http://dx.doi.org/10.18623/rvd.v22.n5.3733

HAND, FOOT AND MOUTH DISEASE REINFECTION AMONG CHILDREN IN SOUTHERN VIETNAM, 2017–2023

REINFECÇÃO POR DOENÇA MÃO-PÉ-BOCA EM CRIANÇAS NO SUL DO VIETNÃ, 2017–2023

Article received on: 7/21/2025
Article accepted on: 10/27/2025

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Abstract

Objectives: To describe the temporal and epidemiological characteristics of HFMD reinfection and identify demographic and clinical factors associated with reinfection among children in Ca Mau Province, southern Vietnam, from 2017 to 2023. Methods: A descriptive cross-sectional analysis was conducted using 2017–2023 surveillance data from the Centers for Disease Control and Prevention (CDC) of Ca Mau and Bac Lieu provinces, now administratively unified as Ca Mau Province. All reported HFMD cases diagnosed according to Ministry of Health guidelines were included. Descriptive statistics, chi-square tests, and logistic regression were performed using Stata 16.0 to determine factors associated with reinfection. Results: Among 30,174 HFMD cases, 912 (3.0%) were identified as reinfections. Reinfections occurred year-round, peaking in October–November, with moderate seasonal variation (coefficient of variation = 0.92). The mean interval between the first and second episodes was 419.8 ± 377.7 days. Reinfection was significantly associated with age 24–59 months (OR = 5.75; 95% CI: 3.78–8.76), male sex (OR = 1.18; 95% CI: 1.03–1.36), rural residence (OR = 0.76; 95% CI: 0.65–0.90 for urban), and epidemic year (OR = 1.60; 95% CI: 1.39–1.85) ($p < 0.05$). Conclusions: HFMD reinfection remains a persistent public health concern in southern Vietnam, characterized by seasonal clustering and repeated infections among preschool-aged children. Enhanced surveillance, hygiene promotion in childcare

Resumo

Objetivos: Descrever as características temporais e epidemiológicas da reinfecção por DMPE (Doença Mão-Pé-Boca) e identificar os fatores demográficos e clínicos associados à reinfecção entre crianças na Província de Ca Mau, sul do Vietnã, no período de 2017 a 2023. Métodos: Foi realizada uma análise descritiva transversal utilizando dados de vigilância de 2017–2023 dos Centros de Controle e Prevenção de Doenças (CDC) das províncias de Ca Mau e Bac Lieu, agora unificadas administrativamente como Província de Ca Mau. Todos os casos de DMPE notificados e diagnosticados de acordo com as diretrizes do Ministério da Saúde foram incluídos. Estatísticas descritivas, testes qui-quadrado e regressão logística foram realizados no Stata 16.0 para identificar fatores associados à reinfecção. Resultados: Entre 30.174 casos de DMPE, 912 (3,0%) foram identificados como reinfecções. As reinfecções ocorreram ao longo de todo o ano, com pico em outubro–novembro e variação sazonal moderada (coeficiente de variação = 0.92). O intervalo médio entre o primeiro e o segundo episódio foi de 419,8 ± 377,7 dias. A reinfecção esteve significativamente associada à idade entre 24–59 meses (OR = 5,75; IC95%: 3,78–8,76), sexo masculino (OR = 1,18; IC95%: 1,03–1,36), residência rural (OR = 0,76; IC95%: 0,65–0,90 para urbano) e ano epidêmico (OR = 1,60; IC95%: 1,39–1,85) ($p < 0,05$). Conclusões: A reinfecção por DMPE continua sendo um importante desafio de saúde pública no sul do

facilities, and development of multi-serotype vaccines are essential to mitigate recurrent HFMD transmission in endemic regions.

Keywords: Hand, Foot and Mouth Disease. Reinfection. Enterovirus. Children. Epidemiology. Vietnam.

Vietnã, caracterizada por aglomeração sazonal e episódios repetidos entre crianças em idade pré-escolar. O reforço da vigilância, a promoção de higiene em creches e escolas, e o desenvolvimento de vacinas multisserótipos são essenciais para reduzir a transmissão recorrente da DMPE em regiões endêmicas.

