REVIEW ARTICLE

Hand, foot, and mouth disease in children: a systematic review

José Uberli Herrera Ortiz* [1,a]; Aníbal Oblitas Gonzáles [1,a]; Wilder Ovidio Carranza Carranza [1,a]

ABSTRACT

Hand, foot and mouth disease is a recurring contagious infection in children living under poor sanitary conditions, especially in developing countries, where a substantial increase in the disease has been reported in recent years. The study aimed to describe and analyze the occurrence of such disease in children, focusing on the most outstanding theoretical aspects that characterize it. For this purpose, a systematic review of the literature was conducted in PubMed, Google Scholar and Latin American and Caribbean Literature in Health Sciences (LILACS) using logical operators such as "EMPB" OR "Coxsackie A16" AND "Children" AND "Coxsackievirus Infections" AND "Child." A total of 584 research studies in Spanish and English published between 2010 and 2022 were identified, from which, after a scientific quality assessment process using checklists, quality criteria and relevant strength of recommendation and the PRISMA method, 40 articles were selected, to which three gray literature records were added, and 43 records were selected for quantitative data analysis. Hand, foot and mouth disease has a higher incidence in the Asian continent (India, Singapore, Japan and China), where epidemic outbreaks occur every year, mainly affecting the child population. It is caused by several serotypes such as A5, A7, A10, B1, B2, B3 and B5; however, Coxsackievirus A16 (CA16) and Enterovirus A71 (EVA71) are the most frequent among children. The disease causes fever, papulovesicular rash on the hands, feet and genitalia, as well as ulcerative lesions in the mouth. Its incubation period is four to six days, and it is transmitted by direct contact with secretions, fecal material or contaminated objects; its diagnosis is clinical and based on epidemiological history. As there is no specific treatment, only general measures are taken to alleviate the symptoms and prevent dehydration. Currently, there are outbreaks and serotypes that cause various complications, such as encephalitis, myocarditis, hepatitis, acute hemorrhagic conjunctivitis, enteric diseases and herpangina, among others. For this reason, strict epidemiological surveillance of cases and contacts is required, along with health education and communication interventions that reduce the risks of spread and infection.

Keywords: Hand, Foot and Mouth Disease; Child; Coxsackievirus Infections (Source: MeSH NLM).

INTRODUCTION

Hand, foot and mouth disease (HFMD) is a highly contagious exanthematous condition, common in children [1-3], caused by Coxsackievirus A16 (CA16) and Enterovirus A71 (EVA71), although it can also be caused by serotypes A5, A7, A10, B1, B2, B3, and B5. In 2022, a series of HFMD outbreaks occurred worldwide, which has drawn the attention of the scientific community and healthcare systems due to its atypical manifestations [1-5]. Its incidence has been higher in tropical regions, particularly in populations with poor hygiene and overcrowding [6].

The name "coxsackievirus" comes from the place where it was first identified, located in New York. It comprises two subgroups: serotype B6, capable of causing complications in humans such as encephalitis, myocarditis and hepatitis; and serotype A, which causes acute hemorrhagic conjunctivitis, enteric diseases and herpangina. In both cases, some children may present onychomadesis (painless and complete shedding of the nail as a late sequela) [7].

In its typical form, HFMD presents with general malaise and odynophagia, followed by fever, mouth pain and abdominal pain. The maculopapular mucocutaneous rash (pathognomonic feature) is located on the oral mucosa, hands, feet and sometimes on the gluteal region. This rash rapidly evolves into gray vesicles of 3 to 7 mm, surrounded by an erythematous halo in an oval, linear or crescent shape. The vesicles form crusts and disappear within approximately 7 to 10 days. Therefore, the diagnosis is based on clinical manifestations and the epidemiological history of the infected individual [8-14].

HFMD is endemic in Southeast Asia, where epidemic outbreaks occur every year, mainly affecting children. Moreover, its epidemiological significance is based on the short incubation period (mean = 4 to 6 days) and its high transmissibility from person to person through direct contact with secretions (nasal, oral), the fecal-oral route or contaminated objects [15-19].

