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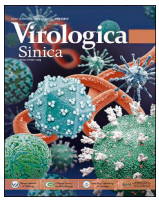

Research Article

The epidemiology and disease burden of enterovirus infections among hospitalized children in China: An 8-year national cross-sectional study

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ABSTRACT

Enterovirus (EV) infections represent a significant global and national health concern in children, leading to various complications. Although most children with EV infections generally have a favorable prognosis, a small proportion may still develop severe complications. This study aimed to analyze the epidemiological characteristics, disease spectrum, and disease burden of EV infections in China. A total of 163,714 hospitalized children with EV infections from 37 member hospitals of the Futang Research Center of Pediatric Development were identified between Jan 1st, 2016 and Dec 31st, 2023, accounting for 1.49% of all pediatric hospitalizations. Most cases occurred in infants aged 28 days to $\leq$ 1 year (42.29%) and toddlers aged 1 to $\leq$ 3 years (39.93%), with a male predominance (male-to-female ratio, 1.62 : 1). Severe cases of EV infections can be life-threatening and increase the burden of disease. The median LOS for EV infections were 5 days, with an average hospitalization cost of $587.37. EV infections can affect multiple organs, including the heart, brain, and respiratory system and were associated with severe complications, including myocarditis, encephalitis, and meningitis. These findings underscore the substantial disease burden of EV infections and highlight the need for targeted prevention strategies in young children.

INTRODUCTION

Enteroviruses (EVs), members of the *Picornaviridae* family, are non-encapsulated RNA viruses that posed significant global public health challenges. Human-infecting EVs include 15 species and 116 serotypes of EVs have been identified, but the majority lack corresponding vaccines (Zell et al., 2017; Jartti et al., 2024). Transmission primarily occurs via the fecal-oral route, and respiratory droplets also play a key role. Most infections have favorable outcomes, with certain clinical manifestations linked to specific EV types.

The main pathogens that cause EV infections are coxsackievirus (CV), echovirus, and Enterovirus A71 (EV-A71) (Wang et al., 2025). Infections caused by CV represent a global public health concern, as this virus can cause a wide range of diseases, including encephalitis, meningitis and myocarditis, in some cases, long-term neurodegenerative disease (Han et al., 2020; Jmii et al., 2021). Although most CV infections are mild and self-limiting, severe disease may occur and result in life-threatening complications, particularly myocarditis and encephalitis (Han et al., 2020). Similarly, echovirus are major etiological agents of viral encephalitis (VE) and viral meningitis (VM) in children and are widely distributed worldwide, with higher prevalence in Asia and Europe. Echovirus has approximately 30 serotypes, and most echovirus infections are asymptomatic or self-limiting. However, a subset of echovirus serotypes has been associated with severe organ damage. For

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example, echovirus 11 (E11) has been implicated in severe neonatal sepsis, hepatic injury and multi-organ failure. Likewise, EV-A71 infection primarily causes hand, foot and mouth disease (HFMD). Additionally, EV-A71 infection can result in central nervous system (CNS) complications, including aseptic meningitis, brainstem encephalitis, and acute flaccid paralysis (AFP). Epidemiologically, EV-A71 is predominantly prevalent in the Asia-Pacific region, where it has caused large-scale outbreaks, with occasional cases reported in North America, Oceania and Europe (Bello and Roshorm, 2022). In China, EV-A71 has been widely distributed, particularly in Shandong, Guangdong, and Anhui provinces, and is associated with significant neurological consequences, such as VE and VM (Guan et al., 2012; Messacar et al., 2020). Following the development of EV-A71 vaccines, an inactivated whole-virus vaccine approved in China in 2016 has been proven high efficacy in reducing the incidence of severe HFMD and EV-A71 infections in regions including Yunnan, Zhejiang, and Henan (Li et al., 2019; Jiang et al., 2021; Kinobe et al., 2022; Wu et al., 2022).

Although most EV infections are self-limiting, certain EV serotypes can cause clinical manifestations ranging from mild illnesses, such as HFMD and herpangina, to severe complications including severe CNS infections, neonatal sepsis, myocarditis, and pericarditis (Uprety et al., 2019; Uprety and Graf, 2020; Tarris et al., 2021; Lloyd et al., 2022). Among these manifestations, HFMD is the most prevalent pediatric illness, caused by multiple EVs, including EV-A71, coxsackievirus A16 (CVA16), coxsackievirus A6 (CVA6), and coxsackievirus A10 (CVA10) (Jin et al., 2018). The disease is primarily characterized by herpetic or ulcerative lesions on the hands, feet, and oral mucosa. Although most cases are self-limiting, a subset of infections can progress to severe disease or, in rare instances, result in death and the disease exhibits particularly high morbidity and mortality rate among children under 5 years old. The public health impact of HFMD has been extensively reported in China. For example, HFMD has been included in the Ministry of Health' list of Category C infectious diseases under the Law of the People's Republic of China on Prevention and Control of Infectious Diseases (Harvala et al., 2021; Han et al., 2022). In addition, studies have investigated the disease's health-related quality of life and economic burden in cities in Shanghai, Zhengzhou, and Kunming (Zhou et al., 2024), as well as the spatial and temporal patterns of HFMD epidemics in Xinjiang Province (Xie et al., 2021). However, in addition to HFMD, many other EV-associated diseases, such as encephalitis, meningitis and myocarditis, lack research on the disease burden and epidemiological trends of these diseases.

This study aims to analyze the epidemiological characteristics and disease spectrum of EV infections in children across mainland region of China from 2016 to 2023. This study will enhance understanding of the epidemiologic characteristics and clinical impact of EV infections by exploring the differences in the disease burden of different EV infections in China and provide a basis for formulating effective preventive and control measures.