Palavras-chave: *Doença Mão-pé-boca. Reinfecção. Enterovírus. Crianças. Epidemiologia. Vietnã.*

1 INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a common, highly contagious viral infection that predominantly affects children under five years of age. The disease is characterized by fever, vesicular rashes on the hands, feet, and oral mucosa, and is generally mild and self-limiting; however, severe neurological or cardiopulmonary complications may occur, especially in Asia-Pacific countries [1-3]. HFMD has become a substantial global public health issue because of its high morbidity, potential for reinfection, and economic impact due to outbreaks that frequently occur in early childhood institutions such as kindergartens and daycare centers [4-6]. Globally, HFMD is endemic in most regions but exerts the greatest disease burden in East and Southeast Asia. In China, more than seven million cases were reported from 2008 to 2012, corresponding to an annual incidence of 1.2 per 1,000 person-years and hundreds of deaths, mostly among children under five [7-9]. Korea documented approximately 1.8 million cases in children under six from 2011 to 2017, with distinct seasonal peaks in summer [10]. Severe and fatal outbreaks have also been documented in Vietnam and neighboring countries, including the emergence of EV-A71 subgenogroup B5 in recent years [1, 11]. Although HFMD occurs worldwide, cases reported in Europe and North America are typically milder and increasingly associated with CV-A6 [12, 13].

Vietnam has experienced recurrent, large-scale outbreaks of HFMD over the past decade, resulting in significant morbidity and mortality among young children. The disease, primarily caused by EV-A71, has been associated with severe neurological and cardiopulmonary complications [14-16]. Although EV-A71 remains the primary pathogen responsible for severe HFMD, other enteroviruses such as Coxsackievirus A6, A10, and A16 also contribute substantially to Vietnam’s HFMD burden [16-18].

Seroprevalence studies have shown that approximately 23.5% of children in southern Vietnam have been infected with EV-A71 by the age of one, with the median age of infection around three years [19, 20]. Maternal antibodies decline by six months of age, leaving infants susceptible during the critical early childhood period [19]. Despite the high disease burden, there is currently no specific antiviral therapy or licensed vaccine for HFMD in Vietnam, even though inactivated EV-A71 vaccines have been successfully implemented in China [11, 16, 21]. This underscores the need for sustained surveillance, public health preparedness, and targeted preventive measures to mitigate future outbreaks.

Given the persistent recurrence of HFMD and the lack of long-lasting immunity against multiple circulating enterovirus serotypes, reinfection has emerged as an important but underexplored aspect of the disease's epidemiology in Vietnam. Understanding the frequency, temporal distribution, and determinants of HFMD reinfection is critical for improving outbreak prediction, prevention strategies, and vaccine policy development. Therefore, this study aims to describe the epidemiological characteristics of HFMD reinfection among children in a southern Vietnam province from 2017 to 2023 and to identify the demographic and clinical factors associated with reinfection risk.

2 MATERIALS AND METHOD

2.1 Study design and settings

This study employed a descriptive cross-sectional design using secondary surveillance data on hand, foot and mouth disease (HFMD) cases reported from January 2017 to December 2023. The data were collected from the infectious disease reporting systems of the Centers for Disease Control and Prevention (CDC) of both Ca Mau and Bac Lieu provinces. Following the administrative reorganization on June 12, 2025, the current Ca Mau Province comprises the territories of the former Ca Mau and Bac Lieu provinces. Therefore, to ensure data consistency over time, HFMD cases from both provinces during 2017–2023 were included in this analysis. After the June 12, 2025, the expanded Cà Mau Province now spans approximately 7,942.4 km² with a population estimated at around 2.14 million to 2.61 million people. The new province lies at the

southernmost tip of Vietnam's Mekong Delta, featuring coastal and estuarine landscapes, low-lying terrain, extensive mangrove and canal systems, and a predominantly rural population engaged in fishing, aquaculture, and agriculture. Ethnically, it is home chiefly to Kinh people, with significant Khmer Krom and Hoa communities, reflecting multicultural settlement patterns. Urban centres, particularly around the provincial capital Cà Mau City, contrast with more remote and geographically dispersed rural communes, influencing access to health services and environmental exposure opportunities.