The prevalence varies and is higher in countries such as China, where EVA71 causes an average of 500 to 900 child deaths per year [20]. In Cuba, between 2017 and 2018, 507 cases were reported among children under five years of age,

1 Universidad Nacional Autónoma de Chota, School of Health Sciences, Professional School of Nurses, Chota, Peru.
[a] Professional title in Nursing, PhD in Health.
*Corresponding author.

all of whom made good progress [7]. In Peru, according to the Centro Nacional de Epidemiología, Prevención y Control de Enfermedades (CDC-Perú, National Center for Epidemiology and Disease Control and Prevention - Peru), as of June 30, 2022, 734 cases of children infected with HFMD were reported across 10 regions of the country. The regions with the highest prevalence were Ucayali (260 cases), San Martín (184 cases), Cajamarca (101 cases), Amazonas (30 cases), Apurímac (126 cases), Huánuco (18 cases), Lima (6 cases), Cusco (4 cases), and Loreto and Piura (2 cases each) [21]. However, it is important to note that in Peru, these figures may be higher due to underreporting of the disease.

Enclosed spaces such as educational institutions and day care centers are common sites of transmission. Additionally, since no specific treatment is available, general measures to alleviate symptoms and prevent dehydration are essential [22,23]. Currently, there are outbreaks and serotypes that cause various complications, such as myocardial damage, type 1 diabetes mellitus and neurological complications [2,24,25]. Consequently, strict epidemiological surveillance of cases and contacts is required to reduce spread and infection.

SEARCH STRATEGY

The study was conducted based on the PRISMA method statement [26] (Figure 1).

