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Hand, foot, and mouth disease in children: forecasting of future research direction using bibliometric analysis

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ABSTRACT: Since 1997, hand, foot, and mouth disease (HFMD) has become a common health problem in Southeast Asia. Various types of research have been conducted and published to handle HFMD. However, until now, many children, especially in the Asia-Pacific region, including Indonesia, still have HFMD-causing enterovirus (EV) infection. By conducting a bibliometric analysis of the literature published over the last 27 years (1997–2024), the direction of HFMD research in children can be predicted, thus research areas that have the potential and still need to be developed for future better HFMD treatment can be known. The important HFMD research topics predicted to continue to develop were identified through keyword analysis, which was subsequently mapped using a network approach. Based on this study, it can be concluded that HFMD research is predicted to lead to the development of synbiotic supplements, which can reduce HFMD severity, especially in children, by utilizing a genome-wide association study (GWAS) and machine learning.

KEYWORDS: Bibliometric analysis; genome-wide association study; hand, foot, and mouth disease; machine learning; synbiotic supplement.

▪ INTRODUCTION

Hand, foot, and mouth disease (HFMD) is an infectious disease caused by various enteroviruses (EV), which occurs in adults and children and can have a severe outcome, especially on the health of children under five years of age. This disease is also known as Singapore Flu. Human enterovirus A71 (EV-A71 or EV71) and coxsackievirus A16 (CV-A16 or CA16) are considered common pathogens and the main cause of HFMD[1,2]. This disease usually improves in 7–10 days and leaves no marks on the skin. However, further complications can also occur, such as encephalitis, aseptic meningitis, myocarditis, pulmonary edema, acute flaccid paralysis, and even death [1],[3].

Since 1997, HFMD has become a common health problem in Southeast Asia and continues to increase in Asia-Pacific, including Japan, Malaysia, Singapore, Vietnam, China, Taiwan, Thailand, and others [4–6]. Indonesia, with an estimated population of 270 million people, of which a third are children, is particularly vulnerable to the HFMD epidemic [7]. In 2008, the largest Asia-Pacific pandemic was reported in China. Then, HFMD was designated as a class C infectious disease by the Chinese Ministry of Health on May 2nd, 2008. HFMD national mortality remains the highest of all class C infectious diseases [5],[8]. Since 2016, three inactivated monovalent EV-A71 vaccines have been launched in China. Wang *et al*. found that the incidence, mortality, and severity rates of HFMD cases declined in the years after the EV-A71 vaccination was introduced [2],[9]. EV-A71 dominated HFMD cases in China from 2008 to 2012. However, over the last decade, there has been an increase in the correlation between CV-A16 and cases of HFMD [8].

Recently, HFMD-related research has not only focused on vaccine development but has begun to move towards other therapies, such as synbiotic supplements (a mixture of probiotics and prebiotics). The study conducted by Guo *et al*. and Shen *et al*. showed dysbiosis in the gut microbiota of patients with HFMD. Synbiotic supplements administration helped to maintain intestinal flora homeostasis and reduced the risk of HFMD [10],[11]. By conducting a bibliometric analysis study on the literature published over the last 27 years (1997–2024), the direction of HFMD research in children can be predicted, thus research areas that have the potential and still need to be developed for future better HFMD treatment can be known.

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▪ MATERIALS AND METHODS

Materials

The study of forecasting the future research direction for HFMD in children was carried out by bibliometric analysis using the PubMed database (https://pubmed.ncbi.nlm.nih.gov/; accessed on January 31st, 2024) and several computer applications, such as Biblioshiny (the Bibliometrix package in the R program version 4.3.2), and VOSviewer v1.6.20 (https://www.vosviewer.com/download). The research literature on "hand, foot, and mouth disease" published from January 1st, 1997 to January 31st, 2024, became the test subject of this study.

Equipment

This study used a notebook with system model specifications: Dell with Intel(R) Core(TM) i5-10210U CPU @ 1.60GHz 2.11GHz processor; Random Access Memory (RAM) 8 gigabyte, Windows 10.

Methods

Data sources collection

All data was collected from PubMed collection on January 31st, 2024. Articles searched should include "hand, foot, and mouth disease" in the title or abstract. There were no limitations on the types of articles collected, but articles should have an abstract and full text for a more comprehensive analysis. There were 41 articles without full text, thus we did not include them in this study. This bibliometric analysis was conducted on research articles published over 27 years, from 1997 to 2024. Furthermore, the article included in this analysis should meet inclusion criteria: the species tested should be human, ranging in age from 0 to 12 years, and articles should be written in English or Indonesian. Then, all collected articles were saved in PubMed format. Thus, they could be opened in the Biblioshiny and VOSviewer applications for further analysis. The flow chart of the data source extractions was adapted from the study of Zakaria *et al*.[12] is shown in Figure 1.

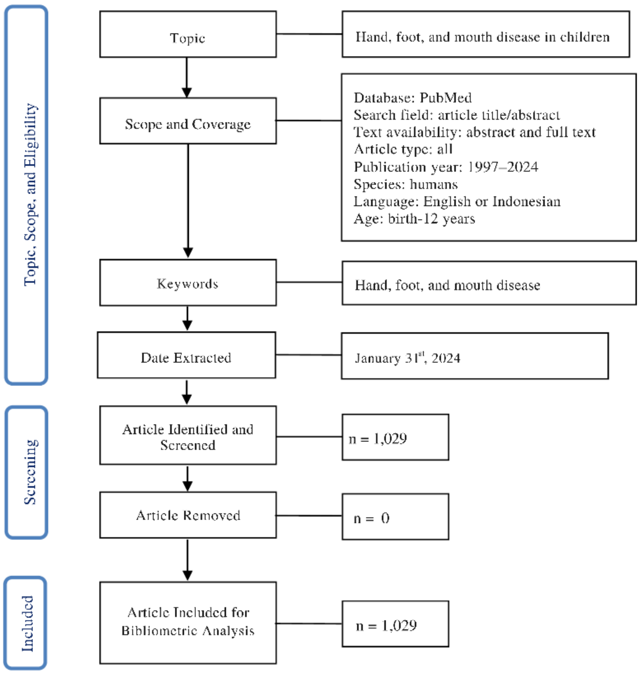


Figure 1. Flow chart of the data source extractions.

Data processing and cleaning

Raw data in PubMed format was imported into the Biblioshiny application. It should be ensured that the number of articles collected from PubMed is appropriate. Then, those data were exported in Excel format. Thus, they could be processed in Microsoft Excel 2010. Duplicate terms should be removed before the data is analyzed with the VOSviewer application. Terms with different editorial writings with the same meaning could be counted into one word.