2.2 Case definition and sample size

HFMD cases were defined according to the Vietnamese Ministry of Health guidelines for Diagnosis and Treatment of Hand, Foot and Mouth Disease (Decision No. 292/QD-BYT 2024) [22]. A confirmed case was identified as a patient presenting with vesicular or papular lesions on the hands, feet, mouth, or buttocks, with or without fever, and diagnosed by a qualified clinician at a healthcare facility. A reinfection case was defined as a subsequent episode of HFMD occurring in the same child after recovery from a previous episode. Each infection episode was coded chronologically (first, second, third, etc.) using the patient's unique hospital or surveillance ID to ensure linkage across years. The study applied a total population sampling approach, including all reported HFMD cases from 2017 to 2023 in both the former Ca Mau and Bac Lieu provinces (now the unified Ca Mau Province). After data cleaning and exclusion of incomplete records, a total of 30,174 individual infection episodes were analyzed.

2.3 Data collection and measurement

Data were extracted from the national communicable disease reporting system (https://baocaobtn.vncdc.gov.vn) and exported into Microsoft Excel format. All children diagnosed with HFMD during 2017–2023 and having complete demographic and clinical information were included. Cases with incomplete or missing data were excluded. The collected variables included patient ID, sex, age (in months), residential address (urban/rural), date of disease onset, hospitalization status, disease severity (Grades 1–4) [22], and reinfection episode number. HFMD severity is classified into four levels based on clinical manifestations and neurological or cardiopulmonary complications. Grade 1

includes uncomplicated cases presenting only with oral ulcers and/or vesicular rash on hands, feet, and mouth. Grade 2a involves mild neurological symptoms such as startle episodes (<2 times/30 min), persistent fever ≥39°C or lasting >2 days with vomiting, lethargy, or irritability. Grade 2b indicates severe neurological complications, with features like frequent startles (≥2 times/30 min), drowsiness, tachycardia (>130–150 bpm without fever), limb tremors, ataxia, cranial nerve palsy, hypertonia, or impaired consciousness (Glasgow < 10). Grade 3 represents autonomic nervous system dysfunction with severe tachycardia (>170 bpm), hypertension, respiratory distress, cold extremities, or mottled skin. Grade 4 is the most critical stage, characterized by respiratory or circulatory failure, including apnea, cyanosis, pulmonary edema, and shock (unmeasurable or low blood pressure, narrowed pulse pressure ≤25 mmHg) [22]. Reinfection was defined as a subsequent HFMD episode occurring in the same child after an interval of at least 25 days following recovery from a mild case or 60 days after a severe case [23].

2.4 Statistical analysis

Data entry and cleaning were performed using EpiData version 3.02, and statistical analyses were conducted with Stata version 16.0 (StataCorp LLC, College Station, TX, USA). Descriptive statistics were used to summarize categorical and continuous variables. The seasonal index was calculated as the mean number of reinfected cases in a specific month divided by the mean number of reinfected cases in all months, while the coefficient of variation (standard deviation/mean) was computed to assess the magnitude of seasonal fluctuation. The chi-square test was used to compare categorical variables between reinfected and non-reinfected groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using binary logistic regression to identify factors associated with reinfection. A p-value < 0.05 was considered statistically significant.

2.5 Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of the Ca Mau Center for Disease Control and Prevention (Code 6/260525-74/QĐ-CĐYTCM), ensuring compliance with ethical standards for research involving human data.

3 RESULTS

Table 1 shows the distribution of HFMD reinfection cases by month and year from 2017 to 2023 in Ca Mau Province. A total of 30,174 HFMD cases were recorded, including 912 reinfections (3.0%). The monthly proportion of reinfection ranged from 2.3% to 3.9%, peaking in March and May. By year, reinfection increased over time, with the highest proportions in 2021 (4.0%) and 2023 (4.4%), and the lowest in 2017 (1.0%).