RESULTS

Prevalence of EV infection in children

This study included cases with a primary diagnosis of EV infection from 37 hospitals across 7 regions in China between 2016 and 2023 (Fig. 1). A total of 163,714 patients were hospitalized for EV infections, representing 1.49% of all hospital admissions (163,714 out of 10,974,595). Table 1 provides detailed demographic and clinical data, including age, gender, year, season, region, and patient disposition. Males composed of 61.82% (101,206 cases) and females accounted for 38.18% (62,508 cases), with a male to female ratio of 1.62 : 1. The highest proportion of cases occurred in children aged 28 days to 1 year, making up 42.29% (69,236 cases), followed by children aged 1–3 years (65,376 cases, 39.93%). Children over 12 years old accounted for the least proportion (146 cases, 0.09%). Seasonal trends revealed that EV infection hospitalizations peaked during summer and fall (June to August), while fewer cases were reported in winter and spring (Fig. 2). The annual number of hospitalizations for EV infections remained high from 2016 to 2019, with decreases during the COVID-19 epidemic from 2020 to 2023 (Fig. 2). The largest number of cases occurred in 2016 (35,777 cases, 21.85%), while 2022 recorded the lowest (5507 cases, 3.36%). In terms of regional distribution, most of the patients came from east China (93,715 cases, 57.24%), whereas south China (6139 cases,

Fig. 1. The geographical locations of each region and its constituent provinces on the map of China.

Table 1
Demographic information of children hospitalized with EV infection from January 1, 2016, to December 31, 2023 (n = 163,714).

Categories	Hospitalization, n (%)
Age group	
≤28 days	182 (0.11)
28 days< ~ ≤1 years old	69,236 (42.29)
1< ~ ≤3 years old	65,376 (39.93)
3< ~ ≤6 years old	25,265 (15.43)
6< ~ ≤12 years old	3509 (2.14)
>12 years old	146 (0.09)
Gender	
Male	101,206 (61.82)
Female	62,508 (38.18)
Seasons	
Spring	9960 (6.08)
Summer	52,415 (32.02)
Autumn	69,541 (42.48)
Winter	31,798 (19.42)
Years	
2016	35,777 (21.85)
2017	32,445 (19.82)
2018	31,658 (19.34)
2019	22,787 (13.92)
2020	11,377 (6.95)
2021	13,696 (8.37)
2022	5507 (3.36)
2023	10,467 (6.39)
Regions	
Northeast China	8993 (5.49)
North China	13,896 (8.49)
East China	93,715 (57.24)
South China	6139 (3.75)
Central China	17,943 (10.96)
Northwest China	16,372 (10.00)
Southwest China	6656 (4.07)
Residence	
Urban	88,768 (54.51)
Rural	74,065 (45.49)
Disposition	
Unprescribed discharge	8376 (5.12)
Death	31 (0.02)
Discharge on medical advice	154,315 (94.26)
Transfer to community health services/ township health centers on medical advice	24 (0.01)
Transfer to hospital on medical advice	140 (0.09)
Other	828 (0.51)

3.75%) had the fewest. The proportion of hospitalized children residing in urban and rural areas was not significantly different, with 54.51% (88,768 cases) and 45.49% (74,065 cases), respectively. Regarding patient outcomes, most individuals (154,315 cases, 94.26%) discharged on medical advice (Table 1).

Prevalence and distribution of EV-associated diseases

Among all patients with EV infections, HFMD accounted for the largest proportion of all cases (117,704 cases, 71.90%), followed by herpangina (45,335 cases, 27.67%), and only 675 cases (0.41%) of other EV infectious diseases. Among the other EV-related infections, enteritis was identified in 84 cases, all attributed to CV enteritis. Encephalitis was documented in 88 patients, comprising 82 cases of CV encephalitis and 6 echoviral encephalitis. Meningitis affected 66 individuals, with 3 cases linked to CV and 63 to EV. Myocarditis was rare, occurring in only 3 patients, all with CV involvement. Additionally, 21 cases of bronchitis were reported, exclusively associated with CV acute bronchitis. The age, gender, season, year, and region composition of two major diseases were presented in Table 2. HFMD and herpangina were prevalent in children aged 28 days to 1 year (49,742 cases, 42.26%; 19,290 cases, 42.55%) and 1–3 years old (48,902 cases, 41.55%; 16,293 cases, 35.94%), with a predominance of male children (74,132 cases, 62.98%, 26,661 cases, 58.81%). Hospital admissions for HFMD showed a sharp annual decline, dropping from 19,178 cases in 2016 to 3026 in 2022, with a slight resurgence observed in 2023. Geographically, the majority of HFMD and herpangina cases were reported from eastern China (73,325 cases, 62.30%; 20,048 cases, 44.22%) (Table 2).

Analysis of the spectrum of other diseases related to EV infections

To assess the occurrence of other diseases associated with EV infection, we conducted a statistical evaluation of the disease spectrum in pediatric patients with EV infection, excluding cases of HFMD and herpangina. Among 136 individuals diagnosed with echovirus infection, 6 cases were diagnosed with echovirus encephalitis, all of whom were males and the most (4 cases) were from the northeast (Table 4). In comparison, among the 292 patients diagnosed with CV infection, 193 patients presented with CV-related diseases such as CV acute bronchitis (21 cases), CV enteritis (84 cases), CV meningitis (3 cases), CV

