

Online Supplementary Materials

Table S1. Adherence to JoGH’s GRABDROP guidelines items.

JoGH guideline items
1. Please list all papers published by each co-author in previous 3 years that were based on secondary analysis of a big data repository None of the authors have published papers based on secondary analysis of large-scale data repositories in the past three years.
2. Please explain the key elements of your study design and the use of the available datasets that make your study an original scientific contribution This study was designed as a country-level scoping synthesis to characterise the global epidemiological and etiological patterns of hand, foot, and mouth disease (HFMD) based on available global evidence. By systematically collecting and synthesising data from heterogeneous sources(national surveillance systems and published studies), we provide a structured overview of HFMD epidemiology across countries. Detailed country-specific information is presented in the Supplementary Materials to support transparency and reproducibility. A key element of our study is the focus on country-level mapping of evidence, which allows us to identify substantial heterogeneity in surveillance and data availability for both epidemiological and etiological patterns across regions. Our findings highlight that many countries lack systematic surveillance data or have very limited published evidence on HFMD epidemiology and serotype distributions. The originality of this study lies in its integrated, country-level perspective, moving beyond traditional narrative reviews focused on pathogens, clinical features or vaccine development. Instead, it provides a comprehensive synthesis of available evidence and explicitly identifies critical data gaps. Additionally, changes in major circulating serotypes highlight the need for more comprehensive and accessible data, as well as standardised diagnostic and laboratory detection procedures. Overall, our study provides a foundation for future research and underscore the importance of developing unified surveillance systems, standardizing diagnostic and reporting approaches, and improving global data comparability for HFMD.
3. Please list all publications that addressed similar research questions in the same dataset and indicate where you cited them in your paper The following relevant review articles addressing similar research topics were cited in the Introduction section and Results of this manuscript. Additional information, including data from official surveillance websites, was extracted from the following review papers to ensure comprehensiveness, particularly for countries with limited publicly available data (as described in the Methods section). 1. Huang, C.Y., S.B. Su, and K.T. Chen, A review of enterovirus-associated hand-foot and mouth disease: preventive strategies and the need for a global enterovirus surveillance

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- network. *Pathog Glob Health*, 2024. 118(7-8): p. 538-548.
2. Zhu, P., et al., Current status of hand-foot-and-mouth disease. *J biomed sci*, 2023. 30(1): p. 15.
3. Leung, A.K.C., et al., Hand, Foot, and Mouth Disease: A Narrative Review. *Recent Adv Inflamm Allergy Drug Discov*, 2022. 16(2): p. 77-95.
4. Puenpa, J, Wanlapakorn, N, Vongpunswad, S, et al. 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

To our knowledge, no previous studies have conducted a country-level synthesis using a comparable dataset or approach. Therefore, the present study represents a distinct scoping synthesis rather than a reanalysis of an existing dataset.

4. Please explain how you addressed multiple testing through an appropriately rigorous statistical threshold and indicate this in the methods section

This study was designed as a descriptive scoping review, focusing on summarizing and synthesizing available epidemiological and etiological data across countries. No formal statistical hypothesis testing or inferential comparisons were performed. Therefore, issues related to multiple testing and adjustment for statistical significance thresholds are not applicable in this context. This has been clarified in the Methods section of the revised manuscript.

5. Please declare to what extent have AI chatbots been used in developing your paper and to which parts of the paper did they contribute

ChatGPT was used solely for language editing to improve clarity and readability. It did not contribute to study design, study selection, data synthesis, interpretation of results, or the formulation of conclusions. All content and scientific decisions were made by the authors.

Following material provided detail descriptions on country-specific epidemiology and etiology of hand, foot, and mouth disease (HFMD), and HFMD case reports in adults and pregnant in different countries. The summary on EV-associated HFMD outbreaks by years and countries since 2000 were detailed in **Table S2**.

Section 1 Descriptions on epidemiology and etiology of HFMD in countries

China

Since the largest-scale outbreak in Fuyang city, Anhui Province, in 2008, HFMD has emerged as a significant public health concern in China[1]. In 2008, HFMD was classified as a category III notifiable infectious disease and has since been monitored by a national surveillance system[1]. According to the Guidelines on prevention and control of HFMD(2009 version), throat swab or stool specimens were required to be collected from clinically diagnosed HFMD cases for laboratory serotype analysis[2].

Surveillance data from 2023 indicated a total of 1,673,481 reported cases of HFMD was, with an incidence of 118.71 per 100,000[3](**Figure S1**). Notably, a meta-analysis indicated that the recessive infection rate of HFMD-associated enterovirus (EV) among healthy individuals in China ranged from 4.59% to 44.12%[4]. Analysis has shown a sharp decrease in severe illness rate and mortality of HFMD across all age groups following the use of the EV-A71 vaccine, with reductions of 62.20% and 83.78%, respectively[5]. Additionally, the timing of the HFMD epidemic peak was delayed by 1-2 months[5]. However, HFMD continued to cause numerous local outbreaks, as Zhejiang Province had reported, a total of 47 HFMD and HA outbreaks occurred from 2021 to 2023[6].

In general, the proportions of each serotype in laboratory-confirmed cases[7] and outbreak cases[8] of HFMD in different years were shown in the **Figure S2** and **Figure S3**. A review on HFMD in China revealed that from 2008 to 2012, the predominant serotypes were EV-A71(50.56%) and CV-A16(28.88%) [9]. From 2013 to 2019, EV-A71, CV-A16, CV-A6 and CV-A10 co-circulated. During this period, the prevalence of CV-A6 and CV-A10 increased, while that of EV-A71 decreased[1,9]. CV-A16 and CV-A6 became the predominant serotypes particularly during 2016 and 2020[9]. Still, most severe and fatal cases were associated with EV-A71 infection, accounting for over 60% and 90% of such cases, respectively[2,10,11].

The serotypes causing HFMD also exhibited regional variation, differing among provinces and even cities. Studies indicated a continuously high CV-A16 infection rate in southern China from 2008 to 2014[12]. After a period of lower epidemic activity in 2015-2017, an upsurge of CV-A16 infection was observed in 2018-2019, likely resulting from the introduction(s) from Southeast Asia[12]. The causative serotypes in Yunnan Province

changed to non-EVA71/non-CVA16 enteroviruses from 2008 to 2019 [13], a trend also observed in Gansu Province from 2010 to 2021[14]. EV-A71 was the dominant serotype in Hubei Province during 2010–2019, especially in 2016[15]. CV-A16 was the main EV causing HFMD in Shanxi Province from 2009 to 2020, with an average proportion of 33.06%[16]. In Jiangxi Province, EV-A71 remained the dominant serotype causing severe HFMD until 2017, after which the proportion of other EVs significantly increased, accounting for 100% of cases in 2021 and 2023[17]. In Zhejiang province, there was a shift from CV-A16 in 2021 and 2022 to CV-A6 in 2023[6]. In Shiyan, Hubei Province, data from 2009 to 2019 suggested that CV-A6 may have been the most common serotype in hospitalized HFMD cases[18].