Table 1

Distribution of HFMD Reinfection cases by Month and Year (2017–2023)

	Time	Non-reinfection	Reinfection			Total (n)	Reinfection (%)
			2 infections (n)	3 infections (n)	4 infections (n)		
Month	January	1,384	49	2	0	1,435	3.6
	February	852	20	0	0	872	2.3
	March	829	33	1	0	863	3.9
	April	906	21	0	0	927	2.3
	May	1,222	45	4	1	1,272	3.9
	June	1,805	49	1	0	1,855	2.7
	July	1,656	53	1	0	1,710	3.2
	August	1,796	48	5	0	1,849	2.9
	September	3,109	85	4	0	3,198	2.8
	October	6,379	186	15	0	6,580	3.1
	November	5,768	169	3	0	5,940	2.9
	December	3,556	112	5	0	3,673	3.2
Year	2017	3,783	36	1	0	3,820	1.0
	2018	5,496	133	6	0	5,635	2.5
	2019	5,569	178	7	1	5,755	3.3
	2020	2,427	63	5	0	2,495	2.7
	2021	1,897	76	2	0	1,975	4.0
	2022	3,390	96	1	0	3,487	2.8
	2023	6,700	288	19	0	7,007	4.4
	Total	29,262	870	41	1	30,174	3.0

Table 2 presents the seasonality index and coefficient of variation of HFMD reinfection. The total number of reinfections was 912, with a mean monthly case count

of 13.0 ± 10.45. Reinfection peaked in October (n = 201; seasonality index = 2.64) and November (n = 172; index = 2.27), followed by December and September. The coefficient of variation ranged from 0.54 to 1.27, indicating moderate monthly variation, with the highest consistency observed in May.

Table 2

Seasonality index and coefficients of variation of HFMD reinfection in Ca Mau province, 2017–2023

Month	Reinfection (n)	Seasonality Index	Mean	Standard Deviation	Coefficient of Variation
January	51	0.67	7.29	8.20	1.12
February	20	0.26	2.86	2.98	1.04
March	34	0.45	4.86	6.15	1.27
April	21	0.28	3.00	3.39	1.13
May	50	0.66	7.14	3.89	0.54
June	50	0.66	7.14	6.55	0.92
July	54	0.71	7.71	7.25	0.94
August	53	0.70	7.57	8.02	1.06
September	89	1.18	12.71	10.15	0.80
October	201	2.64	28.71	27.00	0.94
November	172	2.27	24.57	19.60	0.80
December	117	1.54	16.71	15.25	0.91
Total / Mean	**912**	**1.00**	**13.00**	**10.45**	**0.92**

Table 3 summarizes the time intervals between consecutive HFMD reinfections. Among 912 reinfected patients, 870 experienced a second infection, 41 a third infection, and one a fourth infection. The mean interval between the first and second infections (T2–1) was 419.8 ± 377.7 days, between the second and third (T3–2) was 335.9 ± 315.5 days, and between the third and fourth (T4–3) was 72 days, showing a general shortening trend with each subsequent episode.

Table 3

Distribution of time intervals between consecutive HFMD reinfections in Ca Mau province, 2017–2023

Interval type	Definition	N	Mean (days)	SD	Min	p25	Median (p50)	p75	Max
T2–1	Interval from the 2nd onset to the 1st onset	870	419.8	377.7	26	137	335	526	2373
T3–2	Interval from the 3rd onset to the 2nd onset	41	335.9	315.5	26	116	244	394	1428
T4–3	Interval from the 4th onset to the 3rd onset	1	72.0	-	72	72	72	72	72

Table 4 describes demographic and clinical characteristics of HFMD patients with and without reinfection. Of 30,174 patients, reinfection occurred in 3.0%. Reinfection was more frequent among children aged 24–59 months, males (3.2%), rural residents (3.2%), and inpatients (4.0%). The proportion increased with disease severity, reaching 7.8% in grade 2b and 6.7% in grade 4. Reinfection was also more common during epidemic years (4.4%) than non-epidemic years (2.6%), with all associations statistically significant ($p < 0.05$).