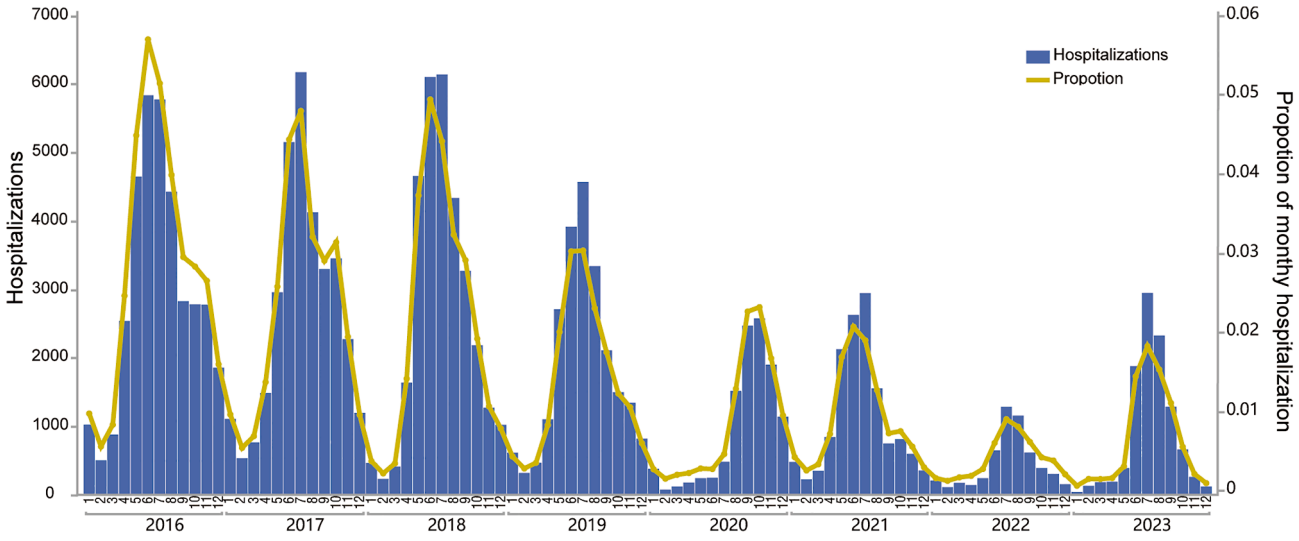

Fig. 2. Number and proportion of children hospitalized with EV infections from Jan 1st, 2016 to Dec 31st, 2023.

Table 2
Demographic information of children hospitalized with HFMD and herpangina.

Categories	HFMD (n, %)	Herpangina (n, %)	Other (n, %)	χ^2	*P* value
Age group				6906.303	<0.0001
≤28 days	46 (0.04)	70 (0.15)	66 (9.78)		
28 days< ~ ≤1 years old	49,742 (42.26)	19,290 (42.55)	204 (30.22)		
1< ~ ≤3 years old	48,902 (41.55)	16,293 (35.94)	181 (26.81)		
3< ~ ≤6 years old	16,873 (14.34)	8243 (18.18)	149 (22.07)		
6< ~ ≤12 years old	2040 (1.73)	1399 (3.09)	70 (10.37)		
>12 years old	101 (0.09)	40 (0.09)	5 (0.74)		
Gender				241.566	<0.0001
Male	74,132 (62.98)	26,661 (58.81)	413 (61.19)		
Female	43,572 (37.02)	18,674 (41.19)	262 (38.81)		
Seasons				621.048	<0.0001
Spring	6920 (5.88)	2931 (6.47)	109 (16.15)		
Summer	37,452 (31.82)	14,780 (32.60)	183 (27.11)		
Autumn	48,891 (41.54)	20,376 (44.95)	274 (40.59)		
Winter	24,441 (20.76)	7248 (15.99)	109 (16.15)		
Years				6101.56	<0.0001
2016	29,178 (24.79)	6500 (14.34)	99 (14.67)		
2017	25,072 (21.30)	7283 (16.06)	90 (13.33)		
2018	23,095 (19.62)	8477 (18.70)	86 (12.74)		
2019	15,695 (13.33)	6875 (15.16)	217 (32.15)		
2020	7830 (6.65)	3508 (7.74)	39 (5.78)		
2021	7291 (6.19)	6312 (13.92)	93 (13.78)		
2022	3026 (2.57)	2454 (5.41)	27 (4.00)		
2023	6517 (5.54)	3926 (8.66)	24 (3.56)		
Regions				6498.351	<0.0001
Northeast China	4984 (4.23)	4009 (8.84)	0 (0)		
North China	8610 (7.31)	5221 (11.52)	65 (9.63)		
East China	73,325 (62.30)	20,048 (44.22)	342 (50.67)		
South China	4477 (3.80)	1659 (3.66)	3 (0.44)		
Central China	9949 (8.45)	7829 (17.27)	165 (24.44)		
Northwest China	11,222 (9.53)	5080 (11.21)	70 (10.37)		
Southwest China	5137 (4.36)	1489 (3.28)	30 (4.44)		
Residence				792.996	<0.0001
Urban	61,278 (52.36)	27,136 (60.13)	354 (53.23)		
Rural	55,758 (47.64)	17,996 (39.87)	311 (46.77)		
Disposition				65.604	<0.0001
Unprescribed discharge	6030 (5.12)	2315 (5.11)	31 (4.59)		
Death	27 (0.02)	3 (0.01)	1 (0.15)		
Discharge on medical advice	110,864 (94.19)	42,811 (94.43)	640 (94.81)		
Transfer to community health services/township health centers on medical advice	8 (0.01)	16 (0.04)	0 (0)		
Transfer to hospital on medical advice	122 (0.10)	18 (0.04)	0 (0)		
Other	653 (0.55)	172 (0.38)	3 (0.44)		

HFMD, Hand, foot, and mouth disease.

encephalitis (82 cases), and CV myocarditis (3 cases). The most frequently observed diseases were CV enteritis and encephalitis, while meningitis and myocarditis were the least common among hospitalized patients (Table 3). To analyze the distribution of these diseases across variables such as time, month, age, and geographic location, frequency distribution graphs were generated (Fig. 3). CV enteritis and CV encephalitis accounted for the largest number of CV infection cases in 2016–2018, and acute bronchitis increased among CV infection cases in 2019–2023 (Fig. 3A). The proportions of CV encephalitis and CV acute bronchitis were elevated in June (Fig. 3B). Age-based analysis showed that CV enteritis predominated among neonatal EV infections. CV enteritis accounted for the largest proportion of EV infections in children aged 28 days to 1 year and 1–3 years, and the number of cases of acute bronchitis and encephalitis also increased (Fig. 3C). Regionally, CV encephalitis occurred mainly in infected patients in north and northwestern China. CV enteritis occurred mainly in infected patients in eastern China, while the number of cases in southern and southwestern China was relatively low, and acute bronchitis occurred mainly in infected patients in central China (Fig. 3D).