Molecular characteristic analysis of different EVs that published between 2020 and 2025 were conducted at the country, province and city levels. Analysis of EV-A71 were performed in Beijing[19] and Xiamen[20]; CV-A16 analyses were conducted nationwide[21,22] and in Beijing[23], Guangdong[24], Shanxi[25] and Shenyang[26]; CVA6 analyses were performed nationwide[27-29] and in Beijing[30-32], Hebei[33], Guangxi[34], Henan[35], and Linyi[36]; and the analysis of CV-A10 were conducted in Zhejiang[37], Shanghai[38], and Taiyuan[39].

In addition to four main serotypes of EV, cases caused by other EVs had also been reported: CV-A4 was reported in mainland China in 2011[40], and was identified in Jiangsu Province from 2016 to 2018[41]. An outbreak caused by CV-A4, with febrile illness and influenza-like illnesses as the main symptoms, was reported in Shandong Province in 2021[42]. Sparse HFMD cases caused by CV-A5 have been reported in China[40], and it was one of the major serotypes causing epidemics from 2016 to 2017 in Hubei Province[43]. There had also been reports of HFMD caused by CV-A8 in China[44].

Study also indicated that aforementioned EVs may also cause HFMD with central nervous system (CNS) complications. A study showed that the serotypes causing CNS complications were EV-A71 (40%), followed by CV-A4 (17%), CV-A2 (13%), CV-A10 (10%), CV-A6 (7%), and CV-A16 (4%)[45]. Another study identified the serotypes causing severe HFMD cases and deaths included CV-A2, CV-A4, CV-A6, CV-A9, and CV-A10[33]. Furthermore, research showed that CV-A1 may be related to severe HFMD cases[46]. Analyses also indicated that CVB were also important agent associated with HFMD[47], such as CV-B1[48], CV-B2[49], and CV-B4, a potential virus that could cause HFMD outbreak[50]. Studies had also shown that echovirus could cause HFMD, such as E3[33,51], E9[52], E11[33], and E30[53].

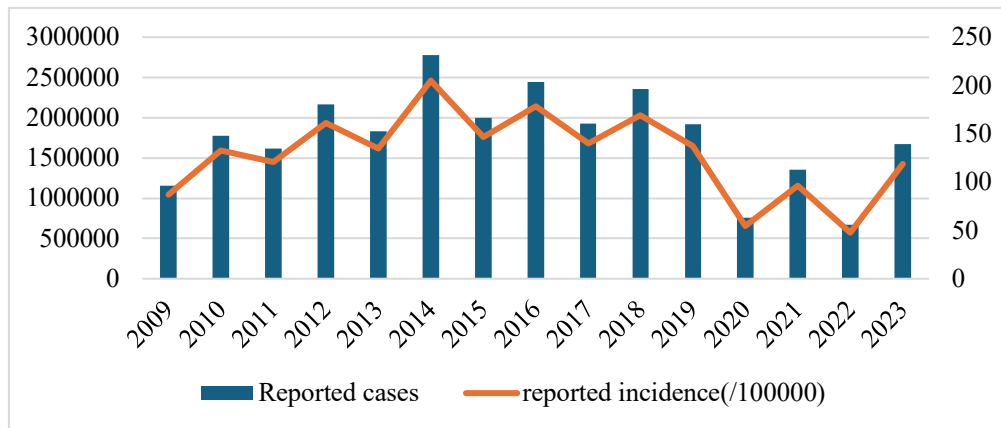


Figure S1. Reported cases and incidence rates of HFMD in China, 2009-2023[3]

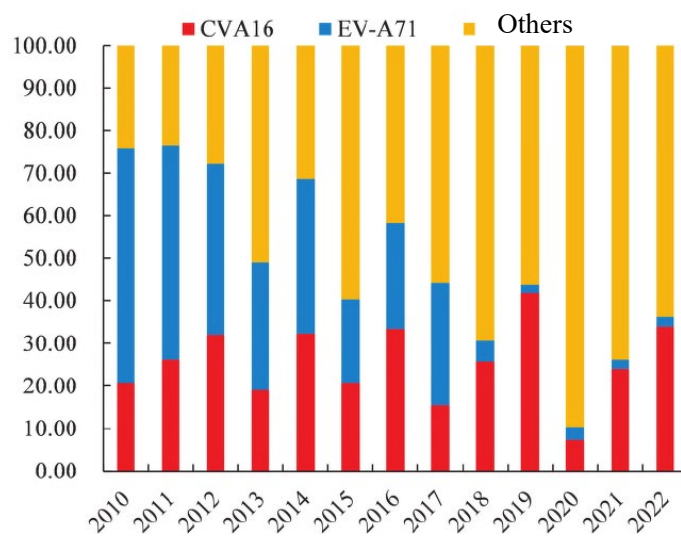


Figure S2. Serotype distributions of laboratory-confirmed HFMD in China, 2010-2022[7]

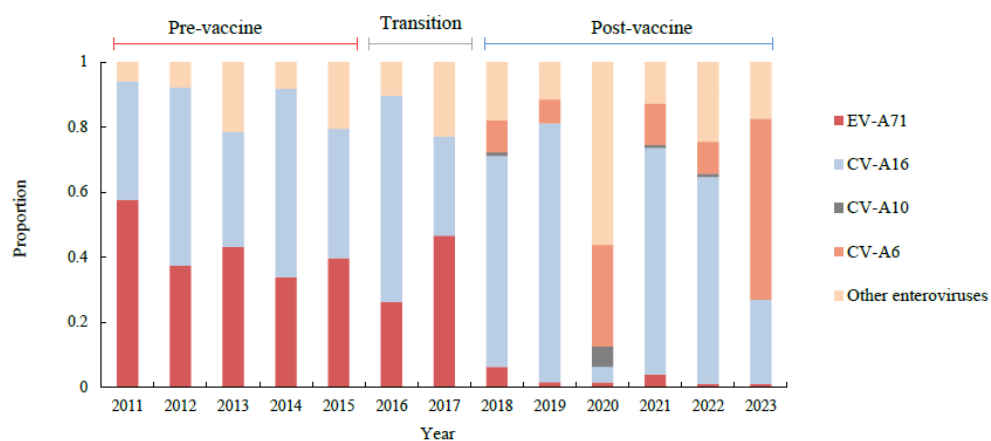


Figure S3. Serotype distributions in HFMD outbreak cases, 2011-2023[8]

The pre-vaccine time was from 2011 to 2015. The vaccine transition time was between 2016 and 2017. The post-vaccine time was from 2018 to 2023

Vietnam

In Vietnam, the first HFMD case was reported in 2003[54]. An outbreak caused by CV-A16 and EV-A71 occurred in 2005[55,56], followed by an increase in reported cases from 2007 to 2009[56]. The largest HFMD outbreak in Vietnam occurred from February 2011 to July 2012, resulting in 174,677 cases and 200 deaths upon hospital admission[54].