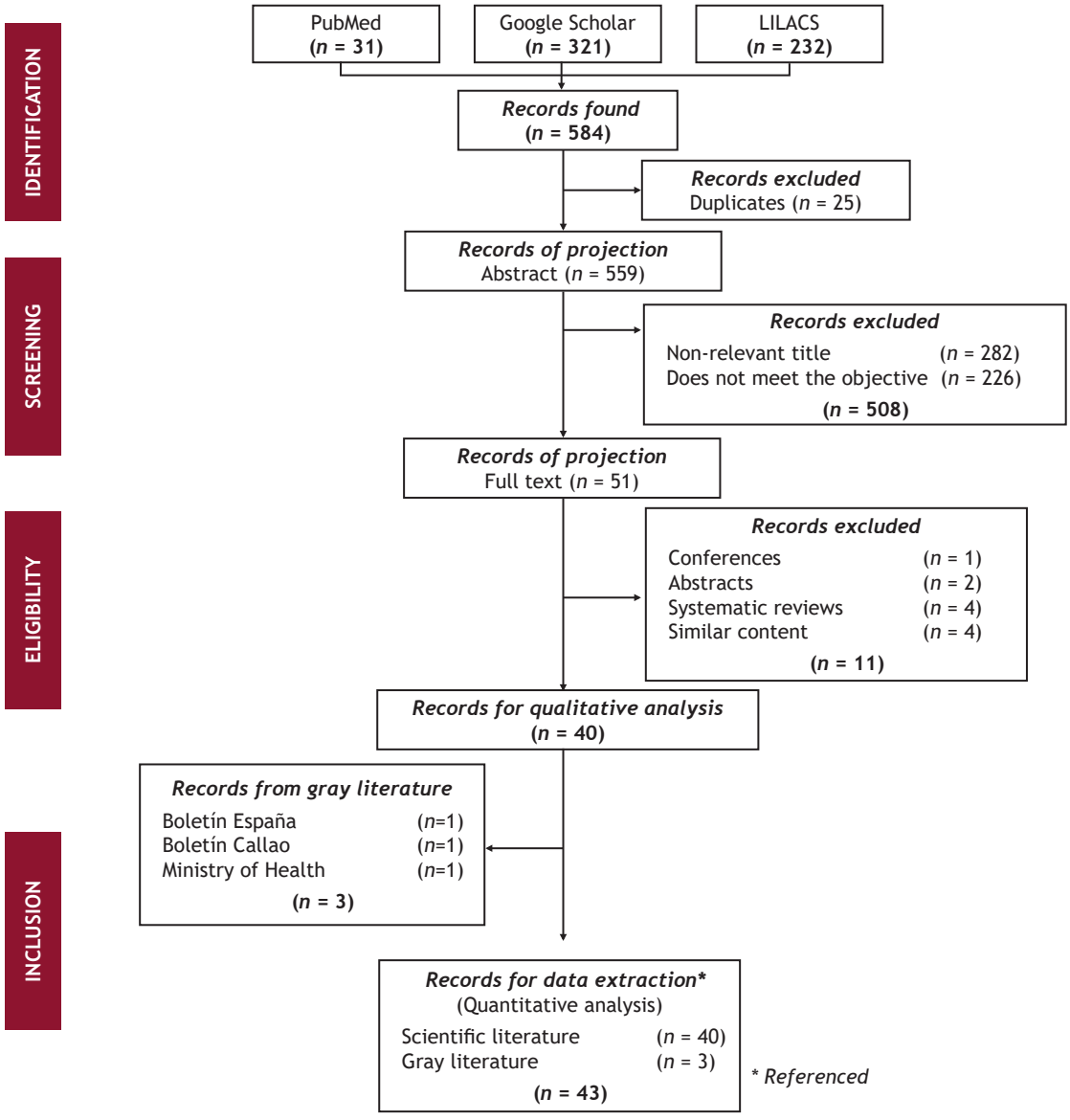

Figure 1. Study selection process

A bibliographic search was conducted in English and Spanish using PubMed, Google Scholar and LILACS, considering the logical operators "EMPB" OR "Coxsackie A16" AND "Children" and "Coxsackievirus Infections" AND "Child." A total of 584 publications were identified (PubMed = 31, Google Scholar = 321 and LILACS = 232), along with three records from gray literature (Boletín España [*n* = 1], Boletín España [*n* = 1] and Ministry of Health [*n* = 1]). The following studies were excluded: 25 due to duplication, 508 during the projection of abstracts (282 for not being relevant based on the title and 226 for not complying with the objective) and 11 during the projection of full text (one for being a conference paper, two for being abstracts, four for being systematic reviews and four for having similar content). After the analysis, 40 publications were selected, with three additional records from gray literature. Finally, we included 43 studies for the extraction and quantitative analysis of data published between January 2010 and June 2022. Throughout the process, the criteria of quality evidence and the grading of recommendation strength were considered to ensure the quality of the evaluation and the systematized information.

The selection process was carried out by three researchers and two subject matter experts (an internist and a pediatrician), who validated the clinical information contained in each selected study. When selecting information, ethical principles were observed and respected, with no discrimination or actual or potential bias derived from any source that could be interpreted as having an interest in the results [27].

Clinical features of HFMD

Clinical manifestations usually present in a specific manner in most cases, in contrast to those with multiorgan involvement and severe complications (Table 1). They usually present with fever and a papulovesicular rash on the hands, feet [1,7,28-30] and genitalia, along with an ulcerative enanthem in the mouth [9,31]. Additional symptoms include general malaise, odynophagia [7,9] and respiratory symptoms [9,29,31]. When diagnosis is not possible based on clinical manifestations, laboratory tests are necessary, showing leukocytosis with a left shift, C-reactive protein (CRP) (30 mg/L) [1] and increased alkaline phosphatase [32].

Table 1. Main clinical features of HFMD

Specific signs	Authors
Fever	Sapia et al. (2016) [1] Guo et al. (2020) [28] Rodríguez-Zúñiga et al. (2017) [9] Sun et al. (2018) [29] Velástegui et al. (2016) [30] Hoffmann et al. (2020) [31] Romero et al. (2020) [7]
Macules, papules and blisters on the hands, feet, mouth, folds, thorax, perineal region and genitalia	Sapia et al. (2016) [1] Rodríguez-Zúñiga et al. (2017) [9] Velástegui et al. (2016) [30] Hoffmann et al. (2020) [31] Romero et al. (2020) [7]
General malaise and odynophagia	Rodríguez-Zúñiga et al. (2017) [9] Romero et al. (2020) [7]
Respiratory symptoms	Rodríguez-Zúñiga et al. (2017) [9] Sun et al. (2018) [29] Romero et al. (2020) [7]
Leukocytosis with a left shift, CRP 30 mg/l and increased alkaline phosphatase	Sapia et al. (2016) [1] Qin et al. (2019) [32]

Transmission of HFMD

The transmission of enteroviruses (CA16 and EVA71) occurs via the fecal-oral or respiratory route. In newborns, vertical transmission can occur (before, during or after delivery) and probably through breastfeeding. Horizontal transmission is also prevalent; it occurs among family members or as nosocomial transmission in day care centers and/or enclosed spaces [33-36]. The incubation period ranges from four to six days and most commonly affects children under 10 years of age [9,12]. While the majority develops symptoms, a considerable number of

cases are asymptomatic [29]. Transmission occurs through direct contact with vesicular fluid and oral or respiratory secretions. Additionally, evidence shows that enteroviruses can be detected in feces for up to 10 weeks postinfection and in the oropharynx for nearly four weeks, due to the innate environmental stability of enteroviruses that facilitates their spread [37].