It is important to recognize that the databases used limitations heavily influence the results, meaning that significant studies may be overlooked. Additionally, this study only included articles written in English or Indonesian, which led to the underrepresentation of research output from non-English or Indonesian-speaking countries, even if their work may be highly relevant. Bibliometric analysis tends to focus on the quantity of publications, which does not always reflect the quality of research. However, bibliometric analysis plays a crucial role in understanding research trends, providing an overarching view of the volume and spread of scientific work across various fields. Therefore, this study helps map collaboration networks and offers valuable insights for researchers, institutions, and policymakers, particularly regarding HFMD treatment.

Data analysis

Two analyses were conducted using Biblioshiny, including keyword analysis at the document level and science mapping in terms of conceptual structure. Keyword analysis at the document level consists of the Most Frequent Words, WordCloud, TreeMap, Words' Frequency over Time, and Trend Topics. Meanwhile, science mapping in terms of conceptual structure is carried out using a network approach, including a Co-occurrence Network, Thematic Map, and Thematic Evolution. In addition, analysis was also conducted with VOSviewer v1.6.20 to confirm the results of the Biblioshiny analysis through visualization of the network and overlay.

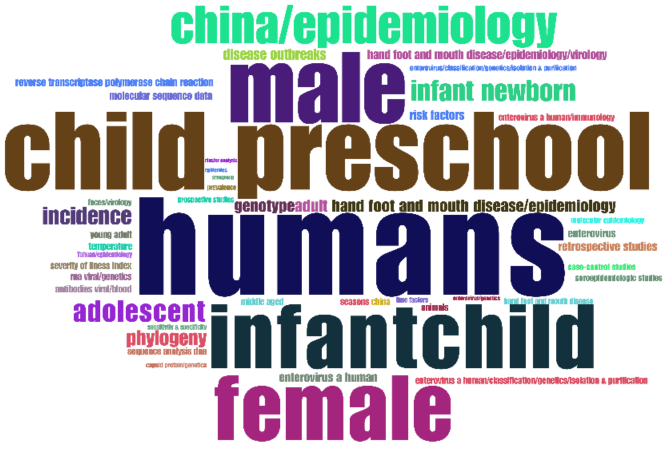
▪ RESULTS AND DISCUSSION

Keyword analysis

All articles from PubMed related to HFMD, published from 1997 to 2024, and met the inclusion criteria were 1.029 documents (Supplementary Table S1). The average annual production of articles on HFMD in children has increased almost 11 times since 2010. The annual growth rate is 4.32%. From 1997 to 2009, the average HFMD article production was 6 per year. Meanwhile, from 2010 to January 2024, its average increased to 63.4 per year (Supplementary Table S2).

Out of 2.473 terms in 1.029 documents, the Most Frequent Word analysis revealed that 'humans' was a keyword in all documents. Keywords 'child preschool' and 'infant' ranked second and third, with the percentage of occurrence in 1.029 documents at 76.09% and 68.32%, respectively. The top 10 most frequent words can be seen in Supplementary Table S3. The top 50 most frequent words were visualized in WordCloud and TreeMap in Figures 2a and 2b (see also Supplementary Table S4). The more prominent the word displayed in WordCloud or the larger the TreeMap box, the higher the occurrence frequency of that keyword in 1.029 documents.

(a)



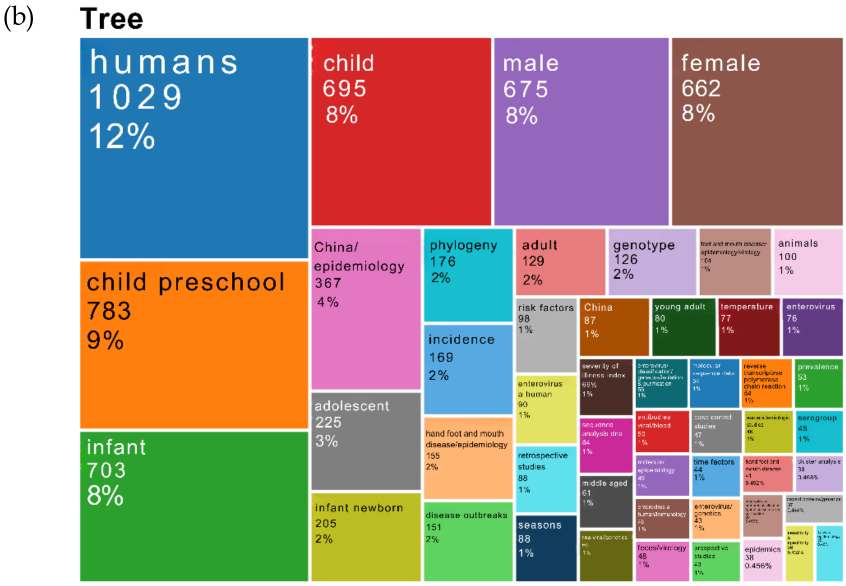


Figure 2. Top 50 most frequent words: (a) WordCloud; (b) TreeMap.

A meta-analysis study related to HFMD conducted by Wang *et al*. demonstrated that age and gender affected the prevalence of HFMD. The study showed that HFMD cases were mostly experienced by groups of children aged 3–4 years and 4–5 years [5], where this age is included in the preschool age group according to the Centers for Disease Control and Prevention (CDC) [13]. HFMD cases were also more common in boys than girls, with a ratio of 1.5:1 [5]. The results of this meta-analysis were in line with the keyword analysis in this bibliometric study. The keywords of child preschool, male, and female ranked second, fifth, and sixth the most frequently appearing in 1.029 documents.

The Words' Frequency over Time analysis indicated that the annual article production and the number of keyword occurrences were direct proportionally (see also Supplementary Table S5). As previously mentioned, from 2010 to the present, there has been a rapid increase in the average annual article production compared to the 1997–2009 period. The number of occurrences of the top 10 keywords per year also showed a rapid increase since 2010 and peaked in 2019. The top 10 keywords sorted by number of occurrences in 1,029 documents included humans, child preschool, infant, child, male, female, China/epidemiology, adolescent, infant newborn, and phylogeny.