Analysis of EV infections with definite serotype

Three primary pathogens including EV-A71, CV, and echovirus were analyzed in this study. Due to constraints in strain typing at certain hospitals, further subtyping of CV and echovirus was not conducted. The dataset included 184 instances of EV-A71 infection, 136 of echovirus infection, and 292 of CV infection, along with 163,102 cases of EV infections where the serotype was unspecified (Table 4). These infections were prevalent in children aged 28 days to 6 years, with a predominance of male children. Hospital admissions for EV-A71 infections peaked in 2019, reaching 125 cases, but stabilized in later years and dropped to zero by 2022 (Table 4). Echovirus-related hospitalizations remained steady from 2016 to 2019 but declined sharply from 2020 to 2023. In contrast, CV infection admissions showed no significant fluctuations between 2016 and 2023. Geographically, EV-A71 cases were predominantly from east China (174 cases, 95.57%) and north China (10 cases, 5.43%). Most echovirus infections originated in central China (112 cases, 82.35%), while CV infections were primarily reported in east China (150 cases, 51.37%). All patients were discharged following medical advice, with no fatalities recorded.

Length of hospital stay (LOS) and hospitalization expense

Length of hospital stay (LOS) and hospitalization costs for EV infections were analyzed. Overall, the median LOS was 5 days [Interquartile range (IQR) 4–6] and the median total hospitalization cost was $587.37 (IQR 442.99–762.53). The median inspection costs were $268.22 (IQR 174.08–356.79), the median treatment cost was $1.13 (IQR 0–16.98), and

Table 3
Demographic information on children with various EV infections related disease.

Categories	Echovirus encephalitis (n, %)	CV acute bronchitis (n, %)	CV enteritis (n, %)	CV meningitis (n, %)	CV encephalitis (n, %)	CV myocarditis (n, %)	χ^2	*P* value
Age group							18953.56	<0.0001
≤28 days	2 (33.33)	0 (0)	9 (10.71)	1 (33.33)	0 (0)	0 (0)		
28 days< ~ ≤1 years old	0 (0)	5 (23.81)	47 (55.95)	0 (0)	6 (7.32)	2 (66.67)		
1< ~ ≤3 years old	0 (0)	8 (38.10)	26 (30.95)	0 (0)	9 (10.98)	1 (33.33)		
3< ~ ≤6 years old	2 (33.33)	5 (23.81)	2 (2.38)	1 (33.33)	33 (40.24)	0 (0)		
6< ~ ≤12 years old	1 (16.67)	3 (14.29)	0 (0)	0 (0)	31 (37.80)	0 (0)		
>12 years old	1 (16.67)	0 (0)	0 (0)	1 (33.33)	3 (3.66)	0 (0)		
Gender							267.64	<0.0001
Male	6 (100.00)	11 (52.38)	52 (61.90)	3 (100.00)	55 (67.07)	1 (33.33)		
Female	0 (0)	10 (47.62)	32 (38.10)	0 (0)	27 (32.93)	2 (66.67)		
Date of discharge (year)							7682.29	<0.0001
2016	0 (0)	0 (0)	23 (27.38)	0 (0)	34 (41.46)	0 (0)		
2017	0 (0)	0 (0)	45 (53.57)	0 (0)	0 (0)	1 (33.33)		
2018	0 (0)	0 (0)	11 (13.10)	0 (0)	5 (6.10)	0 (0)		
2019	1 (16.67)	3 (14.29)	3 (3.57)	0 (0)	7 (8.54)	0 (0)		
2020	0 (0)	2 (9.52)	1 (1.19)	1 (33.33)	11 (13.41)	0 (0)		
2021	3 (50.00)	5 (23.81)	0 (0)	1 (33.33)	20 (24.39)	1 (33.33)		
2022	1 (16.67)	5 (23.81)	0 (0)	1 (33.33)	4 (4.88)	0 (0)		
2023	1 (16.67)	6 (28.57)	1 (1.19)	0 (0)	1 (1.22)	1 (33.33)		
Regions							9352.73	<0.0001
Northeast China	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
North China	0 (0)	0 (0)	1 (1.19)	0 (0)	39 (47.56)	1 (33.33)		
East China	0 (0)	7 (33.33)	82 (97.62)	1 (33.33)	1 (1.22)	1 (33.33)		
South China	1 (16.67)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
Central China	0 (0)	13 (61.90)	1 (1.19)	0 (0)	0 (0)	1 (33.33)		
Northwest China	4 (66.67)	1 (4.76)	0 (0)	1 (33.33)	42 (51.22)	0 (0)		
Southwest China	1 (16.67)	0 (0)	0 (0)	1 (33.33)	0 (0)	0 (0)		
Residence							845.12	<0.0001
Urban	3 (50.00)	16 (76.19)	26 (30.95)	1 (33.33)	38 (46.34)	1 (33.33)		
Rural	3 (50.00)	5 (23.81)	58 (69.05)	2 (66.67)	44 (53.66)	2 (66.67)		
Disposition							189.36	<0.0001
Unprescribed discharge	1 (16.67)	1 (4.76)	4 (4.76)	1 (33.33)	2 (2.44)	0 (0)		
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
Discharge on medical advice	5 (83.33)	20 (95.24)	78 (92.86)	2 (66.67)	80 (97.56)	3 (100.00)		
Transfer to community health services/ township health centers on medical advice	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
Transfer to hospital on medical advice	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
Other	0 (0)	0 (0)	2 (2.38)	0 (0)	0 (0)	0 (0)		

CV, Coxsackievirus.

the median drug cost was $125.11 (IQR 65.91–205.57, Table 5). Considering the etiology, patients with EV-A71 infection were associated with extended hospital stays, higher costs for inspection and treatments, but comparatively lower for drug. Conversely, echovirus infections incurred the highest medication costs (Table 6). Among diseases related to EVs, CV myocarditis, meningitis, and echovirus encephalitis had the highest burden of disease. CV meningitis resulted in the longest LOS, followed by echovirus encephalitis and CV myocarditis. CV myocarditis had the highest total hospitalization costs, followed by CV meningitis and echovirus encephalitis (Table 7).

Death cases

Out of the 163,714 children with EV infection included in this study, 31 patients (0.0019%) died during hospitalization (Table 8). Notably, the primary diagnoses were HFMD (27 cases), herpangina (3 cases) and EV-A71 infection (1 cases) in these 31 deaths. These patients comprised 20 males and 11 females, all under 6 years of age, with most cases originating from east and north China. The disease burden associated with these deaths is summarized in Table 9, with an average LOS of 2.3 days and a mean total hospitalization cost of $1161.21. Regarding causes of death among the 27 HFMD fatalities, 6 cases were due to severe HFMD, 8 were attributed to multiple organ failure, 10 to viral encephalitis, and 3 to ascending myelitis.