In this regard, a study demonstrated a relationship between the average temperature and the incidence of HFMD, with a temperature threshold for transmissibility of 13.4 °C to 18.4 °C in spring/summer and 14.5 °C to 29.3 °C in autumn/winter, which facilitates its spread and transmission [38].

Diagnosis of HFMD

In most cases, the diagnosis is clinical. However, it sometimes be unclear due to symptoms that overlap with other diseases, such as herpangina and herpes (oral cavity) or varicella (skin). Therefore, differential virological confirmation is necessary [39].

The one-step triplex real-time reverse transcription polymerase chain reaction (RT-PCR) is used for the simultaneous detection of EVA71, CA16 and pan-enterovirus, demonstrating a favorable detection spectrum [5]. The fluorescent quantitative reverse transcription polymerase chain reaction (qRT-PCR) test allows for the determination of the number of viral RNA copies in extracted samples [28]. The monoplex RT-PCR enables the rapid detection of various genogroups of EVA71 [40]. In addition to the aforementioned methods, noninvasive diagnosis for detecting EVA71-specific immunoglobulin A (IgA) in saliva is also available, which is useful in the diagnosis of EVA71 infection [41].

Table 2. Diagnostic tests for HFMD

Test	Description
triplex RT-PCR	It simultaneously detects various HFMD pathogens. (EVA71, CA16 and pan-enterovirus) [5]
qRT-PCR	It detects the number of viral RNA copies in samples [28]
monoplex RT-PCR	It detects various genogroups of EVA71 [40]
Immunoglobulin A (IgA)	It detects EVA71-specific immunoglobulin A (IgA) in saliva [41]

Vaccination against HFMD

Among the three most recognized HFMD vaccines are those based on peptides against EV71, peptide-based bivalent EVA71/CA16 vaccines and peptide-based tetravalent vaccines [42]. Of these, the EVA71 vaccine conjugated with diphtheria toxoid has demonstrated 80 % passive protection in mice following a lethal exposure [43-48]. It is also known that the generated antisera can confer 70 % protection to mice after lethal exposure to EVA71 [49]. Vaccines that could provide human immunity against EVA71 have weak cross-protection against CA16 infection, as seen in the case of VLPs (virus-like particles) and inactivated monovalent EVA71 or CA16 vaccines. To address this issue, a bivalent EVA71/CA16 vaccine was developed by mixing equivalent doses of EVA71 and CA16 VLPs or inactivated EVA71 and CA16, resulting in the production of cross-neutralizing antibodies. The immune sera from vaccinated animals provided passive protection against lethal challenges of both EVA71 and CA16 [50].

There is another bivalent vaccine based on the core protein of the hepatitis B virus that elicits high IgG titers and neutralization against both EVA71 and CA16 [51]. The tetravalent vaccine (EVA71, CA16, CA6 and CA10 VLPs) against HFMD elicits a specific and long-lasting antibody response and provides passive protection against single or mixed infections in mice. However, it is expensive to produce [52].

In the case of vaccination among children, the EVA71 vaccine has been available on the market since 2016. A study in China showed that such vaccination did not decrease its incidence; however, it contributed to decrease the severity of cases as well as the case fatality rate [53]. Another Chinese study showed that after the implementation of the EVA71 vaccine, HFMD incidence caused by EVA71 significantly decreased; nevertheless, cases due to other enteroviruses and CA16 increased [54]. Although vaccine efficacy has been demonstrated through randomized controlled trials, especially in animals, the evidence for the efficacy of the monovalent EVA71 vaccine remains unknown [55].

Antiviral treatment for HFMD

Most cases of HFMD usually resolve on their own; however, the clinical presentation of some is extremely aggressive and requires urgent treatment. Acyclovir, administered orally, is one of the most widely used antivirals, as it has shown satisfactory results; nonetheless, randomized studies and clinical trials are needed to know its mechanisms and beneficial effects. On the other hand, early and prompt

treatment with intravenous immunoglobulin can reduce morbidity and mortality among children [33].

On the other hand, natural peptides such as lactoferrin and melittin, as well as synthetic peptides such as SP40, RGDS and LVLQTM, have shown promising results as potent antivirals against EVA71. Thus, they are considered safe and effective and have a lower likelihood of resistance [56].

