 2020; 35(3):263-265. doi:10.1007/s12250-020-00206-5
3. Baggen J, Thibaut HJ, Strating JRPM, van Kuppeveld FJM. The life cycle of non-polio enteroviruses and how to target it. *Nat Rev Microbiol*. 2018;16(6):368-381. doi:10.1038/s41579-018-00054
4. Kang J, Huang M, Li J, et al. Enterovirus D68 VP3 targets the interferon regulatory factor 7 to inhibit type i interferon response. *Microbiol Spectrum*. 2023;11(3):e0413822. doi:10.1128/spectrum.04138-22
5. Li R, Wang M, Li D, et al. The impact of the COVID-19 pandemic on the number of hand, foot, and mouth disease due to enterovirus 71 infections. *J Infect*. 2023;86(4):e111-e113. doi:10.1016/j.jinf.2023.02.005
6. World Health Organization. WHO to identify pathogens that could cause future outbreaks and pandemics. WHO. 2022. Accessed November 21, 2022. https://www.who.int/news/item/21-11-2022-who-to-identify-pathogens-that-could-cause-future-outbreaks-and-pandemics
7. Anasir MI, Zarif F, Poh CL. Antivirals blocking entry of enteroviruses and therapeutic potential. *J Biomed Sci*. J2021;28(1):10. doi:10.1186/s12929-021-00708-8
8. Chu ST, Kobayashi K, Bi X, et al. Newly emerged enterovirus-A71 C4 sublineage may be more virulent than B5 in the 2015-2016 hand-foot-and-mouth disease outbreak in northern Vietnam. *Sci Rep*. 2020;10(1):159. doi:10.1038/s41598-019-56703-5
9. Moffett DB, Llewellyn A, Singh H, et al. Progress toward poliovirus containment implementation: worldwide, 2019-2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(37):1330-1333. doi:10.15585/mmwr.mm6937a7
10. Uprety P, Graf EH. Enterovirus infection and acute flaccid myelitis. *Current Op Virol*. 2020;40:55-60. doi:10.1016/j.coviro.2020.06.006
11. Puenpa J, Wanlapakorn N, Vongpunsawad S, Poovorawan Y. The history of enterovirus A71 outbreaks and molecular epidemiology in the Asia-Pacific region. *J Biomed Sci*. 2019;26(1):75. doi:10.1186/s12929-019-0573-2
12. Holm-Hansen CC, Midgley SE, Fischer TK. Global emergence of enterovirus D68: a systematic review. *Lancet Infect Dis*. 2016;16(5): e64-e75. doi:10.1016/S1473-3099(15)00543-5
13. Andrés C, Vila J, Creus-Costa A, et al. Enterovirus D68 in hospitalized children, Barcelona, Spain, 2014-2021. *Emerging Infect Dis*. 2022;28(7):1327-1331. doi:10.3201/eid2807.220264
14. Shah MM, Perez A, Lively JY, et al. Enterovirus D68-associated acute respiratory illness: new vaccine surveillance network, United States, July–November 2018–2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(47):1623-1628. doi:10.15585/mmwr.mm7047a1
15. Fall A, Gallagher N, Morris CP, et al. Circulation of enterovirus D68 during period of increased influenza-like illness, maryland, USA, 2021. *Emerging Infect Dis*. 2022;28(7):1525-1527. doi:10.3201/eid2807.212603
16. Ma KC, Winn A, Moline HL, et al. Increase in acute respiratory illnesses among children and adolescents associated with rhinoviruses and enteroviruses, including enterovirus D68: United States, July-September 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(40): 1265-1270. doi:10.15585/mmwr.mm7140e1
17. Benschop KS, Albert J, Anton A, et al. Re-emergence of enterovirus D68 in Europe after easing the COVID-19 lockdown, September 2021. *Euro Surveill*. 2021;26(45):2100998. doi:10.2807/1560-7917.ES.2021.26.45.2100998

18. Midgley CM, Watson JT, Nix WA, et al. Severe respiratory illness associated with a nationwide outbreak of enterovirus D68 in the USA (2014): a descriptive epidemiological investigation. *Lancet Resp Med*. 2015;3(11):879-887. doi:10.1016/S2213-2600(15)00335-5
19. Kidd S, Lopez AS, Konopka-Anstadt JL, Nix WA, Routh JA, Oberste MS. Enterovirus D68-associated acute flaccid myelitis, United States, 2020. *Emerging Infect Dis*. 2020;26(10):e201630. doi:10.3201/eid2610.201630
20. Jiang P, Faase JAJ, Toyoda H, Paul A, Wimmer E, Gorbalenya AE. Evidence for emergence of diverse polioviruses from C-cluster coxsackie A viruses and implications for global poliovirus eradication. *Proc Natl Acad Sci*. 2007;104:9457-9462.