DISCUSSION

With the end of the COVID-19 pandemic, the number of cases of EV infections reduced during the pandemic because of strict precautionary measures such as social isolation and increased hygiene has recently increased again. EV infections can cause severe acute gastroenteritis in children and certain EV infections are associated with severe diseases such as myocarditis, pericarditis, encephalitis and meningitis.

Research on EV infections has primarily examined their etiology in cross-sectional studies (Gao et al., 2021; Mai et al., 2023; Rankin et al., 2023). Investigations into the disease burden of EV infections have focused on HFMD, classified as a category C infectious disease in China, with data limited to cases from Jiangsu Province (Han et al., 2022). The overall case fatality rate for HFMD reported across countries in the Asia-Pacific region varies considerably, ranging from less than 0.5%–19% (Puenpa et al., 2019). However, multicenter studies have yet to explore other conditions linked to EV, such as herpangina, CV enteritis, EV-A71 infection, and CV myocarditis. This study addresses the epidemiology and burden of EV infections, analyzing demographic profiles, disease distribution, hospitalization duration, and costs for pediatric patients over eight years across 37 Chinese hospitals. The result showed that severe complications like myocarditis, encephalitis, and meningitis were linked to significantly higher burdens.

Table 4
Demographic information on children with definitive EV pathogenic infections.

Categories	EV-A71 infection (n, %)	Echovirus infection (n, %)	Coxsackievirus infection (n, %)	Other (n, %)	χ^2	*P* value
Age group					4128.643	<0.0001
≤28 days	1 (0.54)	22 (16.18)	14 (4.79)	145 (0.09)		
28 days< ~ ≤1 years old	61 (33.15)	42 (30.88)	86 (29.45)	69,047 (42.33)		
1< ~ ≤3 years old	70 (38.04)	37 (27.21)	73 (25.00)	65,196 (39.97)		
3< ~ ≤6 years old	44 (23.91)	29 (21.32)	69 (23.63)	25,123 (15.40)		
6< ~ ≤12 years old	8 (4.35)	5 (3.68)	46 (15.75)	3450 (2.12)		
>12 years old	0 (0)	1 (0.74)	4 (1.37)	141 (0.09)		
Gender					2.138	0.5443
Male	106 (57.61)	82 (60.29)	174 (59.59)	100,844 (61.83)		
Female	78 (42.39)	54 (39.71)	118 (40.41)	62,258 (38.17)		
Seasons					155.853	<0.0001
Spring	26 (14.13)	19 (13.97)	59 (20.21)	9856 (6.04)		
Summer	67 (36.41)	40 (29.41)	64 (21.92)	52,244 (32.03)		
Autumn	74 (40.22)	57 (41.91)	105 (35.96)	69,305 (42.49)		
Winter	17 (9.24)	20 (14.71)	64 (21.92)	31,697 (19.43)		
Years					549.939	<0.0001
2016	7 (3.80)	30 (22.06)	62 (21.23)	35,678 (21.87)		
2017	15 (8.15)	21 (15.44)	53 (18.15)	32,356 (19.84)		
2018	3 (1.63)	41 (30.15)	34 (11.64)	31,580 (19.36)		
2019	125 (67.93)	37 (27.21)	42 (14.38)	22,583 (13.85)		
2020	14 (7.61)	0 (0)	23 (7.88)	11,340 (6.95)		
2021	20 (10.87)	4 (2.94)	42 (14.38)	13,630 (8.36)		
2022	0 (0)	2 (1.47)	14 (4.79)	5491 (3.37)		
2023	0 (0)	1 (0.74)	22 (7.53)	10,444 (6.40)		
Regions					890.35	<0.0001
Northeast China	0 (0)	0 (0)	0 (0)	8993 (5.51)		
North China	10 (5.43)	1 (0.74)	42 (14.38)	13,843 (8.49)		
East China	174 (94.57)	16 (11.76)	150 (51.37)	93,375 (57.25)		
South China	0 (0)	1 (0.74)	1 (0.34)	6137 (3.76)		
Central China	0 (0)	112 (82.35)	24 (8.22)	17,807 (10.92)		
Northwest China	0 (0)	5 (3.68)	54 (18.49)	16,313 (10.00)		
Southwest China	0 (0)	1 (0.74)	21 (7.19)	6634 (4.07)		
Residence					5.786	0.1225
Urban	114 (61.96)	72 (56.69)	149 (51.03)	88,433 (54.51)		
Rural	70 (38.04)	55 (43.31)	143 (48.97)	73,797 (45.49)		
Disposition					32.232	0.0060
Unprescribed discharge	5 (2.72)	4 (2.94)	15 (5.14)	8352 (5.12)		
Death	1 (0.54)	0 (0)	0 (0)	30 (0.02)		
Discharge on medical advice	178 (96.74)	131 (96.32)	275 (94.18)	153,731 (94.25)		
Transfer to community health services/township health centers on medical advice	0 (0)	0 (0)	0 (0)	24 (0.01)		
Transfer to hospital on medical advice	0 (0)	0 (0)	0 (0)	140 (0.09)		
Other	0 (0)	1 (0.74)	2 (0.68)	825 (0.51)		

EV-A71, Enterovirus A71; CV, Coxsackievirus.

Previous studies have shown that the prevalence of EV exhibits notable seasonality, with cases primarily occurring during spring and summer before the onset of the COVID-19 (Compagnoli Carmona et al., 2020). However, during the pandemic, this seasonal pattern shifted, with peaks in cases occurring from May to August, likely influenced by non-pharmacological measures. Similarly, the prevalence of HFMD is also clearly seasonal, and higher temperatures and humidity levels strongly linked to increased transmission risk (Zhu et al., 2023). Regions in southern China, such as Guangdong, Guangxi, and Hainan, experience the highest incidence rates due to their humid climates. In addition, an epidemiological study conducted in New York communities found that seasonal peaks in EV infections occur in early spring and early autumn (Halabi et al., 2022). This shift in transmission dynamics during the pandemic underscores the impact of environmental factors on viral prevalence.