Prevention of HFMD

It includes frequent handwashing with soap and water for at least 20 seconds, particularly after toileting, coughing and sneezing; avoiding touching the eyes, nose and mouth (a possible route of infection); cleaning and disinfecting surfaces (such as door handles and children's toys); avoiding contact with infected individuals and sharing personal items with them; and isolating identified cases at home from the onset of symptoms until they resolve. When a case is detected in an educational institution, quarantine should be implemented for the affected classroom and family contacts (parents, siblings, and cousins) for a period of up to 10 days [21,57,58].

On the other hand, taking effective preventive measures is particularly important for the prevention, reduction and control of HFMD. Actions such as intensive intervention of education on hand hygiene for both children and their parents will promote personal hygiene habits [59].

CONCLUSIONS

HFMD is a highly contagious infectious process, mainly caused by CA16 and EVA71. Although it can affect any age group, its incidence is higher in children under 10 years of age. The clinical presentation is typically characterized by fever, papulovesicular rash (localized on the hands, feet and genitalia) and ulcerative lesions in the mouth. It is transmitted through direct contact with secretions (nasal, oral), fecal material (fecal-oral route) and contaminated objects. It is common in Asia (India, Singapore, Japan and China), where epidemic outbreaks occur, mainly affecting the child population. It frequently occurs in enclosed spaces such as educational institutions and day care centers. Generally, diagnosis is clinical and based on epidemiological history. As there is no specific treatment, only general measures are taken to alleviate the symptoms and prevent dehydration. For this reason, a safe vaccine that includes most etiological agents is needed, along with the implementation of epidemiological surveillance programs to prevent its spread.

Author contributions: JUHO, AOG, and WOCC have similarly contributed to the original idea, study design, collection and analysis of the literature, writing of the draft, writing of the article and approval of the final version. Furthermore, they have participated in the conception and design of the article, analysis and interpretation of data, writing of the article, critical revision of the article and approval of the final version.

Funding sources: This article was funded by the authors.

Conflicts of interest: The authors declare no conflicts of interest.

BIBLIOGRAPHIC REFERENCES

1. Sapia EY, Maroni C, Groisman C, Kromer H, Rojo GL, Dastugue M, et al. Genotipificación del virus de la enfermedad mano-pie-boca atípica en un hospital pediátrico de la ciudad de Buenos Aires, Argentina. Arch Argent Pediatr [Internet]. 2020;118(2):199-203.
2. Zhang X, Zhang Y, Li H, Liu L. Hand-Foot-and-Mouth Disease-Associated Enterovirus and the Development of Multivalent HFMD Vaccines. Int J Mol Sci. 2022;24(1):169.
3. Yan R, He J, Liu G, Zhong J, Xu J, Zheng K, et al. Drug Repositioning for Hand, Foot, and Mouth Disease. Viruses [Internet]. 2022;15(1):75.
4. Pinela DA, Moran TT, Sánchez KL, Reina RG. La enfermedad de boca, manos y pie (EBMP). Diagnóstico diferencial. RECIAMUC [Internet]. 2020;4(1):40-8.
5. Zhang S, Wang J, Yan Q, He S, Zhou W, Ge S, et al. A one-step, triplex, real-time RT-PCR assay for the simultaneous detection of enterovirus 71, coxsackie A16 and pan-enterovirus in a single tube. PLoS One [Internet]. 2014; 9(7):e102724.
6. Han Y, Ji H, Shen W, Duan C, Cui T, Chen L, et al. Disease burden in patients with severe hand, foot, and mouth disease in Jiangsu province: a cross-sectional study. Hum Vaccin Immunother [Internet]. 2022;18(5):2049168.
7. Romero MR, Saldaña M, Iser OA, Ponce Y, Gonzales N. Síndrome manos, pies, boca. Casos atendidos en el cuerpo de guardia. Revista Médica Multimed [Internet]. 2020;24(1):140-53.
8. Robinson CR, Doane FW, Rhodes AJ. Report of an outbreak of febrile illness with pharyngeal lesions and exanthem: Toronto, summer 1957; isolation of group A Coxsackie virus. Can Med Assoc J [Internet]. 1958;79(8):615-21.
9. Rodríguez-Zúñiga MJM, Vértiz-Gárate K, Cortéz-Franco F, Qujiano-Gomero E. Enfermedad de mano pie y boca en un hospital del Callao, 2016. Rev Peru Med Exp Salud Publica [Internet]. 2017;34(1):132-8.
10. Delgado-Azañero W, Concha-Cusihuallpa H, Guevara JO. Infección de la mucosa oral por Coxsackie virus: enfermedad de boca-mano-pie. Rev Estomatol Hered [Internet]. 2007;17(1):35-9.
11. Iannuzzelli CG, Caballero JP, Sanz MP, Valle F, Casanova M. Brote de onicomadesis secundaria a enfermedad boca-mano-pie en la provincia de Teruel. Bol Pediatr Arag Rioj Sor [Internet]. 2014;44(2):40-3.
12. Carmona RCC, Machado BC, Reis FC, Jorge AMV, Cilli A, Dias AMN, et al. Hand, foot, and mouth disease outbreak by Coxsackievirus A6 during COVID-19 pandemic in 2021, São Paulo, Brazil. J Clin Virol [Internet]. 2022;154:105245.
13. Zhang J, Li XH, Li XF, Shang X. Etiology and epidemiology of hand, foot and mouth disease in China. Zhonghua Liu Xing Bing Xue Za Zhi [Internet]. 2022;43(5):771-83.