Since 2011, HFMD has been included in the national communicable disease surveillance system (Circular No. 48/2010/TT-BYT)[56,57]. The numbers of reported cases and the incidences of HFMD increased until 2018 (134,657 cases; incidence: 142.24/100,000) [58]. In 2020, the number of reported cases decreased to 83,789, with an incidence of 8.84/100,000[58](**Figure S4**).

Etiological surveillance in Vietnam was primarily set up by research groups at the Pasteur Institute in Ho Chi Minh city (PI HCM) and the National Institute of Hygiene and Epidemiology(NIHE) in Hanoi, beginning in 2005 and 2008, respectively[57].

The NIHE has conducted surveillance in the northern provinces[59]. Results indicated that the dominant serotypes in northern provinces of Vietnam between 2008 to 2018 were EV-A71 (31.7-35.04%), CV-A6 (26.57-28.4%), and CV-A16(20.84-22.4%)[57,60]. An analysis conducted between 2012 and 2017 in Hai Phong and Thai Binh yielded similar results, with the proportions of CV-A6, EV-A71, and CV-A16 being 32.5%, 26.9% and 19.3%, respectively[59]. A study showed that the CV-A6 (47.1%) and EV-A71(32.5%) were the main cause of HFMD in northern Vietnam in 2015-2016[54].

From 2012 to 2021, among all the hospitalized HFMD patients with identified EV detections, EV-A71 accounted for 49.06% of cases, followed by CV-A6(22.99%), CV-A10(9.94%), and CV-A16(7.06%)[61].

A study conducted by Oxford University Clinical Research Unit, Ho Chi Minh City between 2013 and 2015 indicated that the four dominant serotypes in Ho Chi Minh City were EV-A71 (26.2%), CV-A6 (17.8%), CV-A16 (11%), and CV-A10 (7.1%)[62]. Another analysis from 2015 to 2018 showed that EV-A71(28.3%), CV-A6(16.4%), CV-A16(11.5%) and CV-A10(7.9%) were the causative agents[63]. The molecular epidemiology of CV-A16 in southern Vietnam had also been reported[64].

A sudden increase in the prevalence of CV-A10 in 2016 and CV-A2 and CV-A4 in 2017[59]. And in 2018, a large-scale outbreak caused by EV-A71 infection occurred[65]. Additionally, a study on the infection of EV-A71, CV-A6, and CV-A16 among household contacts highlighted the need to consider the household as an additional target for HFMD intervention programs[66].

More recently, a HFMD outbreak occurred in 2023, with a total of 12,600 HFMD cases and 7 deaths reported in Vietnam[67]. A study conducted during this outbreak found that 98.8% of EV-positive samples were positive for EV-A71[67].

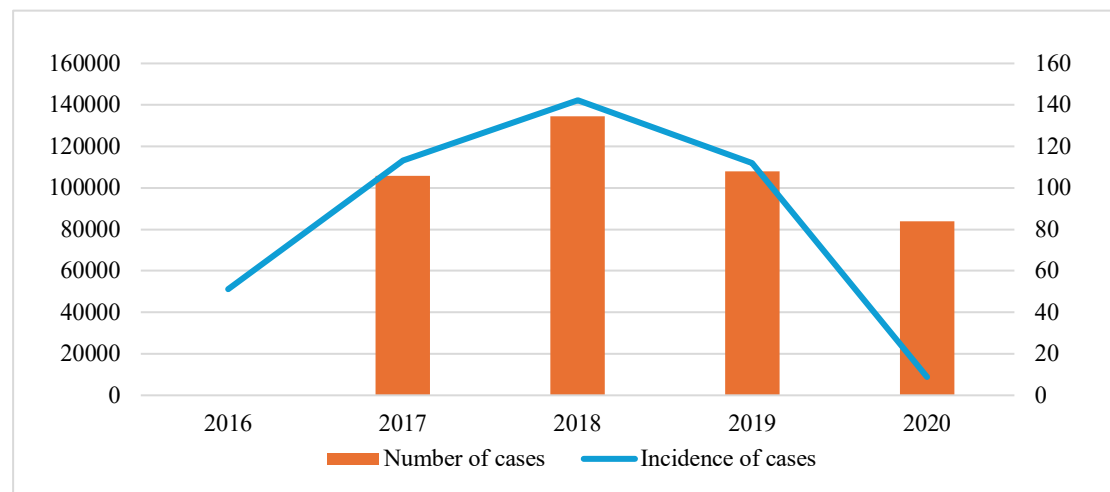


Figure S4. Reported cases and incidence rates of HFMD in Vietnam, 2016-2020[58]

Malaysia

After being first reported in 1997 in Malaysia, HFMD was made a mandatory notifiable disease in 2006 under the Prevention and Control of Infectious Diseases Act 1988 [Act 342] [68]. National incidences of HFMD from 2009 to 2024 were available from the Ministry of Health (**Figure S5**), and the main EVs causing HFMD in 2023 and 2024 were CV-A6 and CV-A16, respectively [69].

The first documented HFMD outbreak, which occurred in Sarawak (East Malaysia) in 1997 and subsequently spread to peninsular Malaysia, was caused by EV-A71 infection, affecting more than 4,000 children and 41 deaths[70,71]. Although CV-A16 was also isolated during that outbreak, only EV-A71 was identified in fatal cases[70]. Since then, EV-A71 epidemics have occurred every 2 to 3 years, in 2000, 2003, 2006, 2008/2009, and 2012[71]. In late 2000, another HFMD outbreak occurred in Malaysia, followed by a recurrence of an outbreak caused by EV-A71 in 2003[72]. An outbreak in late 2005 saw CV-A16 preceded the appearance of EV-A71, which was followed by a larger outbreak in Sarawak in early 2006[72]. In 2007, an outbreak of HFMD was only noted in peninsular Malaysia that was almost purely due to CV-A16[72]. Further epidemics of EV-A71 occurred in 2008, 2009 and 2012[71]. In an outbreak that occurred in peninsular Malaysia in 2010, both EV-A71 and CV-A16 were identified as the main serotypes[72].