In 2010 there was an outbreak of onychomadesis caused by coxsackievirus A6 (CA6) infection in Taiwan. Most of the patients had HFMD before the nail abnormalities appeared. Patients also had desquamation (skin peeling) in unusual places. The phylogenetic analysis conducted by Wei *et al*. (2011) against the CA6 strain based on the viral protein 1 (VP1) gene sequences isolated from Taiwanese patients showed a high degree of similarity with CA6 isolated from Finnish patients in 2008. However, it differed from those circulating in Taiwan from 1998 to 2009. The study also showed no significant differences in age and gender between the CA6 and non-CA6 distribution [14].

The HFMD research Trend Topics shown in Figure 3 were merely keywords that met the following inclusion criteria: the word minimum frequency was five, and the number of words per year was three. A larger blue node indicated higher keyword occurrence frequency. In 2006, the topic of Malaysia epidemiology became a trend. Around 2010, trend topics shifted to Taiwan epidemiology. After that, other topics emerged regarding viral, RNA, sequence analysis, genetics, and polymerase chain reaction (PCR). In 2015–2018, there were many topics regarding the HFMD outbreak in China, infants, child preschool, immunology, and enterovirus. From 2021 until now, the research trend topics have focused on enterovirus, antigens, genetics, and proteomics.

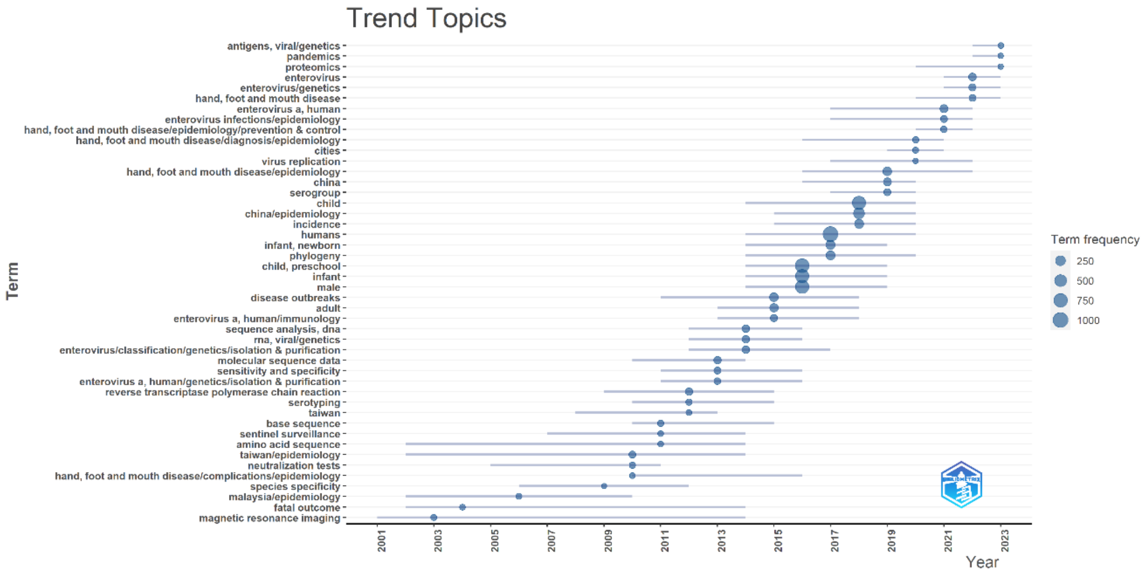


Figure 3. The HFMD research trend topics from year to year.

This bibliometric analysis study showed that since 2010, the production of articles related to HFMD had increased rapidly, and during 2010–2014 most of the research was on viral, RNA, sequences, PCR, and genetics. Within a decade after the human genome project was completed in 2003, DNA sequencing efficiency increased by about 100.000 times [15]. It is important in advancing bioinformatics analysis [16–19]. Since genome sequencing became more affordable and widespread, molecular characterization and phylogenetic analysis of the VP1 gene in EV71 and CA16 could be performed in 2011 in Thailand. The study's results indicated that the prevalence of a type of enterovirus could change yearly [20].

EV71 was first isolated in California in 1969, and its association with HFMD was verified in 1974. The major outbreaks dominated by EV71 occurred in 2008–2009 in China and throughout the Asia-Pacific region, but until then, effective antiviral therapy and vaccines were unavailable [21]. Hence, the development of the EV71 vaccine was urgently needed to stop the spread of the disease. The research results of Yang *et al*. (2011) revealed that neutralizing antibody levels did not correlate with HFMD severity, but cellular immune response correlated with clinical HFMD severity [22]. Therefore, Yang *et al*. concluded that the induction of humoral and cellular immunity should be considered in vaccine development [22–24].

Since 2008 when the need for vaccines began to be urgent, the research related to HFMD has focused on genetic analysis and expressed viral proteins to investigate the characteristics of viral strains that caused epidemics; thus, the diversity could be identified[25,26]. In addition, an analysis of the protein-protein interaction network from the collection of blood samples of pediatric patients with EV71 infection was also carried out to understand the pathogenic mechanism in HFMD[27]. During the period from 2013 to 2014, the focus of research moved towards the development of diagnostic methods including the potential biomarkers discovery[28] and seroprevalence [29],[30] including proteomic analysis[31] to study the epidemiology of HFMD in various epidemic areas [32–35].

From May 2013 to February 2014, following the phase 1 and 2 clinical trials[36,37], three vaccine manufacturers from China, namely Beijing Vigoo Biological, Sinovac Biotech, and Institute of Medical Biology, Chinese Academy of Medical Sciences (CAMS) published results of phase 3 clinical trial demonstrating the efficacy of all three inactivated vaccines against EV71. Overall, these three vaccines' safety and efficacy profiles were good[38–40]. In 2014, the EV71/CA16 bivalent vaccine also began to be widely developed. Evaluation of the EV71/CA16 bivalent vaccine gave promising results with a good safety and efficacy profile; thus, it has the potential to be further developed to prevent the spread of HFMD caused by EV71 and CA16 infection[41–43]. From 2020 until now, research on bivalent vaccines is increasingly being published according to the results of the bibliometric analysis in this study. This may be triggered by the increase in CA16-associated HFMD cases over the past decade [8],[44].

Science mapping by network approach

The network of the top 50 most frequent words was visualized in the Co-occurrence Network (Figure 4). The 50 keywords were divided into three clusters which were distinguished by color. The keyword's frequency increases with the size of the node. The importance of the keyword increases with the node's centrality. The betweenness and closeness determined the central position. The node position can be considered central if the keywords have betweenness and closeness greater than or equal to their median values. Out of the top 50 most frequent words, 21 of them were selected as important keywords (Supplementary Table S6), including thirteen keywords in cluster 1 (red), four keywords in cluster 2 (blue), and four keywords in cluster 3 (green).