21. Mandary M, Poh C. Changes in the EV-A71 genome through recombination and spontaneous mutations: impact on virulence. *Viruses*. 2018;10(6):320. doi:10.3390/v10060320
22. Pons-Salort M, Parker EPK, Grassly NC. The epidemiology of non-polio enteroviruses: recent advances and outstanding questions. *Curr Opin Infect Dis*. 2015;28(5):479-487. doi:10.1097/QCO.0000000000000187
23. Woolhouse ME, Howey R, Gaunt E, Reilly L, Chase-Topping M, Savill N. Temporal trends in the discovery of human viruses. *Proc Biol Sci*. 2008;275(1647):2111-2115. doi:10.1098/rspb.2008.0294
24. Centers for Disease Control and Prevention. Polio enterovirus-transmission. 2020. https://www.cdc.gov/non-polio-enterovirus/about/transmission.html
25. Miwatashi W, Ishida M, Takashino A, et al. Mouse Scarb2 modulates EV-A71 pathogenicity in neonatal mice. *J Virol*. 2022;96(15):e0056122. doi:10.1128/jvi.00561-22
26. Centers for Disease Control and Prevention. Enterovirus D68. 2023. Accessed December 23, 2023. https://www.cdc.gov/non-polio-enterovirus/about/ev-d68.html#future
27. Suresh S, Forgie S, Robinson J. Non-polio enterovirus detection with acute flaccid paralysis: a systematic review. *J Med Virol*. 2018;90(1):3-7. doi:10.1002/jmv.24933
28. Centers for Disease Control and Prevention. Non-polio Enterovirus: Symptoms. 2020. Accessed November 29, 2023. *Non-polio enterovirus: symptoms Non-polio enterovirus: symptoms*. https://www.cdc.gov/non-polio-enterovirus/about/symptoms.html
29. Frost J, Rudy MJ, Leser JS, et al. Telaprevir treatment reduces paralysis in a mouse model of enterovirus D68 acute flaccid myelitis. *J Virol*. 2023;97(5):e0015623. doi:10.1128/jvi.00156-23
30. Ma E, Chan KC, Cheng P, Wong C, Chuang SK. The enterovirus 71 epidemic in 2008: public health implications for Hong Kong. *Int J Infect Dis*. 2010;14(9):e775-e780. doi:10.1016/j.ijid.2010.02.2265
31. Klein M, Chong P. Is a multivalent hand, foot, and mouth disease vaccine feasible? *Hum Vaccines Immunother*. 2015;11(11):2688-2704. doi:10.1080/21645515.2015.1049780
32. Jenista JA, Powell KR, Menegus MA. Epidemiology of neonatal enterovirus infection. *J Pediatr*. 1984;104(5):685-690. doi:10.1016/s0022-3476(84)80944-0
33. Andrés C, Vila J, Creus-Costa A, et al. Enterovirus D68 in hospitalized children, Barcelona, Spain, 2014-2021. *Emerging Infect Dis*. 2022;28(7):1327-1331. doi:10.3201/eid2807.220264
34. Hu Y, Musharrafieh R, Zheng M, Wang J. Enterovirus D68 antivirals: past, present, and future. *ACS Infect Dis*. 2020;6(7):1572-1586. doi:10.1021/acsinfecdis.0c00120
35. Wang J, Hu Y, Zheng M. Enterovirus A71 antivirals: past, present, and future. *Acta Pharm Sin B*. 2022;12(4):1542-1566. doi:10.1016/j.apsb.2021.08.017
36. World Health Organization. Enterovirus 71. 2023. Accessed December 22, 2023. https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/enterovirus-71
37. Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. *Lancet*. 2021;397(10271):334-346. doi:10.1016/S0140-6736(20)32723-9
38. Hu YL, Chen CM, Wang ET, et al. The secular trend of enterovirus A71 after the implementation of preventive measures in Taiwan. *BMC Public Health*. 2022;22(1):1483. doi:10.1186/s12889-022-13916-0
39. Fan W, Mar KB, Sari L, et al. TRIM7 inhibits enterovirus replication and promotes emergence of a viral variant with increased pathogenicity. *Cell*. 2021;184(13):3410-3425 e17. doi:10.1016/j.cell.2021.04.047
40. Cassetti MC, Pierson TC, Patterson LJ, et al. Prototype pathogen approach for vaccine and monoclonal antibody development: a critical component of the NIAID plan for pandemic preparedness. *J Infect Dis*. 2023;227(12):1433-1441. doi:10.1093/infdis/jiac296
41. Neumann G, Kawaoka Y. Which virus will cause the next pandemic? *Viruses*. 2023;15(1):199. doi:10.3390/v15010199
42. Noisumdaeng P, Puthavathana P. Molecular evolutionary dynamics of enterovirus A71, coxsackievirus A16 and coxsackievirus A6 causing hand, foot and mouth disease in Thailand, 2000-2022. *Sci Rep*. 2023;13(1):17359. doi:10.1038/s41598-023-44644-z.
43. Salyer SJ, Silver R, Simone K, Barton Behravesh C. Prioritizing zoonoses for global health capacity building-themes from one health zoonotic disease workshops in 7 countries, 2014-2016. *Emerging Infect Dis*. 2017;23(13):S55-S64. doi:10.3201/eid2313.170418
44. Kelly TR, Karesh WB, Johnson CK, et al. One health proof of concept: bringing a transdisciplinary approach to surveillance for zoonotic viruses at the human-wild animal interface. *Prev Vet Med*. 2017;137(Pt B):112-118. doi:10.1016/j.prevetmed.2016.11.023
45. Schwind JS, Goldstein T, Thomas K, Mazet JA, Smith WA. Capacity building efforts and perceptions for wildlife surveillance to detect zoonotic pathogens: comparing stakeholder perspectives. *BMC Public Health*. 2014;14:684. doi:10.1186/1471-2458-14-684
46. Harvala H, Broberg E, Benschop K, et al. Recommendations for enterovirus diagnostics and characterisation within and beyond Europe. *J Clin Virol* 2018;101:11-17. doi:10.1016/j.jcv.2018.01.008

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