During 2018, a major HFMD outbreak occurred across Malaysia with over 76,000 infected individuals[73]. A study from a teaching hospital in Kuala Lumpur showed that among all

EV-positive samples, the proportion of CV-A6, CV-A16, EV-A71, CV-A10, and CV-B3 were 44%, 40%, 10%, 2%, and 4%, respectively[73]. A study conducted during an outbreak in Beaufort, Sabah, in 2018 showed that 83.3% of samples were positive for CV-A16 and 16.7% for EV-A71[70].

Notably, in 2022, a HFMD outbreak in Malaysia was reported on the social media[74], followed by the dramatically increasing number of reported HFMD cases in 2022 (**Figure S5**)[69]. In 2025, news reports indicated another HFMD outbreak in Malaysia. The number of reported HFMD cases by late May reached 99,601, a 266% increase compared to the same period in the previous year[75,76]

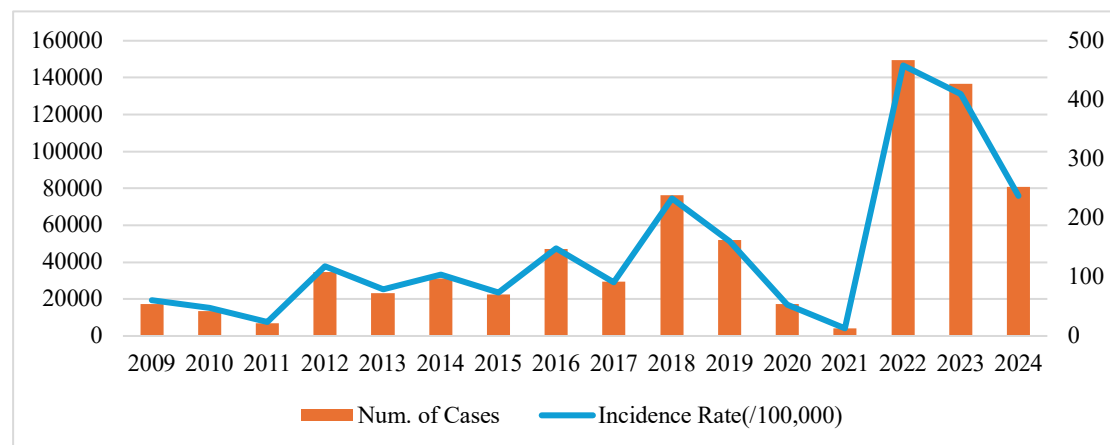


Figure S5. Reported cases and incidence rates of HFMD in Malaysia, 2009-2024[69]

Thailand

HFMD was first noticed in 2000 in Thailand and became a notifiable disease under the Ministry of Public Health (MOPH) in 2001[77].

The first outbreak was recorded in 2012 with 45,464 infected individuals, the largest in a decade[78]. Subsequent outbreaks occurred in 2016 and 2017[65,78]. Confirmed cases from 2011 to 2019, sourced from Bureau of Epidemiology (BoE) National Disease Surveillance (report 506) showed that there was a sharp peak in the number of HFMD cases during the rainy season of each year [78].

EV-A71 was first detected in Thailand in 2001, promoting the launch of a national surveillance program for HFMD to monitor EVs[79]. For the last few decades, EV-A71 and CV-A16 have been the major EV causing HFMD in Thailand[77]. CV-A6 was detected sporadically during 2008 and 2011[80]. In 2012, a large HFMD outbreak caused by CV-A6 was reported, with over 60% of affected children being less than three years of age[77,80]. Following that outbreak, CV-A6 co-circulated with EV-A71 and CV-A16[77], causing epidemics with a clear two-year recurrent cyclical pattern(outbreaks in 2012, 2014, 2016, and

2018)[77,80]. Another nationwide HFMD outbreak in 2017 was caused by EV-A71 and CV-A6[65,78]. More recently, a large outbreak due to CV-A6 occurred between January 2019 and October 2022[77,80]. Serotype analyses during this period showed that 23.7% of samples were positive for CV-A6, 3.7% for EV-A71, 3.4% for CV-A16, and 17.9% for other serotypes[80].

Etiological analysis of other EVs associated with HFMD, such as CV-A4[81], have also been conducted. A study using samples collected between 2000 and 2020 analyzed the molecular evolutionary dynamics of EVs causing HFMD, showing the distribution and proportion of EV genotypes and implying that EV continues to evolve, potentially causing large-scale outbreaks in susceptible populations[77].

According to online news, there were 48,154 reported HFMD cases reported nationwide between January and August, 2025, indicating an outbreak, with most cases occurring in children under five years old[82,83].

Japan

HFMD epidemics occur annually in Japan, typically in the summer season and primarily affecting children, but large-scale epidemics have occurred every two years since 2011[84].

HFMD is classified as a Category V notifiable infectious diseases in Japan, with approximately 3,000 pediatric sentinel sites nationwide reporting on a weekly basis[85]. The prevalences and incidences of HFMD at these sites have been published in the Infectious Disease Weekly Report (IDWR) since 1999 (**Figure S6**) [84-86]. And the data on causative serotypes of HFMD is available by the Infectious Agents Surveillance Report(IASR) [87].

According to these reports, the numbers of HFMD cases varies greatly from year to year[85]. In the decade from 2009 to 2019, the lowest number of cases was in 2016 (69,139 cases), and the highest was in 2019 (402,529 cases)[85,86]. In 2020, the number of cases was much lower than usual (18,364 cases) [85,86]. From 2021 to 2023, the number of reported cases returned to levels comparable to the 2009-2019 period[85]. In 2024, the number of reported HFMD cases has increased since the 15th week, reaching levels similar to pre-COVID 19 era and significantly exceeding the weekly average of the past five years[85].

In 2000 and 2003, major epidemics of HFMD were caused mainly by EV-A71; Smaller epidemics of HFMD continued until 2006, when EV-A71 and CV-A16 were mainly isolated[88]. In 2010, Japan again experienced a large epidemic of HFMD caused mainly by EV-A71 again[88]. Since then, large-scale HFMD outbreaks occurred every 2 years (in 2011, 2013, 2015, and 2017) in Japan, but the major causative EV gradually transferred to CV-A6[84,88].

According to the Infectious Agents Surveillance Report(IASR) [87].The main EVs isolated from HFMD patients in the last five years were CV-A16 and CV-A10 in 2020; CV-A6 and CV-A16 in 2021 and 2022; EV-A71 and CV-A6 in 2023; and CV-A6 and CV-A16 in 2024[85,87].

Additionally, case reports on the clinical features of HFMD caused by CV-A6 have been published[89,90], indicating a possibility associated to onychomadesis[90,91]. Sporadic HFMD cases caused by CV-A5 have also been reported in Japan[40].