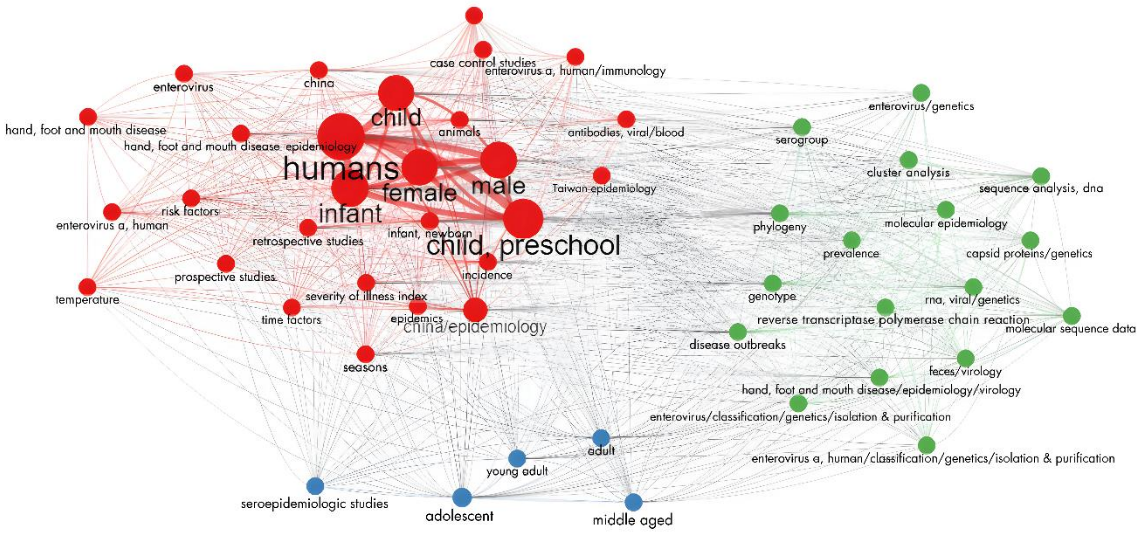
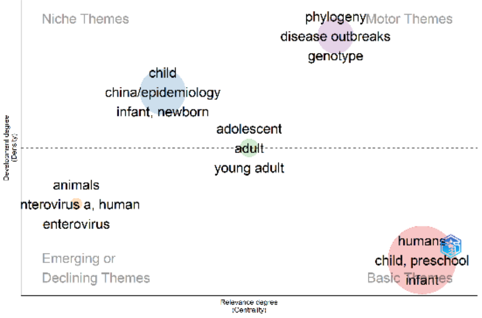


Figure 4. Co-occurrence Network of the top 50 most frequent words.

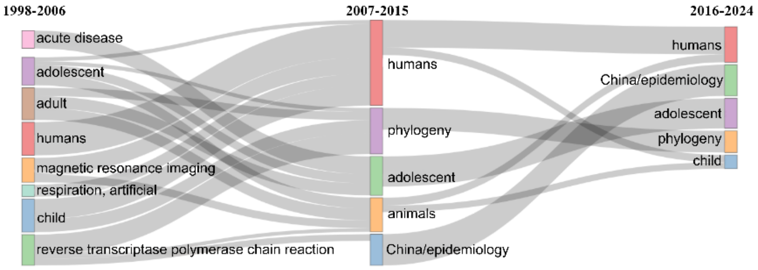
The clustering algorithm used in the thematic map analysis was the same as the Louvain Co-occurrence Network [45]. The Thematic Map shown in Figure 5a demonstrated that HFMD research with topics on the child, China/epidemiology, infant, newborn, phylogeny, disease outbreaks, and genotype would continue to grow. Meanwhile, HFMD research in the adolescent to the adult age group is decreasing. In contrast to the age group of infants to children in preschool, that is still the topic of basic HFMD research and is considered important. Research on HFMD in infants and children in preschool is still actively pursued because this age group is the most vulnerable to HFMD due to their immature immune systems and frequent exposure in daycare settings. Moreover, HFMD has a severe impact on children's health under five years [1],[2]. Meanwhile, research interest in HFMD tends to decrease in older age groups, such as adolescents and adults. This is because HFMD typically manifests as a mild illness in these groups, with symptoms usually being less severe compared to younger children.

This study divided the evolution of research topics regarding HFMD from 1997 to 2024 into three periods: 1997–2006, 2007–2015, and 2016–2024. The Thematic Evolution and Thematic Map for the three time periods are shown in Figures 5b and 5c. Keywords of humans, infants, and child preschool were basic and general HFMD research topics from 1997 until 2006. However, from 2007 until now, the three keywords have shifted from "basic theme" to "motor theme" which means they are topics that continue to grow in HFMD research. Meanwhile, the topics of adolescents, young adults, and adults are increasingly moving towards an "emerging or declining theme", which means the research on these subjects has decreased over time, particularly from 1997 to 2015. Another intriguing finding was the research topics on phylogeny, disease outbreaks, and genotype are increasingly moving towards a high degree of centrality and density This analysis indicated that phylogeny, disease outbreaks, and genotype related to HFMD are basic research topics and are even considered increasingly important and growing.

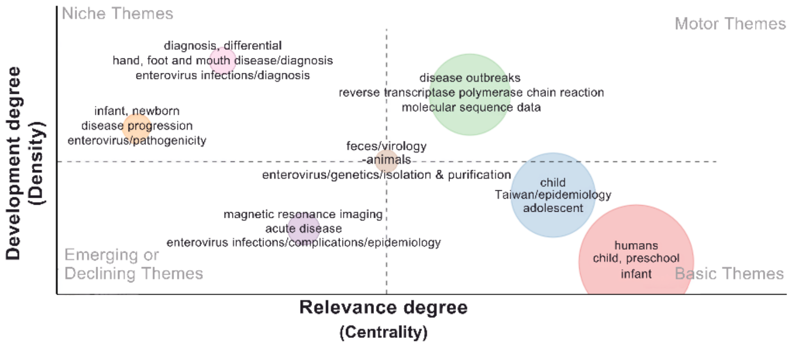
(a)