Regarding regional disparities in reported cases, we found that most cases were reported from east China, with the fewest from south China. This discrepancy may be attributed to an imbalance in the number of hospitals collecting data across provinces for this research. Additionally, variations in pathogen detection techniques across different regions could introduce biases in test results. In economically developed areas or large tertiary hospitals, advanced molecular detection technologies are typically employed. In contrast, primary care hospitals or economically less developed regions may predominantly use methods that potentially exhibit differences in detection sensitivity and specificity. Moreover, the range of EV detection tests offered differs among hospitals in various regions. While some hospitals or research institutions are capable of detecting multiple EV serotypes, such as EV-A71 and CVA16. This limited focus may result in missed data on less common serotypes, further contributing to the regional disparities in reported cases.

Data from the US Centers for Disease Control and Prevention (CDC) indicates that HFMD primarily affects children under the age of five (Pons-Salort et al., 2015). Recent research conducted in Hangzhou, China from 2019 to 2023 revealed findings regarding children diagnosed with HFMD or herpangina, showing that the detection rate of EV was highest in the 3–5 age group (11.25%) (Sun et al., 2024). Furthermore, another study indicated that the positivity rate of EV increased with age, escalating from 0.99% among infants younger than one month to 8.42% in children aged 5 to ≤ 7 years, with the highest positivity observed in this latter group (Jin et al., 2018). In contrast, this study identified infants aged 28 days to 1 year as having the highest proportion of EV infections among various age groups, followed by toddlers aged 1–3 years. All cases analyzed in this study were

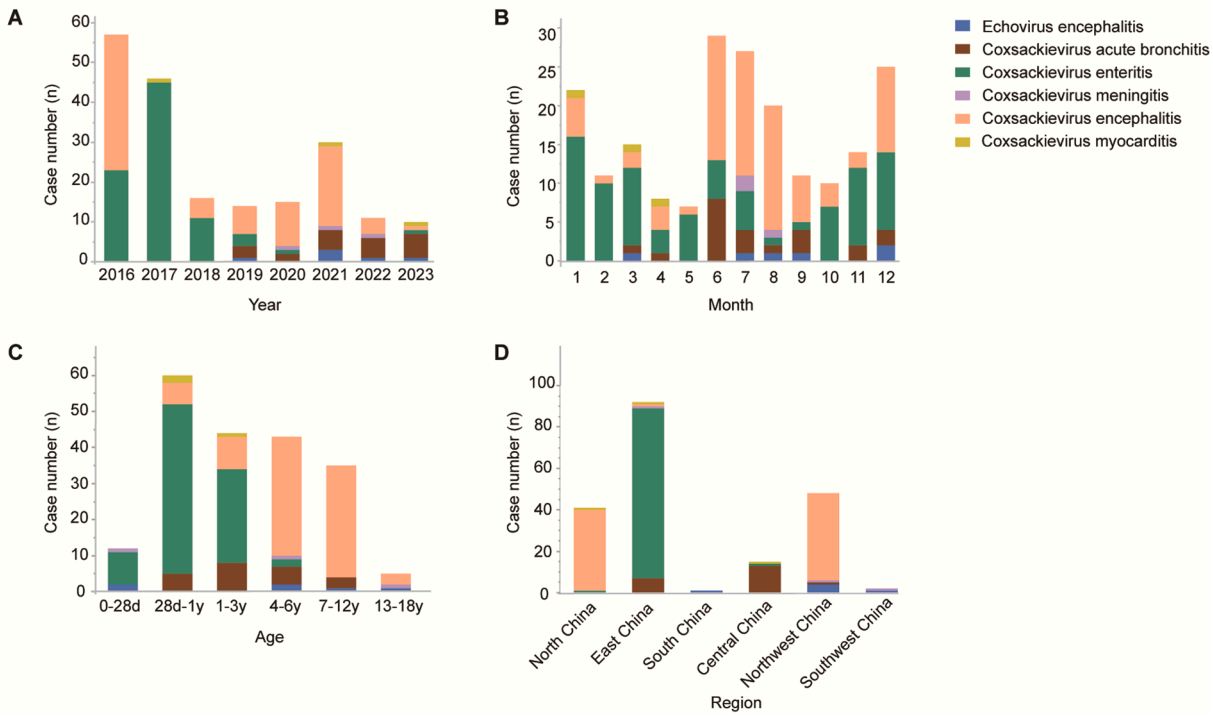

Fig. 3. Proportion of various EV infections related disease by year groups (**A**), months (**B**), age group (**C**), region (**D**).

Table 5
Length of hospital stay (LOS) and hospitalization expense of children with EV infection (total), HFMD, herpangina and other diseases.

Characteristic	Total Median (IQR)	HFMD Median (IQR)	Herpangina Median (IQR)	Other Median (IQR)
LOS (day)	5 (4–6)	5 (4–6)	5 (4–6)	5 (7–9)
Total hospitalization costs (USD)	587.37 (442.99–762.53)	624.47 (480.08–801.70)	491.41 (373.75–643.690)	783.64 (561.47–1455.61)
Inspection costs (USD)	268.22 (174.08–356.79)	290.16 (192.97–368.04)	217.87 (132.83–309.26)	389.05 (250.26–625.57)
Treatment costs (USD)	1.13 (0–16.98)	3.42 (0–17.84)	0 (0–13.86)	0.85 (0–15.42)
Drug costs (USD)	125.11 (65.91–205.57)	142.32 (79.31–227.68)	85.36 (44.35–147.55)	103.61 (0–246.56)

LOS, Length of Hospital Stay; HFMD, Hand, foot, and mouth disease; IQR, interquartile range; USD, United States dollar.

Table 6
Length of hospital stay (LOS) and hospitalization expense of children with the other diseases related to EV infections (Median and IQR).