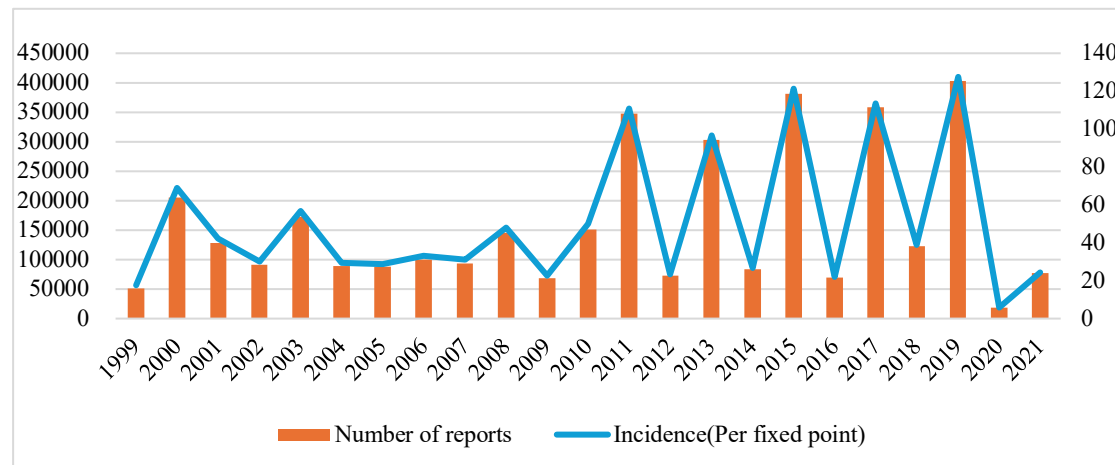


Figure S6. Reported cases and incidence rates of HFMD in Japan, 1999-2021[86]

Korea

The Korea Centers for Disease Control and Prevention launched a national surveillance of enterovirus since 1993[65]. HFMD was monitored through voluntary reporting by pediatricians starting in 2008 and was designated as a national infectious disease in 2009, requiring reporting through a surveillance system[92-94]. According to annual surveillance reports, data of reported HFMD cases are available from 2015 to the present[94]. There was a peak in reported cases in 2019 (1847 cases) [94]. The number of reported cases increased significantly starting in 2022 (from 12 cases in 2021 to 1,180 in 2022, 614 in 2023, and 1,044 in 2024)[94]. No HFMD cases with complication reported in 2020 or 2021[94].

A study used data from the South Korea Health Insurance Review and Assessment Service (HIRA) between 2011 and 2017 showed a total of 1,879,342 HFMD cases in children younger than six years old (8.4 of 100 persons in this age group), with most cases occurring in children under three[92].

EV71 outbreak in Korea was first documented in 2000[95] and HFMD outbreak caused by EV-A71 occurred during 2009 and 2012[55,65]. An analysis using data from Korea Enterovirus Surveillance System (KESS) from 2012 to 2019 identified 1,373 HFMD cases

caused by EVs, including 155 cases with complications[96]. Most cases were in children under five years old. Among HFMD cases, EV-A71 and CV-A6 were the main serotypes (28.9% and 20.4%), followed by CV-A16 (16.4%), CV-A10 (11.8%), and CV-A5(4.2%)[96]. For HFMD with complications, the main viruses were EV-A71 and E18(20.4% each), followed by E30(10.8%), CV-B5(9.7%), and E6(8.6%)[96]. A study in Gwangju showed that EV-A71 and CV-A16 were the main causes of HFMD (23.80% and 20.48%), followed by CV-A6 (19.43%), CV-A10(10.54%), CV-A5(5.12%) and CV-A4(2.41%) from 2011 to 2020[97].

In 2022, an HFMD epidemic occurred in Gwangju, mainly caused by CV-A6, which was the first epidemic since the COVID-19 pandemic began[98].

Singapore

In Singapore, a surveillance system for HFMD, based on notifications from child-care centers, was implemented since 1998[99]. Reporting of the disease became legally mandatory in 2000[99]. Data on reported cases and incidences were available from 2003 to 2018[100].

HFMD was first detected in 1970 in Singapore[99]. Outbreaks caused by CV-A16 and EV-A71 had been reported since then[99]. EV-A71 caused a large HFMD epidemic at the end of 2000(with about 3,800 reported cases)[99] and remain circulating in 2006 and 2008[101], while CV-A16 was the mainly circulating EV in 2005, 2007 and 2009[101]. In 2008, Singapore experienced its largest ever HFMD outbreak caused by EV-A71 and CV-A strains, resulting in 29,686 cases[55]. After late 2009, CV-A6 became the predominant serotype causing HFMD outbreaks[101]. A study of symptomatic paediatric HFMD cases from 2013 to 2018 identified CV-A6 as the major etiological agent(41.0%), followed by EV-A71 (7%), CV-A16 (3.0%), CV-A2 (1.0%) and CV-A10 (1.0%)[102]. Additionally, CV-A4 was reported to have caused illness in Singapore in 2008[40].

Currently, HFMD is not a legally notifiable disease in Singapore; however, educational institutions are required to notify the Ministry of Health (MOH) of any HFMD outbreaks[103].

The Philippines

HFMD is classified as an immediately notifiable disease in the Philippines; samples from suspected cases and their corresponding epidemiological data are collected through the Philippine Integrated Disease Surveillance and Response (PIDSR) for HFMD and Severe Enteroviral Disease[104].

A study that randomly selected and tested uncharacterized EVs from 2012 and 2013 showed an increase in the detection rate of CV-A6 among EV-positive HFMD cases, from 61.9% in 2012 to 88.1% in 2017[104]. The majority of the laboratory-confirmed HFMD cases caused by CV-A6 were young children with a median age of two years old[104]. A cluster of suspected HFMD cases was reported in a school in Balangao, Pangasinan Province, in September 2022[105]. Active case-finding revealed that the majority of cases (78%) were six years old, with CV-A16 being the main serotype(67%)[105].

News reports indicated an HFMD outbreak in the Philippines from January to June 2025, with numbers significantly higher than in the same period of previous year[106-108].

India

India identified the first HFMD case in 2003, with EV-A71 being the causative serotype[109,110]. The first HFMD outbreak was reported in 2003 among children in Calicut(northern Kerala state, southwestern India)[111]. Significant morbidity and mortality were reported in children with EV-A71 infection from Uttar Pradesh (UP) from 2004 to 2006[112]. In 2007, the first large-scale HFMD outbreak occurred in West Bengal[109]. Since then, many small-scale outbreaks have been repeatedly reported from different locations in northeast India, often based on clinical description without laboratory-confirmed reports[109,113].