14. Navarro E, Almagro D, Jaldo R, Del Moral MC, Árbol G, Pérez M, et al. Brote de enfermedad boca-mano-pie y onicomadesis causado por el virus Coxsackie A16, Granada. An Pediatr (Barc) [Internet]. 2015;82(4):235-41.
15. Ang LW, Koh BK, Chan KP, Chua LT, James L, Goh KT. Epidemiology and control of hand, foot and mouth disease in Singapore, 2001-2007. Ann Acad Med Singap [Internet]. 2009;38(2):106-12.
16. Sharma A, Mahajan VK, Mehta KS, Chauhan PS, Manvi S, Chauhan A. Hand, foot and mouth disease: a single centre retrospective study of 403 new cases and brief review of relevant Indian literature to understand clinical, epidemiological, and virological attributes of a long-lasting Indian epidemic. Indian Dermatol Online J [Internet]. 2022;13(3):310-20.
17. Guo J, Cao Z, Liu H, Xu J, Zhao L, Gao L, et al. Epidemiology of hand, foot, and mouth disease and the genetic characteristics of Coxsackievirus A16 in Taiyuan, Shanxi, China from 2010 to 2021. Front Cell Infect Microbiol [Internet]. 2022;12:1040414.
18. Chen G, Huang C, Luo D, Yang J, Shi Y, Li D, et al. Clinical characteristics and treatment overview in hand-foot-and-mouth disease using real-world evidence based on hospital information system. Evid Based Complement Alternat Med [Internet]. 2022;2022(1):1-9.
19. Wu P, Huang L, Kao C, Fan T, Cheng A, Chang L. An outbreak of coxsackievirus A16 infection: comparison with other enteroviruses in a preschool in Taipei. J Microbiol Immunol Infect [Internet]. 2010;43(4):271-7.
20. Yang Z, Zhang Q, Cowling BJ, Lau EH. Estimating the incubation period of hand, foot and mouth disease for children in different age groups. Sci Rep [Internet]. 2017;7(1):16464.
21. Ministerio de Salud del Perú. Actualización de la ocurrencia de brotes de la enfermedad mano, pie y boca (EMPB). Perú [Internet]. Lima: MINSA; 2022 p. 1–3. (Alerta Epidemiológica). Available from: https://www.dge.gob.pe/epipublic/uploads/alertas/alertas_20227_19_162731.pdf
22. Ministerio de Salud del Perú. Boletín Epidemiológico [Internet]. Lima: MINSA; 2022. Available from: https://www.dge.gob.pe/epipublic/uploads/boletin/boletin_202212_22_162519.pdf
23. Tang X, Zhang L, Meng J, Chen H, Cheng Y, Yuan P, et al. Epidemiological Characteristics of Hand, Foot, and Mouth Disease and the Effect of EV71 Vaccination in Chengdu from 2012 to 2020. Sichuan Da Xue Xue Bao Yi Xue Ban [Internet]. 2022;53(6):1074-80.
24. Li J, Zhang C, Li Y, Li C, Zhang S, Wang S, et al. Coxsackievirus A6 was the most common enterovirus serotype causing hand, foot, and mouth disease in Shiyan city, central China. World J Clin Cases [Internet]. 2022;10(31):11358-70.
25. Xing J, Wang K, Wang G, Li N, Zhang Y. Recent advances in enterovirus A71 pathogenesis: a focus on fatal human enterovirus A71 infection. Arch Virol [Internet]. 2022;167(12):2483-501.
26. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. Declaración PRISMA 2020: una guía actualizada para la publicación de revisiones sistemáticas. Rev Esp Cardiol [Internet]. 2021;74(9):790-9.
27. Arévalo RA, Ortuño G, Arévalo DE. Revisiones sistemáticas (1). Revista Médica [Internet]. 2010;16(2):69-80.
28. Guo Y, Liu Y, Song J, Liu P, Wu S, Tan Y, et al. Association of CD14 rs2569190 G/A genetic polymorphism with the severity of enterovirus 71 infection in Chinese children. Virology [Internet]. 2020;548:25-30.