Table 4

Characteristics of patients with and without HFMD reinfection in Ca Mau Province, 2017–2023

Characteristics	Categories	Non-reinfection	Reinfection	Total	p-value
		N (%)	N (%)	N (%)	
Age group (months)	0–11	3,892 (99.3)	29 (0.7)	3,921 (13.0)	<0.001
	12–23	10,456 (97.6)	261 (2.4)	10,717 (35.5)	
	24–35	6,547 (95.9)	282 (4.1)	6,829 (22.6)	
	36–47	3,865 (95.7)	172 (4.3)	4,037 (13.4)	
	48–59	2,075 (95.6)	95 (4.4)	2,170 (7.2)	
	≥60	2,427 (97.1)	73 (2.9)	2,500 (8.3)	
Sex	Female	12,033 (97.3)	338 (2.7)	12,371 (41.0)	0.014
	Male	17,229 (96.8)	574 (3.2)	17,803 (59.0)	
Residence	Rural	22,233 (96.8)	731 (3.2)	22,964 (76.1)	0.004
	Urban	7,029 (97.5)	181 (2.5)	7,210 (23.9)	
Disease severity	Grade 1	13,217 (100.0)	0 (0.0)	13,217 (43.8)	<0.001
	Grade 2a	15,689 (94.7)	883 (5.3)	16,572 (54.9)	
	Grade 2b	271 (92.2)	23 (7.8)	294 (1.0)	
	Grade 3	71 (93.4)	5 (6.6)	76 (0.3)	
	Grade 4	14 (93.3)	1 (6.7)	15 (0.1)	
Hospitalization status	Outpatient	9,479 (99.1)	88 (0.9)	9,567 (31.7)	<0.001
	Inpatient	19,783 (96.0)	824 (4.0)	20,607 (68.3)	
Epidemic year	Non-epidemic	22,562 (97.4)	605 (2.6)	23,167 (76.8)	<0.001
	Epidemic year	6,700 (95.6)	307 (4.4)	7,007 (23.2)	
Total	,	29,262 (97.0)	912 (3.0)	30,174 (100.0)	,

Table 5 presents multivariable logistic regression results on factors associated with HFMD reinfection. Compared with infants aged 0–11 months, older children had higher odds of reinfection, peaking at 48–59 months (OR = 5.75, 95% CI: 3.78–8.76). Males were more likely to be reinfected (OR = 1.18, $p = 0.015$), while urban residents had lower odds (OR = 0.76, $p = 0.001$). The likelihood of reinfection was higher during epidemic years (OR = 1.60, $p < 0.001$). All associations were statistically significant.

Table 5

Factors associated with HFMD reinfection among children in Ca Mau Province, 2017–2023

Variables	Categories	OR	95% CI	p-value
Age group (months)	0–11[a]	1.00	,	,
	12–23	3.37	2.29–4.95	<0.001
	24–35	5.67	3.86–8.33	<0.001
	36–47	5.70	3.84–8.48	<0.001
	48–59	5.75	3.78–8.76	<0.001
	≥60	3.78	2.45–5.83	<0.001
Sex	Male vs. Female[a]	1.18	1.03–1.36	0.015
Residence	Urban vs. Rural[a]	0.76	0.65–0.90	0.001
Epidemic year	Yes vs. No[a]	1.60	1.39–1.85	<0.001

[a] *reference group*

4 DISCUSSION

This study provides a comprehensive analysis of HFMD reinfection patterns among children in Ca Mau Province from 2017 to 2023 using provincial surveillance data. Reinfection accounted for 3.0% of all reported HFMD cases, revealing distinct temporal, demographic, and clinical characteristics. The findings highlight marked seasonality, variation in reinfection intervals, and significant associations with age, sex, residence, and epidemic year, indicating the persistence of HFMD transmission risk and susceptibility in early childhood.