HFMD cases with CV-A16 and CV-A6 as the predominant viruses were reported from Southern and Eastern parts of India in 2009–2010 [110]. From 2013 to 2015, multiple outbreaks were reported from Karnataka, Gujarat, Maharashtra, Assam and the Andaman Islands; CV-A16 was the predominant causative agent, but CV-A6 and EV-A71 were also detected[110]. A study in Dibrugarh and Tezpur in 2014 verified the circulation of CV-A6 and CV-A16 among HFMD cases[109]. Subsequently, another large-scale outbreak of HFMD was reported in Ladakh in 2016[114].

A study conducted in southern India from 2015 to 2017 showed that CV-A6, CV-A16, and CV-A10 accounted for 64%, 15% and 1% of all samples, respectively[115]. Samples collected at a Tertiary Care Hospital in 2016 and 2017 verified that the circulating serotypes were CV-A6 (31.6%) and EV-A71 (21.6%)[116]. Another study during an outbreak in 2017 identified CV-A6 (75%) and CV-A16(25%) as the associated serotypes[117]. Samples collected from HFMD cases from 2017 to 2018 in Western India revealed the presence of CV-A16(57.7%), CV-A6 (40.8%), and E1 (1.4%)[118].

An HFMD outbreak occurred in India in 2022[119,120]. Studies indicated the main serotypes were CV-A6 and CV-A16[110,121,122]. A multicenter study showed that 94.13% of cases

were positive for IgM antibodies to CV-A6, CV-A16 or EV-A71, with antibodies against CV-A6 being the most commonly detected[122]. Multiple studies conducted during HFMD outbreaks confirmed the main circulation of CV-A16 and CV-A6[110,112]. A study in Navi Mumbai, Maharashtra showed 56.5% of samples collected from children were positive for CV-A6, 15.9% for CV-A16, and 1.4% for CV-A4; one case of co-infection (CV-A16 and CV-A6) was also reported[121]. Another study in Karnataka showed that CV-A16 (68.4%) and CV-A6(31.6%) were the main causative agent of HFMD[123]. HFMD cases continued to be reported in 2023, with most cases occurring in children under three years old[124].

Overall, no surveillance system for HFMD was specified in India. However, HFMD cases have been continually reported in India, with CV-A6 and CV-A16 being the most common serotypes. Molecular analysis of CV-A16[111,125] and CV-A6[126] were also conducted. The HFMD outbreak in 2022 caused serious concern due to the potential risk of future epidemics and the possibility of multiple co-occurring disorders[122,127]. Additionally, case reports related to HFMD during outbreaks[128] and possible complications, such as onycholysis[129], had also been reported.

Indonesia

There is no specific surveillance system for HFMD in Indonesia. HFMD cases were reported in Yogyakarta in 2014, although the exact number of patients was not identified[130]. An HFMD outbreak occurred in Banjarmasin, Indonesia in 2016 and reported 18 cases positive for EV-A71 serotype [130]. According to research from the Virology Laboratory Centre for Biomedical and Basic Health Technology at the National Institute of Health Research Centre, among 48 suspected cases from 2008 to 2021, 26 (54%) were caused by EVs, including 3 cases of EV-A71 (6.25%)[130].

A serosurvey conducted in Bandung city and the West Bandung region between 2022 and 2023 showed a high seroprevalence of EV-A71 IgG, indicating the circulation of EV-A71[130].

In 2025, HFMD cases caused by EV-A71 are required to be reported in hospitals under the categories of “acute meningoencephalitis syndrome” or “acute rash syndrome” in the guideline Technical Guidelines for Sentinel Surveillance of Emerging Infectious Diseases in Hospitals[131].

The United States

There is no specific surveillance system for HFMD in the United States. As introduced in the main text, the National Enterovirus Surveillance System (NESS) was designated to collect basic data on specimens positive for enterovirus or human parechovirus in the United States since the 1960s[55,132]. NESS showed that the most frequently detected EVs was CV-B4 in 2023 and EV-D68 in 2024[133], but these cannot fully reflect HFMD-specific etiological patterns.

HFMD caused by CV-A6 was reported in Boston in 2012[134]. A study recorded a total of 27,996 HFMD cases from 2005 to 2013 in California, without etiological data[135].

An outbreak of neurologic disease caused by EV-A71 occurred in Colorado during 2003 and 2005[55]. Again in 2018, Children's Hospital Colorado noted another outbreak, during which EV-A71 was later identified in 58% of those with enterovirus neurological disease, 93% had findings suggestive of meningitis, 72% showed evidence of encephalitis, and 23% met the case definition of acute flaccid myelitis[136]. In the same year, an atypical outbreak of HFMD among college students at a mid-size university in the mid-Atlantic U.S. was reported, with all tested samples positive for CV-A6[137]. Another HFMD outbreak reported at a university occurred between mid-September and mid-October, 2023[138]. As diagnoses were made clinically, no etiological data was available[138].

Brazil

Although notification is not mandatory in Brazil, frequent outbreaks associated with CV-A6 are reported, particularly in settings such as daycare centers and schools[139].

Notably, CV-A6 was rarely associated with HFMD in Brazil until 2016[139]. A previous study identified CV-A16 and CV-A6 as the main serotypes of HFMD in approximately 75 stool samples typed from eight Brazilian states between 2009 and 2016[140]. During 2018, Brazil experienced widespread HFMD outbreaks caused by CV-A6[141]. Another study in Belém, in the Amazon region, found CV-A6 in about 82% of blood samples from HFMD patients in 2019[139,140]. A study reported on HFMD outbreaks in Sao Paulo State during 2021 identified a total of 4,718 related cases, with 92.98% of cases being children aged 1-4 years old and a seropositive rate of 27.5% for CV-A6[142].

In addition to CV-A6, other EV serotypes have also been reported to be associated with HFMD in Brazil, including coxsackievirus types CV-A1, CV-A2, CV-A4, CV-A5, CV-A9, CV-A16, CV-A24, and CV-B5; echovirus types E11, E13, E14, E18, and E25; and enterovirus types EV-A71, EV-C99, and EV-C116[139]. Case reports about sequelae of HFMD, such as onychomadesis, have also been documented[143].

France

A nationwide network, the PARI Medical Observatory, was established in May 2017 with the support of several French pediatric associations[144,145]. Electronic medical records (EMR) from primary care pediatricians are automatically extracted and sent to the Observatory for processing[144,145]. The network is designated for the prospective surveillance of common pediatric infectious diseases in outpatient settings, including HFMD/herpangina (HA)[146].

A citywide sentinel surveillance system of HFMD/HA was set up in 2010, with results showed that the predominant serotypes were CV-A10 (39.9%) and CV-A6 (28%), followed by CV-A16 (17.5%) and EV-A71 (6.3%); the predominant clinical presentation was HA (63.8%) and this was frequently associated with clinical signs of HFMD (48%)[147].