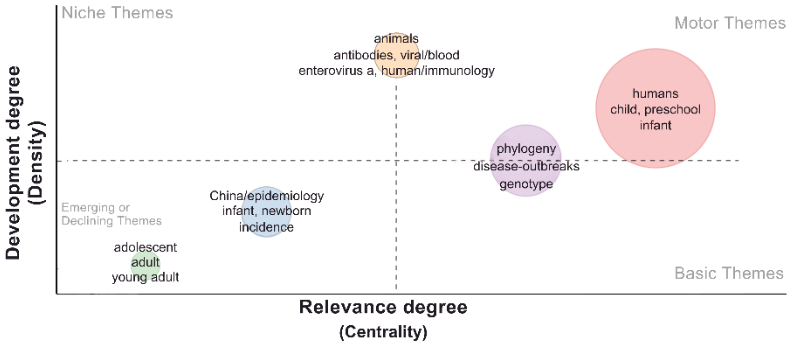
(b)



(c) **1997–2006 period**



2007–2015 period



2016–2024 period

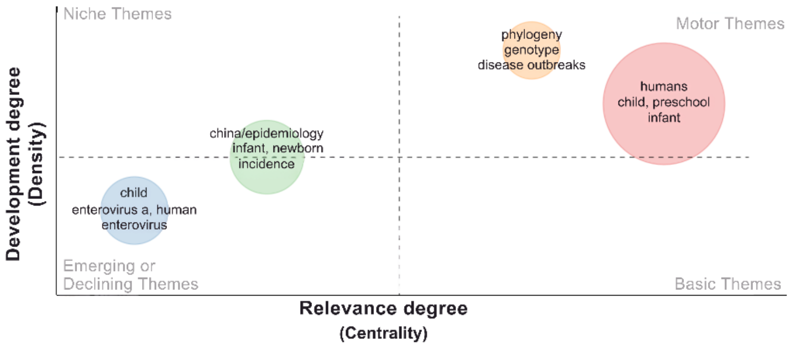


Figure 5. Thematic Map and Thematic Evolution: (a) Thematic Map of the top 250 most frequent words; (b) Thematic Evolution of the top 250 most frequent word; (c) Thematic Maps on three time periods.

In 2014, publications on genome-wide association studies and gene polymorphisms related to HFMD susceptibility and severity also began to appear, and more were published in 2020 [46]. Those research aimed to investigate the association between single nucleotide polymorphisms (SNPs) on the severity of EV71 and CA16 infections and the expression of interleukin-10 (IL-10), for example in the type I IFN receptor 1 (IFNAR1) gene [47], [2′-5′-oligoadenylate synthetase 1 (OAS1) rs10774671[41], OAS3 rs1859330 G/A [48], IL-10-592 [49], scavenger receptor class B member 2 (SCARB2)[50], toll-like receptor 3 (TLR3) [51], and interferon-induced transmembrane protein 3 (IFITM3) [52]. Since 2017, research subjects on machine learning have been published; however, not as frequently as polymorphism research. Researchers attempted to develop an algorithm that has a high level of sensitivity, specificity, accuracy, and area under the receiver operating characteristic/ROC curve (AUC) in identifying and predicting the risk of HFMD severity in children from electronic medical record data [53–55].

HFMD-related keywords mapping with VOSviewer

Figure 6a maps keywords/terms extracted from titles and abstracts in 1.029 PubMed documents related to HFMD. Among 17,879 terms, 1,364 were detected appearing more than five times. Of the 1.364 terms, 60% were considered the most relevant. Eventually, 818 terms were selected. After passing the data cleaning stage, where terms with the same meaning were considered one word, the remaining 751 terms were mapped and divided into five clusters. Cluster 1 (red) contains 189 terms with environmental categories, such as air pollution, climate change, daily temperature, high-risk area, HFMD transmission, rainfall, socioeconomic factors, urban areas, weather factors, wind speed, and several names of cities/regions in China. Cluster 2 (green) contains 176 terms with categories of signs, symptoms, and complications of disease, such as acute flaccid paralysis, atopic dermatitis, cardiopulmonary complication, central nervous system complication, encephalomyelitis, febrile illness, hyperglycemia, hypertension, leukocytosis, maculopapular rash, onychomadesis, pulmonary edema, seizure, tachycardia, tremor, and tachypnea. Cluster 3 (blue) contains 161 terms with genetic categories, such as amino acid sequence, complete genome, genetic diversity, phylogeny, mutation, molecular epidemiology, viral RNA, and several strains of coxsackievirus & enterovirus. Cluster 4 (yellow) contains 137 terms with categories of examinations and markers, such as biomarker, CD4, IgG, IgM, enzymes, cytokines, chemokines, cerebrospinal fluid, inflammation, interferon, interleukin, tumor necrosis factor, T cells, single nucleotide polymorphism, and peripheral blood mononuclear cell. Cluster 5 (purple) contains 88 terms with treatment categories, such as antiviral drugs, monoclonal antibodies, vaccination, and neutralizing antibody titer.

In Figure 6b, the terms/keywords were extracted into a color gradient from purple to yellow, which showed the year of publication from old to new. The node size was directly proportional to the occurrence frequency of the term. A larger node indicated higher keyword occurrence frequency. In the early years, research focused on the disease's signs, symptoms, and complications. Then, it shifted to examinations and markers. Meanwhile, topics that have emerged in recent years apart from vaccination have not been widely developed, such as genetic diversity, genetic evolution, phylogeny, and whole genome sequence.