Characteristic	Echovirus encephalitis Median (IQR)	CV acute bronchitis Median (IQR)	CV enteritis Median (IQR)	CV meningitis Median (IQR)	CV encephalitis Median (IQR)	CV myocarditis Median (IQR)
LOS (day)	10 (7–15.3)	4 (4–5)	5 (3–6)	12 (8–25)	8 (7–12)	10 (7–21)
Total hospitalization costs (USD)	1535.07 (1003.41–2010.78)	582.44 (449.95–664.94)	538.31 (431.36–685.26)	1995.79 (1583.44–4347.47)	1598.75 (1010.64–2515.86)	3241.51 (1213.24–3601.92)
Inspection costs (USD)	409.35 (353.32–847.41)	338.68 (213.96–445.34)	215.18 (159.51–275.66)	1276.99 (1214.10–1339.87)	549.723 (376.189–792.07)	531.14 (427.31–634.95)
Treatment costs (USD)	111.76 (65.61–146.14)	0 (0–52.06)	0 (0–0.45)	42.44 (38.20–266.81)	17.68 (0–98.61)	8.46 (0–16.92)
Drug costs (USD)	107.66 (77.84–501.36	75.77 (28.42–100.32)	118.04 (77.53–186.66)	856.99 (464.39–1249.57)	380.56 (175.31–713.04)	761.18 (0–1522.38)

LOS, Length of Hospital Stay; CV, Coxsackievirus; IQR, interquartile range; USD, United States dollar.

hospitalized children due to EV infections. While the overall infection rate among children under one year is lower, their hospitalization rate is disproportionately high, likely due to their immature immune systems. Numerous studies have shown that younger children with EV infections often develop more severe complications, leading to increased hospitalization rates (Chuang and Huang, 2019; Zhang et al., 2021; Tomatis et al., 2023). These findings highlight the urgent need for enhanced preventive measures and targeted healthcare strategies to protect young children from the severe consequences of EV infections.

Due to the high disease burden caused by EV-A71 infection, the EV-A71 vaccine was approved for use in China in 2016. Subsequently, its implementation has partially modified the epidemiology of EV infections, although coverage remains lower than that of vaccines included in the National Immunization Programs (NIPs). A 2019 cross-sectional survey revealed that coverage of non-NIP vaccine is generally lower, with most vaccines achieving rates below 50%, in contrast to NIP vaccines. Specifically, first-dose coverage of the EV-A71 vaccine reached 39.5%, while second-dose coverage was 23.9%. Among the

Table 7
Length of hospital stay (LOS) and hospitalization expense of children with EV infection whose pathogens can be identified (Median and IQR).

Characteristic	EV-A71 infection Median (IQR)	Echovirus infection Median (IQR)	CV infection Median (IQR)	Other Median (IQR)
LOS (day)	7 (5.3–9.0)	7 (5–8.8)	6 (4–8)	5 (4–6)
Total hospitalization costs (USD)	818.13 (648.05–1086.10)	723.55 (501.19–1431.19)	659.88 (521.65–1212.73)	586.91 (442.71–747.49)
Inspection costs (USD)	430.14 (343.89–568.59)	300.20 (216.17–429.22)	332.64 (219.58–535.00)	269.01 (173.87–356.37)
Treatment costs (USD)	4.39 (0–10.00)	0 (0–0)	0 (0–21.22)	1.13 (0–16.98)
Drug costs (USD)	0 (0–0)	176.13 (88.94–318.80)	119.63 (58.65–252.12)	125.19 (66.04–205.54)

LOS, Length of Hospital Stay; EV-A71, Enterovirus A71; CV, Coxsackievirus; IQR, interquartile range; Inspection costs: Charges for pathological diagnosis, laboratory diagnosis, imaging diagnosis, and clinical diagnostic procedures; Treatment costs: Charges for hospitalization, medications, supportive care, rehabilitation services, and follow-up consultations for ongoing disease monitoring and management; USD, United States dollar.

Table 8
Basic sociodemographic information of 31 dead children hospitalized for EV infections.

Categories	Number
Age group	
28 days< ~ ≤1 years old	12
1< ~ ≤3 years old	14
3< ~ ≤6 years old	5
Gender	
Male	20
Female	11
Seasons	
Spring	3
Summer	17
Autumn	9
Winter	2
Years	
2016	10
2017	13
2018	2
2019	2
2020	4
Regions	
North China	9
East China	18
South China	2
Southwest China	2
Residence	
Urban	11
Rural	20

regions surveyed, Shanghai reported the highest first-dose coverage at 65.5%, followed by Jiangxi (54.6%), Henan (50.7%) and Chongqing (49.5%) (Zhang et al., 2022). A study conducted by the Chinese Center for Disease Control and Prevention evaluated the epidemiological impact of the EV-A71 vaccination program (Hong et al., 2022). Following its implementation, the proportion of HFMD cases attributable to EV-A71 declined by 28.3%, while the incidence of severe cases decreased by 60.7%, indicating a pronounced reduction in disease severity. Notably, the proportion of affected children under three years of age also declined. Furthermore, the geographical distribution of HFMD cases shifted across most provinces, reflecting changes in regional transmission dynamics (Hong et al., 2022).

Notably, the EV-A71 vaccine was associated with a delay of 1–2 months in the peak of HFMD outbreaks, likely due to increased population immunity (Hong et al., 2022). In contrast, the current study primarily focuses on hospitalizations resulting from EV infections in children following vaccination from 2016 to 2023 and does not incorporate data from prior to 2016. Consequently, this limitation hampers a comprehensive assessment of the long-term impact of the vaccine on epidemic patterns of enterovirus-related hospitalizations. Epidemiological surveillance of HFMD in China from 2011 to 2023 indicates that outbreaks primarily occur between May and September, with a secondary peak observed in the southern regions from September to November (Liu et al., 2025). Our study found that, with the exception of 2020, hospitalizations peaked between May and August during this period. Importantly, although our study specifically focused on hospitalized children with EV infections, the overall epidemic trends closely align with those of HFMD.