Between 2010 and 2018, CV-A6 was the predominant serotypes (50.4%) among the 1,946 EV-associated HFMD cases reported during the ambulatory surveillance[144]. The detection rates varied from 24% in 2013 to 64% in 2015[144]. Of the cases, 22% of children had typical HFMD and 72% had atypical HFMD[144]. It was worth noting that nationwide HFMD sentinel surveillance was interrupted between 2015 and 2017[144].

A study reported eight cases of EV-A71 infection diagnosed in Marseille in 2019 and 2020, indicating the circulation of this virus[148]. An HFMD outbreak occurred in France in 2021, with 3,403 cases reported (47% higher than in 2018-2019)[146]. An analysis conducted during this outbreak showed that CV-A6 was the predominant EV(49.5%), followed by CV-A16 (22.1%) and CV-A5 (11.1%)[146]. Results indicated that CV-A6 and CV-A16 were mostly associated with atypical HFMD (79.8% and 61.9%, respectively), while CV-A5 was more frequently associated with herpangina alone (52.4%)[146].

England

In England, 952 HFMD cases that mainly attributed to CV-A16 were reported in 1994[149]. The number of laboratory-confirmed EV-A71 detections reported by health authorities showed a biennial pattern and a slight increasing trend between 2006 and 2013, with peak years reporting no more than 50 detections; in contrast, the number of laboratory-confirmed CV-A6 detections showed a clear increasing trend over time, surpassing 150 detections per year since 2014[150,151].

Studies showed that seroprevalences of EV-A71 and CV-A6 increased from 32% and 54% in infants aged 6-11 months to more than 75% by 10 years of age[151]. Atypical HFMD was linked to newly emerging variants of CV-A6 infection in children in Edinburgh in 2014[152]. Additionally, the molecular epidemiology of CV-A6 has been analyzed[153].

A study using daily HFMD consultation rates from 2017 to 2022 provided an epidemiological overview of disease trends, with the mean weekly consultation rate for HFMD being 1.53 per 100,000 registered patients[154].

A HFMD case caused by CV-A16 was reported in a 13-month-old girl and her 5-year-old brother, who developed rashes one week after returning from a family holiday to Kerala in May 2022[155].

Hungary

Since HFMD is not a notifiable disease in Hungary, no surveillance data on its incidence is available[156]. However, results from studies showed the infections of HFMD. A study reporting on EV types detected in clinical specimens from 2010 to 2018 showed 43% of HFMD cases were CV-A6 infections[156]. Another study of samples collected from 2020 to 2024 in patients with symptoms such as HFMD, encephalitis, or meningitis who tested positive for EVs showed that 52.80% of samples were CV-A6, others included CV-A10(4.80%), CV-B4(2.40%), CV-B5(2.40%), CV-A16(0.80%), E6(4.00%), E11(0.80%), E18(0.80%), E9(0.70%), and EV-A71(2.40%)[157].

Spain

In Spain, there is surveillance system for EVs, and the Spanish National Centre for Microbiology (CNM) has increasingly received more samples from local outbreaks and sporadic cases of HFMD that occurred in different regions, both for virological diagnosis and/or type identification since 2010[158].

During 2008 and 2012, several outbreaks and sporadic cases that associated to typical HFMD, atypical HFMD, or onychomadesis presentations occurred in different regions of Spain[158,159]. The research using samples collected from 2006 to 2020 through poliovirus and non-polio enterovirus (NPEV) surveillance showed that typical and atypical HFMD had a proportion of 58.4% and 38% of all cases, respectively, with the most frequent EV detected being CV-A6 (60.9%)[159]. CV-A16 was the only causative serotype of HFMD in 2010, however, by the end of the year and during 2011, CV-A6 became predominant. In 2012, both CV-A6 and CV-A16 circulated[158]. A study in Barcelona showed that CV-A6 was the most frequently detected EV among the EV-A viruses (70%) and was associated with atypical HFMD (78%)[160].

Additionally, cases caused with neurologic disease caused by EV-A71 were also reported in Spain[161,162].

Other countries

Italy Although there is no formal surveillance system for HFMD in Italy, a study showed that from 2012 to 2022, internet search activities followed a constant trend with peaks in November-December and in June[163]. Additionally, a case report described a 3.9-year-old boy developed Guillain–Barré syndrome (GBS) ten days after the diagnosis of HFMD[164]. And some HFMD cases may present in unusual locations, as described in some case reports[165].

Uruguay An HFMD outbreak occurred between April and June 2019, affecting at least 179 children in Paysandú Province[166]. A study showed that most samples collected during this outbreak were positive for CVA6 and CVA16, with only one cases associated with CVA10[166]. In September 2022, two children were hospitalized with presumptive rhombencephalitis, exhibiting symptoms of HFMD[167].

Cape Verde In July 2023, an alert was received from the Integrated Disease Surveillance and Response Service (SVIR) in Cape Verde regarding an increasing number of cases with fever and cutaneous rash, mostly in children under two years old. A study indicated that this may be the first-ever reported outbreak of CV-A6 associated with atypical HFMD in children in the country[168].

Russia A study in the Ural Federal District and Western Siberia of Russia in 2023 showed that HFMD was the prevailing clinical manifestation (36.7%) of all diseases caused by non-polio enteroviruses (NPEVs), and CV-A6 was the most common serotype in HFMD cases (47.87%)[169].

Serbia In Belgrade, Serbia, a total of 20 HFMD outbreaks were registered between 2015 and 2019. The year 2016 had a higher number of epidemics, involving 102 children from kindergartens[170]. Another study indicated that most cases (72.29%) occurred in children under six years old, but no etiological data were indicated[171].

Mexico Several apparent HFMD cases among children in a daycare center in Mexico City in 2012 suggested the existence of this disease[172]. A laboratory-confirmed case of HFMD in a 5-year-old male in Merida City in the Yucatan Peninsula of Mexico, with EV-A71 as the

etiological agent, was reported, providing the first peer-reviewed evidence of HFMD in the countries[172].

Iran A cross-sectional study conducted in 2015 showed 56.7% of samples collected from children aged 6 months to over 31 years old were positive for EV-A71 neutralizing antibody, with the presence of the antibody increasing with age[173].

Ireland An increase in the number of inpatient admissions for HFMD was noted in a hospital in 2023 compared to 2012 and 2013[174].

Palestine An outbreak occurred in the Jenin district in 2024, and a characterization of CV-A16 was analyzed using samples collected during the outbreak[175].

Peru A case of previously healthy five-year-old girl who presented with HFMD and subsequently developed onychomadesis one month later was reported[176].

Saudi Arabia A case was reported of a 6-year-old girl who present with HFMD symptoms again, six months after a similar presentation, although recurrence of HFMD is rare in children[177].