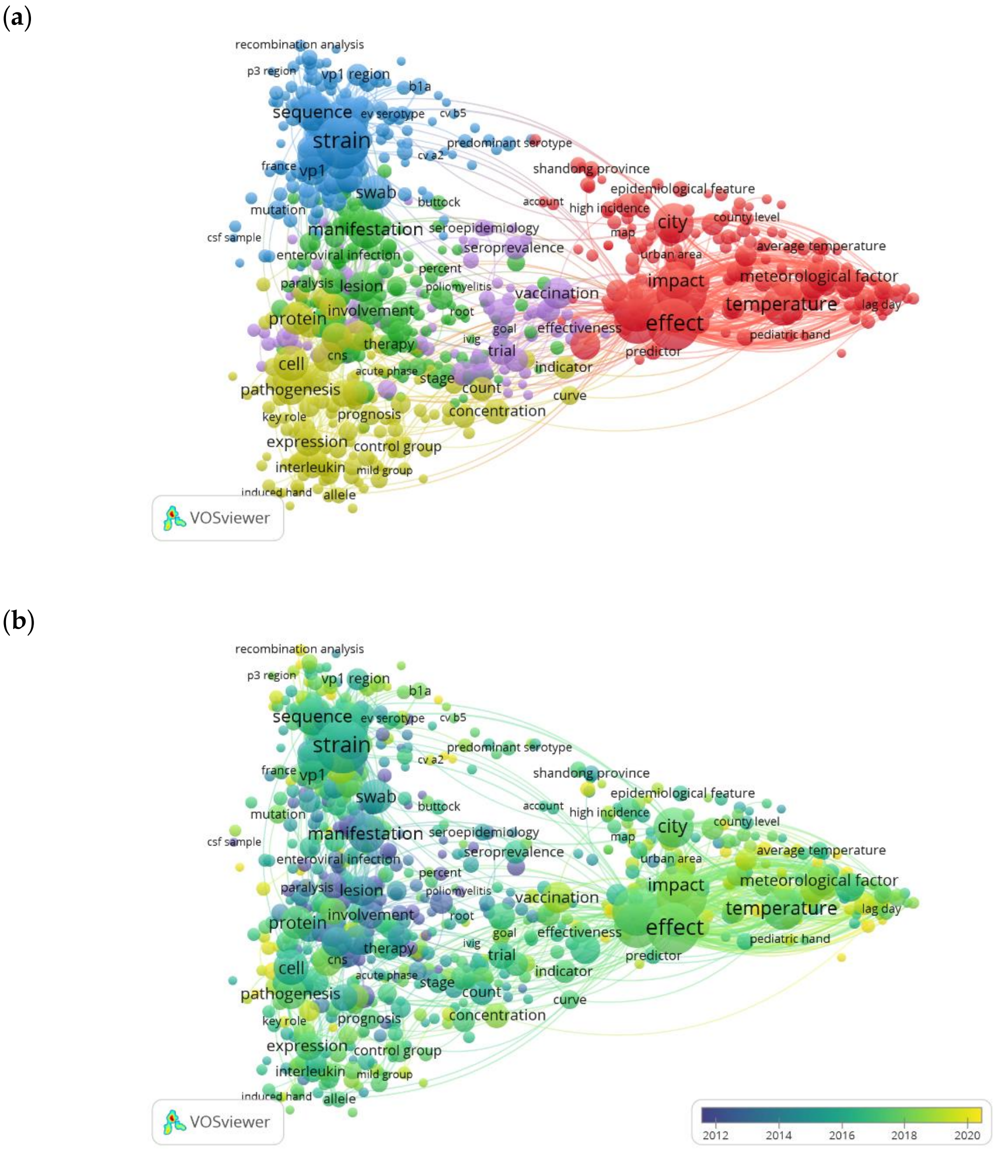


Figure 6. Mapping of keywords extracted from titles and abstracts in HFMD-related research articles using VOSviewer: (a) Network visualization; (b) Overlay visualization.

Despite not ranking highly in the analyses of Biblioshiny and VOSviewer, synbiotic supplementation and machine learning were also intriguing keywords besides gastrointestinal microbiome. These research topics have been widely published since 2019. The study conducted by Li *et al*. (2019) showed that the intestinal mucosal barrier and host immune function could be compromised by gut microbiota dysbiosis, which was characterized by a decrease in butyrate-producing bacteria and an increase in inflammatory bacteria[56–59]. Compared to children in good health, the gut microbiota of HFMD patients was less diverse and abundant[60,61]. The gut microbiota dysbiosis also promoted enterovirus invasion[56]. This issue was considered to exacerbate HFMD cases. Since several studies have found that probiotics are effective as a biotherapeutics substance to overcome gut microbiota dysbiosis, which may cause several diseases, for instance, dyslipidemia[62] and immune system disorders, Zhang *et al*. (2019) thought that synbiotic supplements administration to children with severe HFMD might be helpful[63]. Unfortunately, investigations on the gut microbiota profile of HFMD patients are relatively uncommon in a large population[10]. However, this opens novel areas of research related to HFMD that can be massively developed in the future.

▪ CONCLUSION

The key trends in research focus have been identified through this bibliometric analysis of the literature on Hand, Foot, and Mouth Disease (HFMD) in children from 1997 to 2024. The study shows a significant concentration of research on epidemiology, clinical symptoms, and vaccine development, while studies on gut microbiota dysbiosis which was considered to exacerbate HFMD cases remain underexplored. Therefore, innovative treatments such as synbiotic supplements have not been widely developed. The analysis predicts that future HFMD research is likely to shift toward genome studies with the assistance of machine learning in developing synbiotic supplements that can reduce the risk of HFMD severity. Briefly, addressing these research gaps is essential for improving treatment strategies and ultimately reducing the global burden of HFMD in children.

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REFERENCES

[1] Direktorat Jenderal Pelayanan Kesehatan. “Mengenal penyakit tangan, kaki, dan mulut (flu Singapura),” accessed February 5, 2024. https://yankes.kemkes.go.id/view_artikel/944/mengenal-penyakit-tangan-kaki-dan-mulut-flu-singapura.

[2] Y. Wu, T. Wang, M. Zhao, S. Dong, S. Wang, and J. Shi, “Spatiotemporal cluster patterns of hand, foot, and mouth disease at the province level in Mainland China, 2011–2018,” *PLoS One*, vol. 17, no. 8, pp. 1–25, 2022.

[3] Y. Xu, Y. Zheng, W. Shi, L. Guan, P. Yu, J. Xu, *et al.*, “Pathogenic characteristics of hand, foot and mouth disease in Shaanxi Province, China, 2010–2016,” *Scientific Reports*, vol. 10, no. 989, pp. 1–11, 2020.

[4] A. Sharma, V. K. Mahajan, K. S. Mehta, P. S. Chauhan, S. Manvi, and A. Chauhan, “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 Dermatology Online Journal,* vol. 13, no. 3, pp. 310–320, 2022.

[5] X. F. Wang, J. Lu, X. X. Liu, and T. Dai, “Epidemiological features of hand, foot and mouth disease outbreaks among Chinese preschool children: a meta-analysis,” *Iranian Journal of Public Health*, vol. 47, no. 9, pp. 1234–1243, 2018.

[6] L. Yi, H. Zeng, H. Zheng, J. Peng, X. Guo, L. Liu, *et al.*, “Molecular surveillance of coxsackievirus A16 in Southern China, 2008–2019,” *Archives of Virology*, vol. 166, no. 6, pp. 1653–1659, Jun. 2021.

[7] University of Oxford. “Hand, foot and mouth diseases in Indonesia,” accessed February 12, 2024. https://www.research.ox.ac.uk/map/hand-foot-and-mouth-diseases-in-indonesia.

[8] L. Huang, T. Wang, X. Liu, Y. Fu, S. Zhang, Q. Chu, *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*, vol. 22, no. 1468, pp. 1–10, 2022.