In addition to HFMD and herpangina, the two most common diseases caused by EV infections, we also focused on the prevalence and disease burden of other EV-associated diseases in this study. We also find CV infection can cause myocarditis, which strain causes the severe cardiovascular disease remained unknown due to the lack of genotyping. In terms of research on the disease burden of EV-associated diseases, current research focuses on HFMD and other diseases caused by EV infections have not been studied in depth (Han et al., 2022). In this study, we counted the costs and LOS for each of the EV-related diseases and found that CV myocarditis, meningitis, and echovirus encephalitis had the highest disease burden among EV-related diseases. Certain types of EV can cause severe infections and even death (Yang et al., 2022). According to Chinese Center for Disease Control and Prevention statistics, 3704 deaths caused by HFMD were reported in China from 2008 to 2022, mainly in children under 3 years old (Gao et al., 2024). Previous studies have reported a significant decrease in the number of deaths caused by severe HFMD after 2016 (Hong et al., 2022). In our study, the age of the death cases was mainly under 6 years old, mainly reported in east China, with more males than females. The disease burden is highest among infants and young children. The median LOS of 5 days and associated costs reflect the significant healthcare resources required to manage these infections. These findings highlight the significant healthcare burden of EV infections in children, emphasizing the need for targeted prevention and resource allocation.

Table 9
Disease burden of 31 dead children hospitalized for EV infections.

Categories	Mean	Standard Deviation	Median	First Quartile	Third Quartile
LOS (day)	2.3	2.4	1	1	3
Total hospitalization costs (USD)	1161.21	847.66	1157.60	586.30	1508.32
Inspection costs (USD)	292.24	267.97	282.10	5.09	387.42
Treatment costs (USD)	34.55	54.64	8.49	0	59.91
Drug costs (USD)	164.71	144.39	119.67	50.11	1936.3273.93

LOS, Length of Hospital Stay; USD, United States dollar.

This study has several limitations, including the lack of detailed genotyping for EVs, which limits the ability to correlate specific strains with clinical outcomes. Data collection on EV-A71, CV, and echovirus is limited due to variations in nucleic acid testing and viral detection methods in different hospitals. Moreover, the information contained within the medical record cover sheets in this study was insufficiently comprehensive, with details regarding each hospital's specific diagnostic criteria and testing methodologies proving inaccessible. Additionally, the most frequently seen patients with EV infections are outpatients, while our database only contains data on hospitalized children and milder cases treated in outpatient settings are not captured, so little is known about the overall incidence of EVs.

CONCLUSIONS

This study reveals the significant disease burden of EV infections among hospitalized children in China, highlighting the need for targeted prevention measures. It underscores the high prevalence of HFMD and herpangina and identifies severe complications like myocarditis and encephalitis.

MATERIALS AND METHODS

Study area and data source

This research was conducted in the People's Republic of China, which has 298 million children. Futang Research Center of Pediatric Development (FRCPD) is the first non-profit social service organization engaged in children's medical research in China. The FRCPD collaborates with 69 member hospitals across 31 provinces, autonomous regions, and municipalities, and over 3000 primary healthcare facilities. In this study, the data from the FUTURE database was extracted and analyzed to identify cases with a primary diagnosis of EV infections across 37 hospitals from January 1, 2016, to December 31, 2023, details of these organizations and their respective regions provided in Supplement Table S1. EV infections included conditions such as CV-related illnesses (enteritis, encephalitis, meningitis, myocarditis, and acute bronchitis), echovirus infections, EV-A71 infections, HFMD, severe HFMD, and herpangina based on the 10th Revision of International Statistical Classification of Diseases and Related Health Problems (WHO, ICD-10) codes (https://icd.who.int/browse10/2016/en). The corresponding ICD-10 codes for the primary diagnosis are shown in Supplement Table S2.

Inclusion and exclusion criteria

This retrospective study focused exclusively on children under the age of 18 who were hospitalized due to EV infections, classified as HFMD, CV infections, EV-A71 infections, and others (Supplementary Table S2) according to ICD-10 codes. We collected basic medical information from the FUTURE database, with diagnoses of EV infections made based on clinical and etiological criteria. Children who did not meet the primary diagnostic requirements or whose primary discharge diagnosis indicated another severe illness were excluded. Outpatients and patients with incomplete medical record data or for whom quality control was not possible were excluded.

Study design

Basic patient information such as gender, age, year and season of admission, and place of residence were collected. Disease burden indicators, such as length of stay (LOS), total cost of hospitalization, and expenses related to diagnostic tests, treatments, and medications were also recorded. Patients were categorized into six age groups: neonates ($\leq$ 28 days), infants (28 days $< \sim \leq$ 1 year), toddlers (1 $< \sim \leq$ 3 years), preschoolers (3 $< \sim \leq$ 6 years), school-aged children (6 $< \sim \leq$ 12 years), and adolescents (>12 years). Regional classifications included east, south, west, central, north, northeast, southwest, and northwest China. East China comprises Shandong Province, Zhejiang Province, Jiangxi Province, Jiangsu Province, Anhui Province and Fujian Province. South China comprises Guangdong Province and Guangxi Zhuangzu Autonomous Region. Central China comprises Henan Province, Hubei Province, and Hunan Province. North China comprises Inner Mongolia Autonomous Region, Hebei Province, Beijing, and Shanxi Province. Northeast China comprises Heilongjiang Province, Jilin Province, and Liaoning Province. Southwest China comprises Yunnan Province and Guizhou Province. Northwest China comprises Gansu Province, Qinghai Province, the Xinjiang Uygur Autonomous Region, Ningxia Huizu Autonomous Region, and Shaanxi Province.

Statistical analysis

For non-normally distributed continuous variables, data were expressed as median (interquartile range, IQR) and compared between groups using the Kruskal-Wallis test. Categorical variables were expressed as numbers or proportions and were compared between groups by χ^2 tests. P value < 0.05 was considered statistically significant.

DATA AVAILABLITY

The data generated during the current study are available from the corresponding author on a reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Beijing Children's Hospital at Capital Medical University, China (Approval Number: 2024-Y-228-D). To ensure privacy, all data were anonymized and deidentified.

AUTHOR CONTRIBUTIONS

Yi Wang: formal analysis, investigation and writing-original draft. Fei Li: formal analysis, supervision, writing-review & editing. Hui Xu: data curation, methodology. Yiliang Fu: formal analysis, supervision. Guoshuang Feng: data curation and methodology. Hanwen Zhang: formal analysis. Juan Huang: formal analysis. Xiangpeng Chen: project administration, conceptualization, methodology, supervision. Zhengde Xie: project administration, conceptualization, funding acquisition.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.virs.2026.05.011.

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