29. Sun BJ, Chen HJ, Chen Y, An XD, Zhou BS. The risk factors of acquiring severe hand, foot, and mouth disease: a meta-analysis. Can J Infect Dis Med Microbiol [Internet]. 2018(1):1-12.
30. Velástegui J, Cova L, Galarza Y, Fierro P, León Baryolo L, Bustillos A. A case report of hand, foot, and mouth disease with necrotizing mucocutaneous lesions. Medwave [Internet]. 2019;19(7):e7683.
31. Hoffmann AJ, Latrous M, Lam JM. Atypical hand-foot-and-mouth disease. CMAJ [Internet]. 2020;192(3):e69.
32. Qin L, Dang D, Wang X, Zhang R, Feng H, Ren J, et al. Identification of immune and metabolic predictors of severe hand-foot-mouth disease. PLoS One [Internet]. 2019;14(5):e0216993.
33. Chuang YY, Chering YC. Enteroviral infection in neonates. J Microbiol Immunol Infect [Internet]. 2019;52(6):851-7.
34. Saguil A, Kane SF, Lauters R, Mercado MG. Hand-Foot-and-Mouth disease: rapid evidence review. Am Fam Physician [Internet]. 2019;100(7):408-14.
35. Cabrera D, Ramos A, Espinosa E. Enfermedad boca mano pie. Presentación de un caso. Medisur [Internet]. 2018;16(3):469-74.
36. Nicola AC, Malpica R. Enfermedad de boca-mano-pie y virus Coxsackie. Reporte de un caso. Multiciencias [Internet]. 2012;12(3):300-4.
37. García C. Enfermedad gloso-mano-peda. Rev Méd Sinerg [Internet]. 2018;3(4):9-12.
38. Xu J, Yang M, Zhao Z, Wang M, Guo Z, Zhu Y, et al. Meteorological factors and the transmissibility of hand, foot, and mouth disease in Xiamen City, China Front Med (Lausanne) [Internet]. 2021;22(7):597375.
39. Mukherjee S, Babu NA, Rajesh E, Mastán KMK. Viral lesions of oral cavity. Indian J Forensic Med Toxicol [Internet]. 2020;14(4):1108-13.
40. Volle R, Joffret ML, Ndiaye K, Fernandez-Garcia MD, Razafindratsimandresy R, Heraud JM, et al. Development of a new internally controlled one-step real-time RT-PCR for the molecular detection of enterovirus A71 in Africa and Madagascar. Front Microbiol [Internet]. 2020;11:1907.
41. Changbing W, Yi C, Tiantian X, Xingui T, Jianbin Z, Wenkuan L, et al. A novel method to diagnose the infection of enterovirus A71 in children by detecting IgA from saliva. J Med Virol [Internet]. 2020;92(8):1059-64.
42. Anasir MI, Poh CL. Advances in antigenic peptide-based vaccine and neutralizing antibodies against viruses causing Hand, Foot, and Mouth disease. Int J Mol Sci [Internet]. 2019;20(6):1256.
43. Foo DGW, Alonso S, Chow VTK, Poh CL. Passive protection against lethal enterovirus 71 infection in newborn mice by neutralizing antibodies elicited by a synthetic peptide. Microbes and Infection [Internet]. 2007;9(11):1299-306.
44. Huang L, Wang T, Liu X, Fu Y, Zhang S, Chu Q, et al. Spatial-temporal-demographic and virological changes of hand, foot and mouth disease incidence after vaccination in a vulnerable region of China. BMC Public Health [Internet]. 2022;22(1):1468.
45. Bian L, Gao F, Mao Q, Sun S, Wu X, Liu S, et al. Hand, foot, and mouth disease associated with coxsackievirus A10: more serious than it seems. Expert Rev Anti Infect Ther [Internet]. 2019;17(4):233-42.
46. Hu L, Maimaiti H, Zhou L, Gao J, Lu Y. Changing serotypes of hand, foot and mouth disease in Shanghai, 2017-2019. Gut Pathog [Internet]. 2022;14(1):12.