[9] J. Wang, L. Jiang, C. Zhang, W. He, Y. Tan, and C. Ning, “The changes in the epidemiology of hand, foot, and mouth disease after the introduction of the EV-A71 vaccine,” *Vaccine*, vol. 39, no. 25, pp. 3319–3323, 2021.

[10] X. Guo, Z. Lan, Y. Wen, C. Zheng, Z. Rong, T. Liu, *et al.*, “Synbiotics supplements lower the risk of hand, foot, and mouth disease in children, potentially by providing resistance to gut microbiota dysbiosis,” *Frontiers in Cellular and Infection Microbiology*, vol. 11, pp. 1–12, 2021.

[11] C. Shen, Y. Xu, J. Ji, J. Wei, Y. Jiang, Y. Yang, *et al.*, “Intestinal microbiota has important effect on severity of hand foot and mouth disease in children,” *BMC Infectious Diseases*, vol. 21, no. 1062, pp. 1–16, 2021.

[12] R. Zakaria, A. Ahmi, A. H. Ahmad, Z. Othman, K. F. Azman, C. B. Ab Aziz, *et al.*, “Visualising and mapping a decade of literature on honey research: bibliometric analysis from 2011 to 2020,” *Journal of Apicultural Research*, vol. 60, no. 3, pp. 359–368, 2021.

[13] CDC. "Centers for Disease Control and Prevention 2021 Child development: preschooler (3-5 years old) | CDC," accessed February 13, 2024. https://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/preschoolers.html.

[14] S. H. Wei, Y. P. Huang, M. C. Liu, T. P. Tsou, H. C. Lin, T. L. Lin, *et al*., "An outbreak of coxsackievirus A6 hand, foot, and mouth disease associated with onychomadesis in Taiwan, 2010," *BMC Infectious Diseases*, vol. 11, no. 346, pp. 1–6, 2011.

[15] T. J. Treangen and S. L. Salzberg, "Repetitive DNA and next-generation sequencing: computational challenges and solutions," *Nature Reviews Genetics*, vol. 13, no. 1, pp. 36–46, 2011.

[16] F. Syahbanu, P. E. Giriwono, R. R. Tjandrawinata, and M. T. Suhartono, "Molecular analysis of a fibrin-degrading enzyme from Bacillus subtilis K2 isolated from the Indonesian soybean-based fermented food moromi," *Molecular Biology Reports*, vol. 47, no. 11, pp. 8553–8563, 2020.

[17] W. T. Ismaya, R. R. Tjandrawinata, and H. Rachmawati, "Lectins from the edible mushroom *Agaricus bisporus* and their therapeutic potentials," *Molecules*, vol. 25, no. 2368, pp. 1–16, 2020.

[18] W. T. Ismaya, R. R. Tjandrawinata, B. W. Dijkstra, J. J. Beintema, N. Nabila, and H. Rachmawati, "Relationship of *Agaricus bisporus* mannose-binding protein to lectins with β-trefoil fold," *Biochemical and Biophysical Research Communications*, vol. 527, no. 4, pp. 1027–1032, 2020.

[19] F. Nailufar, R. R. Tjandrawinata, and M. T. Suhartono, "Thrombus degradation by fibrinolytic enzyme of Stenotrophomonas sp. originated from Indonesian soybean-based fermented food on Wistar rats," *Advances in Pharmacological and Pharmaceutical Sciences,* vol. 2016, no. 4206908, pp. 1–9, 2016.

[20] J. Puenpa, A. Theamboonlers, S. Korkong, P. Linsuwanon, C. Thongmee, S. Chatproedprai, *et al*., "Molecular characterization and complete genome analysis of human enterovirus 71 and coxsackievirus A16 from children with hand, foot and mouth disease in Thailand during 2008-2011," *Archives of Virology*, vol. 156, no. 11, pp. 2007–2013, 2011.

[21] D. Zhang, J. Lu, and J. Lu, "Enterovirus 71 vaccine: close but still far," *International Journal of Infectious Diseases*, vol. 14, no. 9, pp. e739–e743, 2010.

[22] C. Yang, C. Deng, J. Wan, L. Zhu, and Q. Leng, "Neutralizing antibody response in the patients with hand, foot and mouth disease to enterovirus 71 and its clinical implications," *Virology Journal*, vol. 8, no. 306, pp. 1–6, 2011.

[23] R. R. Tjandrawinata, L. W. Susanto, and D. Nofiarny, "The use of *Phyllanthus niruri* L. as an immunomodulator for the treatment of infectious diseases in clinical settings," *Asian Pacific Journal of Tropical Disease*, vol. 7, no. 3, pp. 132–140, 2017.

[24] R. R. Tjandrawinata, A. W. Amalia, H. Tuna, V. N. Said, and S. Tan, "Molecular mechanisms of network pharmacology-based immunomodulation of huangqi (*Astragali Radix*)," Jurnal Ilmu Kefarmasian Indonesia, vol. 20, no. 2, pp. 184–195, 2022.

[25] J. Li, J. Yang, X. Fan, Z. Sun, Y. Sun, H. Li, *et al*., "Genetic analysis of the P1 region of human enterovirus 71 strains and expression of the 55 F strain VP1 protein," *Virologica Sinica*, vol. 27, no. 1, pp. 10–18, 2012.

[26] X. Liu, N. Mao, W. Yu, Q. Chai, H. Wang, W. Wang, *et al*., "Genetic characterization of emerging coxsackievirus A12 associated with hand, foot and mouth disease in Qingdao, China," *Archives of Virology*, vol. 159, no. 9, pp. 2497–2502, 2014.

[27] L. Deng, H. L. Jia, C. W. Liu, K. H. Hu, G. Q. Yin, J. W. Ye, *et al*., "Analysis of differentially expressed proteins involved in hand, foot and mouth disease and normal sera," *Clinical Microbiology and Infection*, vol. 18, no. 6, pp. E188–E196, 2012.

[28] J. Hyeon, S. Hwang, H. Kim, J. Song, J. Ahn, B. Kang, *et al*., "Accuracy of diagnostic methods and surveillance sensitivity for human enterovirus, South Korea, 1999–2011," *Emerging Infectious Diseases*, vol. 19, no. 8, pp. 1268–1275, Aug. 2013.

[29] B. Bai, H. Shen, Y. Hu, J. Hou, Z. Liu, R. Li, *et al*., "Serological survey of a new type of reovirus in humans in China," *Epidemiology and Infection*, vol. 142, no. 10, pp. 2155–2158, 2014.