The findings of this study reveal that HFMD in Ca Mau Province displays distinct temporal and seasonal characteristics consistent with regional and global epidemiological patterns. Reinfection occurred year-round but was concentrated during the latter half of the year, peaking in October and November. This seasonal concentration aligns with the climatic conditions of southern Vietnam, characterized by high humidity and moderate temperatures conducive to enterovirus survival and transmission. Such temporal clustering mirrors patterns reported in other subtropical regions, HFMD incidence commonly peaks in late spring to summer (May–September) in temperate East Asian countries such as China, Korea, and Japan [10, 24-26], whereas tropical countries like Malaysia and Singapore experience year-round transmission with periodic large outbreaks every 2–3 years [27-29].

The overall reinfection rate of 3.0% observed in Ca Mau is comparable to large-scale estimates in China, where the cumulative reinfection probability reached approximately 4% within 39 months following the initial episode [30]. Recent evidence

from Jiulongpo District, Chongqing, China, further supports these findings, reporting a 5.48% reinfection rate between 2009 and 2023, with 71.5% of cases occurring within two years of the first episode and clear bimodal peaks in April–July and October–November [23]. This suggests that despite differences in geography and climate, the reinfection burden among children is similar across Asian countries with endemic HFMD circulation. The persistence of reinfections in Ca Mau likely reflects the co-circulation of multiple enterovirus serotypes and limited cross-protective immunity between them. Studies from China and Singapore have confirmed that most reinfections are caused by different serotypes rather than recurrence of the same strain, underscoring the importance of serotype-specific immunity in HFMD pathogenesis [25, 28]. Cyclical patterns of HFMD activity are evident in Ca Mau and are consistent with reports from China, Malaysia, and other Southeast Asian regions where epidemic and reinfection waves tend to occur every 2–3 years [24, 25, 27]. These cycles are largely driven by the periodic accumulation of susceptible young children and the replacement of dominant serotypes in the population. In tropical regions, subclinical or "occult" infections also play an important role in sustaining viral transmission between epidemic peaks. For instance, in Singapore, approximately 17.1% of healthy children tested positive for enterovirus without any symptoms [6], highlighting the silent reservoir contributing to community spread.

Analysis of the time intervals between consecutive HFMD episodes in Ca Mau revealed a progressive shortening trend with subsequent reinfections. The mean interval between the first and second infections was approximately 420 days, between the second and third 336 days, and between the third and fourth 72 days. These findings suggest that while immunity after the initial infection may provide temporary protection, it wanes over time, allowing for susceptibility to new infections, particularly with different viral serotypes. Large-scale studies across Asia have reported similar intervals, with most reinfections occurring within one to three years after the initial episode and some as early as a few months, depending on exposure intensity and circulating strains [1, 2, 31]. Evidence from China further supports this pattern, where 71.5% of reinfected patients experienced recurrence within two years and intervals ranged widely from 26 to 3,863 days [23]. The variation in reinfection timing reflects both host-related immunity factors and viral ecology in high-transmission environments.

Clinically, most HFMD reinfections in Ca Mau were mild to moderate, aligning with global data indicating that 86% of HFMD cases are mild, 13% asymptomatic, and

only about 1% severe or critical [1, 2, 4]. Reinfections are typically less severe than primary infections due to partial immunity, although repeated exposures can still provoke symptomatic illness. The symptomatic hospitalization rate, estimated at around 6% globally (range: 2.8–14.9%), is consistent with the predominance of mild inpatient cases observed in this study. Findings from Chongqing also indicated that reinfection risk and clinical presentation were more frequent among children older than three years and those attending kindergartens, suggesting that social exposure rather than disease severity drives recurrence [23].

HFMD reinfection in Ca Mau was strongly associated with young age, particularly among children aged 24–59 months, consistent with global observations that 75–90% of HFMD cases and reinfections occur in those under five years [29, 32, 33]. The highest vulnerability typically lies in the 1–3-year age range, after which immunity develops through repeated exposures [29, 32]. Reinfection within this window is likely driven by incomplete cross-protection between enterovirus serotypes and frequent close contact in daycare or kindergarten settings [28, 34]. Similar findings were reported in China, where children over three years and kindergarten attendees showed significantly elevated reinfection risk [23]. Male children also had a higher odds of reinfection, reflecting a pattern observed across Asia with male-to-female ratios between 1.45:1 and 1.8:1 [29, 32, 33]. Behavioral factors such as greater physical activity and social interaction, as well as possible biological susceptibility, have been proposed to explain this disparity [28, 35].