47. Hong J, Liu F, Qi H, Tu W, Ward MP, Ren M, et al. Changing epidemiology of hand, foot, and mouth disease in China, 2013-2019: a population-based study. Lancet Reg Health West Pac [Internet]. 2022;20:100370.
48. Liu LL, Liu ZK, Zhang L, Li N, Fang T, Zhang DL, et al. Epidemiological and etiological characteristics of hand, foot and mouth disease among children aged 5 years and younger in Ningbo (2016 to 2019). Beijing Da Xue Xue Bao Yi Xue Ban [Internet]. 2021;53(3):491-7.
49. Tian X, Su X, Li X, Li H, Li T, Zhou Z, et al. Protection against enterovirus 71 with neutralizing epitope incorporation within adenovirus type 3 hexon. PloS One [Internet]. 2012;7(7):e41381.
50. Sun S, Jiang L, Liang Z, Mao Q, Su W, Zhang H, et al. Evaluation of monovalent and bivalent vaccines against lethal Enterovirus 71 and Coxsackievirus A16 infection in newborn mice. Hum Vaccin Immunother [Internet]. 2014;10(10):2885-95.
51. Xu L, He D, Yang L, Li Z, Ye X, Yu H, et al. A broadly cross-protective vaccine presenting the neighboring epitopes wthin the VP1 GH loop and VP2 EF loop of Enterovirus 71. Sci Rep [Internet]. 2015;5(31):12973.
52. Zhang W, Dai W, Zhang C, Zhou Y, Xiong P, Wang S, et al. A virus-like particle-based tetravalent vaccine for hand, foot, and mouth disease elicits broad and balanced protective immunity. Emerg Microbes Infect [Internet]. 2018;7(1):94.
53. Li J, Hongchao J, Xin T, Xueshan X, Tian H. Epidemiological characteristics of hand, foot, and mouth disease in Yunnan Province, China, 2008-2019. BMC Infect Dis [Internet]. 2021;21(1):751.
54. Han Y, Chen Z, Zheng K, Li X, Kong J, Duan X, et al. Epidemiology of hand, foot, and mouth disease before and after the introduction of Enterovirus 71 vaccines in Chengdu, China, 2009–2018. Pediatr Infect Dis J [Internet]. 2020;39(10):969-78.
55. Du Z, Huang Y, Bloom MS, Zhang Z, Yang Z, Lu J, et al. Assessing the vaccine effectiveness for hand, foot, and mouth disease in Guangzhou, China: a time-series analysis. Hum Vaccin Immunother [Internet]. 2021;17(1):217-23.
56. Lalani S, Gew LT, Poh CL. Antiviral peptides against Enterovirus A71 causing hand, foot and mouth disease. Peptides [Internet]. 2021;136:170443.
57. Gobierno de Aragón. Información de Salud Pública para profesionales sanitarios [Internet]. Aragón: Boletín epidemiológico de Aragón; 2018 p. 1–2. Available from: https://www.aragon.es/documents/20127/674325/BEsA_201844.pdf/34ae2c0b-02f7-8444-1679-13ebcd268707
58. Leung AKC, Lam JM, Barankin B, Leong KF, Hon KL. Hand, foot, and mouth disease: a narrative review. Recent Adv Inflamm Allergy Drug Discov [Internet]. 2022;16(2):77-95.
59. Guo N, Ma H, Deng J, Ma Y, Huang L, Guo R, et al. Effect of hand washing and personal hygiene on hand food mouth disease: A community intervention study. Medicine (Baltimore) [Internet]. 2018;97(51):e13144.

Corresponding author:
José Uberli Herrera Ortiz
Address: Jr. Santa Asunción n.° 241. Chota, Cajamarca.
Telephone: (+51) 976 003 080
E-mail: juherrerao@unach.edu.pe

Reception date: March 30, 2023
Evaluation date: April 28, 2023
Approval date: May 25, 2023

ORCID iDs
José Uberli Herrera Ortiz https://orcid.org/0000-0001-8491-1132
Anibal Oblitas Gonzales https://orcid.org/0000-0002-3578-7558
Wilder Ovidio Carranza Carranza https://orcid.org/0000-0001-5365-9499