Argentina A case was reported of a 4-year-old boy infected with HFMD caused by CVA6[178].

Canada A case of typical HFMD was reported in 2020[179].

Greece CV-A4 was reported to have caused illness in Greece in 2009–2010[40].

Table S2. Summary on EV-associated HFMD outbreaks by years and countries since 2000

Years	Countries	Etiology	Results
2000[55,99]	Singapore	EV-A71	Total cases: 3,790
2000[180]	Korea	EV-A71	N.A.
2000[88]	Japan	EV-A71	N.A.
2000[180] [71]	Malaysia	EV-A71	Total cases: <169
2003[72,180]	Malaysia	EV-A71 and CV-A16	Total cases: <107
2003[88]	Japan	EV-A71	N.A.
2005[55,56]	Vietnam	EV-A71 and CV-A16	Total cases: 764 Deaths: 3
2003[111]	India	EV-A71	N.A.
2006[72,180]	Malaysia	EV-A71 and CV-A16	Total cases: 2,599
2006[88]	Japan	EV-A71 and CV-A16	N.A.
2006[180]	Brunei	EV-A71	Total cases: <1,681
2007[72]	Malaysia	CV-A16	Cases: 5,380
2007[109]	India	N.A.	N.A.
2008-2015[55,65]	China	EV-A71 and CV-A16	Total cases: 12,256,102 Severe: 123,261 Deaths: 3,322
2008[55]	Singapore	EV-A71, CV-A6, CV-A10	Total cases: 29,686 Deaths: 47
2008[134]	Finland	CV-A6 and CV-A10	Total cases: 317
2009-2012[55,65]	Korea	EV-A71	Total cases: 7,385 Deaths: 5
2010[88]	Japan	EV-A71	N.A.
2010[147]	France	CV-A6 and CV-A10	N.A.
2011[88]	Japan	CV-A6	N.A.
2012[65]	Cambodia	EV-A71	Severe cases: 59 Deaths: 52
2011-2012[54,65]	Vietnam	EV-A71	Total cases: 174,677 Deaths: 200
2012-2013[65]	Australia	EV-A71	Total cases: 119 Deaths: 4
2012[134] [77,78,80]	Thailand	CV-A6	Total cases: 45,464
2010-2012[158,159]	Spain	EV-A71, CV-A16, CV-A6	N.A.
2012-2013[134]	New Zealand	CV-A6	Cases: 98
2013[88]	Japan	CV-A6	N.A.
2013[113]	India	N.A.	Total cases: 47
2013[55]	Russian	EV-A71	Total cases: 78
2015[88]	Japan	CV-A6	N.A.
2016[114]	India	N.A.	Cases: 465

2016[170]	Serbia	N.A.	Cases: 102
2016[130]	Indonesia	N.A.	N.A.
2017[55,65,78]	Thailand	EV-A71 and CV-A6	Total cases: 70,733 Deaths: 3
2017[134]	Japan	CV-A6	Total cases: 6,173
2018[65]	Vietnam	EV-A71	Total cases: >53,000 Deaths: 6
2018[70,73]	Malaysia	CV-A6 and CV-A16	Total cases: >76,000
2018[141]	Brazil	CV-A6	N.A.
2018[137]	The U.S.	CV-A6	Cases: 138
2019[166]	Uruguay	CV-A6 and CV-A16	Cases: 179
2021[55]	France	CV-A6	Total cases: 3,403
2021[55]	Brazil	CV-A6	Total cases: 315
2019-2022[80]	Thailand	CV-A6	N.A.
2022[55]	India	CV-A16, EV-A71, CV-A6	Total cases: 196
2022[98]	Korea	CV-A6	Total cases: 277
2022[74]	Malaysia	N.A.	Outbreak 29,000+
2023[67]	Vietnam	EV-A71	Cases:12,600 Death: 200
2023[138]	The U.S.	N.A.	Cases: 60
2023[168]	Cape Verde	CV-A6	N.A.
2024[175]	Palestine	CV-A16	N.A.
2025[75,76]	Malaysia	N.A.	Cases: 99,000+
2025[82,83]	Thailand	N.A.	Cases: 48,000+
2025[106-108]	The Philippines	N.A.	N.A.

1. *this table was updated on the basis of a previous review[55,65,134,180]
2. *N.A. not available.

Section 2 Case reports of HFMD in adolescents and adults, and pregnant women

Infections in adults were often linked to contact with infected children[181]. These case reports emphasized the importance of considering HFMD in the differential diagnosis for adults presenting with unexplained cutaneous lesions and oral symptoms[182]. In Japan, a 19-year-old female patient who had contact with a 3-year-old child two days before symptom onset was clinically diagnosed with HFMD after laboratory tests ruled out syphilis[183].

Case reports of HFMD in adults have documented in Japan[184], Vietnam[185], Indonesia[186], the United States[181,187-191], Canada[192], Italy[193-195], Germany[196], Netherlands[197], Denmark[198], Austria[199], Argentina[200], and Lebanon[201]. Cases with atypical symptoms have been reported in France(cases with)[202], Switzerland[203], and Portugal[182,204,205];

Some cases have involved complications and sequela after HFMD, such as optic Neuritis[206], secondary hypogonadism[207], conjunctivitis[208], unilateral acute idiopathic maculopathy[192,198,209,210], onycholysis and onychomadesis[188], maculopathy and retinopathy[199], encephalomyelitis[185], Guillain-Barré syndrome (GBS)[205], longitudinally extensive transverse myelitis[191];

These cases can be caused by EV-A71[182,185], CV-A4[184], CV-A10[193], CV-A6, which often related to atypical HFMD[195,197,211], and CV-B1 to CV-B6[200].

There are few reports on EV infections during pregnancy due to their low prevalence in the population, but such infections may cause severe neonatal complications[212].

Reports of HFMD during pregnancy[213] have been documented in Italy from 2010 to 2016, Although the role of EVs as causative agents of congenital defects remains uncertain, these cases of unfavorable outcomes suggest a need for caution and careful monitoring of pregnant women with HFMD throughout their gestation. Congenital CV-A6 infection may occur if a woman exhibits HFMD symptoms during the perinatal period[214]. Furthermore, infection with CV-A6 in late pregnancy can lead to fetal myocarditis and meningoencephalitis, with perinatal infection potentially resulting in fulminating multisystem involvement and death[215]. A female patient who was 28-weeks pregnant was diagnosed with HFMD after EV71 was detected in a serum virus antibody test, with a complication of pseudomembranous conjunctivitis[216]. Another case reported a woman who developed HFMD on the second day after spontaneous delivery[217]. A case was reported of an 18-year-old primigravida diagnosed with HFMD at 34 weeks of gestation[212].

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