Residence and epidemic timing also significantly influenced reinfection patterns. In Ca Mau, rural children had higher reinfection odds than their urban counterparts, echoing findings from studies showing that although urban areas tend to have higher HFMD reporting due to density and surveillance, rural and semi-urban zones sustain transmission through household crowding, limited sanitation, and informal childcare [8, 32, 33]. Reinfections were also more likely during epidemic years, reflecting temporal cycles linked to viral serotype shifts, climatic conditions, and the buildup of susceptible hosts [10, 24, 35]. Epidemics in Southeast Asia often follow 2–3-year cycles, and while the introduction of EV-A71 vaccines has reduced severe HFMD, overall transmission remains high due to other co-circulating serotypes such as CV-A6 and CV-A16 [29, 35]. These patterns highlight how demographic, environmental, and virological factors interact to sustain HFMD reinfection risk in endemic regions.

The findings of this study have several important public health implications for HFMD prevention and control in endemic regions such as Ca Mau. The concentration of reinfections among preschool-aged children underscores the need for intensified surveillance and targeted hygiene education in daycare and kindergarten settings. Health authorities should strengthen routine enterovirus monitoring to detect serotype shifts early and anticipate epidemic cycles. Preventive strategies should also focus on rural communities, where reinfection clusters were more common, by improving sanitation, childcare hygiene, and community awareness. Given the higher reinfection risk during epidemic years, adaptive outbreak preparedness plans, such as reinforcing public messaging, ensuring adequate medical resources, and promoting early case detection, are essential. These results also emphasize the potential value of multi-serotype vaccination strategies in the future, as single-serotype vaccines (e.g., EV-A71) are insufficient to prevent reinfection caused by other circulating enteroviruses.

This study has several limitations. First, the analysis relied on surveillance data, which may underestimate the true reinfection rate since mild or asymptomatic cases often go unreported. Second, laboratory confirmation of enterovirus serotypes was unavailable for most cases, preventing determination of whether reinfections were caused by homologous or heterologous strains. Third, behavioral and socioeconomic variables, such as childcare attendance, parental education, and hygiene practices, were not recorded, which may have confounded some associations. Additionally, temporal variations in reporting completeness and diagnostic criteria over the seven-year period could have introduced bias. Despite these limitations, the large dataset and multiyear analysis provide robust evidence on the epidemiology and determinants of HFMD reinfection in southern Vietnam, contributing valuable insights for regional disease control policy

5 CONCLUSION

HFMD reinfection remains a notable component of the disease burden in Ca Mau Province, characterized by seasonal peaks, short reinfection intervals, and clustering among young children. Age, sex, residence, and epidemic year were significant determinants of reinfection risk. These results underscore the need for sustained surveillance, timely public health response, and preventive interventions tailored to

vulnerable pediatric populations to reduce the recurrence and transmission of HFMD in southern Vietnam.

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Authors' Contribution

- Huynh Ngoc Linh: Conceptualized and supervised the study, designed the study protocol, performed data validation, and finalized the manuscript.
- Nguyen The Tan: Conducted data collection, database management, statistical analysis, and assisted in manuscript drafting.
- Ngo Quoc Thong: Contributed to data acquisition, field coordination, data interpretation, and manuscript revision.

All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Data availability

All datasets relevant to this study's findings are fully available within the article.

How to cite this article (APA)

Linh, H. N., Tan, N. T., & Thong, N. Q. (2025). HAND, FOOT AND MOUTH DISEASE REINFECTION AMONG CHILDREN IN SOUTHERN VIETNAM, 2017–2023. *Veredas Do Direito*, 22(5), e223733. https://doi.org/10.18623/rvd.v22.n5.3733