[30] W. Li, L. Yi, J. Su, J. Lu, C. Ke, H. Zeng, *et al*., "Seroprevalence of human enterovirus 71 and coxsackievirus A16 in Guangdong, China, in pre- and post-2010 HFMD epidemic period," *PLoS One*, vol. 8, no. 12, pp. 1–7, 2013.

[31] J. Liu, P. Huang, Y. He, W. Hong, X. Ren, X. Yang, *et al*., "Serum amyloid A and clusterin as potential predictive biomarkers for severe hand, foot and mouth disease by 2D-DIGE proteomics analysis," *PLoS One*, vol. 9, no. 9, pp. 1–9, 2014.

[32] L. V. Akhmadishina, T. P. Eremeeva, O. E. Trotsenko, O. E. Ivanova, M. I. Mikhailov, and A. N. Lukashev, "Seroepidemiology and molecular epidemiology of enterovirus 71 in Russia," *PLoS One*, vol. 9, no. 5, pp. 1–6, 2014.

[33] M. Cabrerizo, D. Tarragó, C. Muñoz-Almagro, E. Amo, M. Domínguez-Gil, J. M. Eiros, *et al.*, "Molecular epidemiology of enterovirus 71, coxsackievirus A16 and A6 associated with hand, foot and mouth disease in Spain," *Clinical Microbiology and Infection,* vol. 20, no. 3, pp. O150–O156, 2014.

[34] P. Linsuwanon, J. Puenpa, S. W. Huang, Y. F. Wang, J. Mauleekoonphairoj, J. R. Wang, *et al.*, "Epidemiology and seroepidemiology of human enterovirus 71 among Thai populations," *Journal of Biomedical Science*, vol. 21, no. 1, pp. 1–13, 2014.

[35] Z. Tao, H. Wang, Y. Li, G. Liu, A. Xu, X. Lin, *et al.*, "Molecular epidemiology of human enterovirus associated with aseptic meningitis in Shandong province, China, 2006–2012," *PLoS One*, vol. 9, no. 2, pp. 1–10, 2014.

[36] Y. P. Li, Z. L. Liang, Q. Gao, L. R. Huang, Q. Y. Mao, S. Q. Wen, *et al.*, "Safety and immunogenicity of a novel human enterovirus 71 (EV71) vaccine: a randomized, placebo-controlled, double-blind, phase I clinical trial," *Vaccine*, vol. 30, no. 22, pp. 3295–3303, 2012.

[37] Y. P. Li, Z. L. Liang, J. L. Xia, J. Y. Wu, L. Wang, L. F. Song, *et al.*, "Immunogenicity, safety, and immune persistence of a novel inactivated human enterovirus 71 vaccine: a phase II, randomized, double-blind, placebo-controlled trial," *The Journal of Infectious Diseases*, vol. 209, no. 1, pp. 46–55, 2014.

[38] R. Li, L. Liu, Z. Mo, X. Wang, J. Xia, Z. Liang, *et al.*, "An inactivated enterovirus 71 vaccine in healthy children," *The New England Journal of Medicine*, vol. 370, no. 9, pp. 829–837, 2014.

[39] S. Lu, "EV71 vaccines: a milestone in the history of global vaccine development," *Emerging Microbes & Infections*, vol. 3, no. 4, pp. 1–2, 2014.

[40] F. Zhu, W. Xu, J. Xia, Z. Liang, Y. Liu, X. Zhang, *et al.*, "Efficacy, safety, and immunogenicity of an enterovirus 71 vaccine in China," *The New England Journal of Medicine*, vol. 370, no. 9, pp. 818–828, 2014.

[41] Y. Cai, Z. Ku, Q. Liu, Q. Leng, and Z. Huang, "A combination vaccine comprising of inactivated enterovirus 71 and coxsackievirus A16 elicits balanced protective immunity against both viruses," *Vaccine*, vol. 32, no. 21, pp. 2406–2412, 2014.

[42] Z. Ku, Q. Liu, X. Ye, Y. Cai, X. Wang, J. Shi, *et al.*, "A virus-like particle based bivalent vaccine confers dual protection against enterovirus 71 and coxsackievirus A16 infections in mice," *Vaccine*, vol. 32, no. 34, pp. 4296–4303, 2014.

[43] S. Sun, L. Jiang, Z. Liang, Q. Mao, W. Su, H. Zhang, *et al.*, "Evaluation of monovalent and bivalent vaccines against lethal enterovirus 71 and coxsackievirus A16 infection in newborn mice," *Human Vaccines & Immunotherapeutics*, vol. 10, no. 10, pp. 2885–2895, 2014.

[44] D. Liu, K. Leung, M. Jit, H. Yu, J. Yang, Q. Liao, *et al.*, "Cost-effectiveness of bivalent versus monovalent vaccines against hand, foot and mouth disease," *Clinical Microbiology and Infection*, vol. 26, no. 3, pp. 373–380, 2020.

[45] Y. Lee, Y. Lee, J. Seong, A. Stanescu, and C. S. Hwang, "A comparison of network clustering algorithms in keyword network analysis: a case study with geography conference presentations," *International Journal of Geospatial and Environmental Research*, vol. 7, no. 3, pp. 1–14, 2020.

[46] Y. Meng, T. Xiong, R. Zhao, J. Liu, G. Yu, J. Xiao, *et al.*, "Genome-wide association study identifies TPH2 variant as a novel locus for severe CV-A6-associated hand, foot, and mouth disease in Han Chinese," *International Journal of Infectious Diseases*, vol. 98, pp. 268–274, 2020.

[47] R. Zou, G. Zhang, S. Li, W. Wang, J. Yuan, J. Li, *et al.*, "A functional polymorphism in IFNAR1 gene is associated with susceptibility and severity of HFMD with EV71 infection," *Scientific Reports*, vol. 5, no. 18541, pp. 1–10, 2015.

[48] Y. Tan, T. Yang, P. Liu, L. Chen, Q. Tian, Y. Guo, *et al.*, "Association of the OAS3 rs1859330 G/A genetic polymorphism with severity of enterovirus-71 infection in Chinese Han children," *Archives of Virology*, vol. 162, no. 8, pp. 2305–2313, 2017.

[49] N. Zhao, H. Chen, Z. Chen, J. Li, and Z. Chen, "IL-10-592 polymorphism is associated with IL-10 expression and severity of enterovirus 71 infection in chinese children," *Journal of Clinical Virology*, vol. 95, pp. 42–46, 2017.

[50] X. Wang, H. Liu, Y. Li, R. Su, Y. Liu, and K. Qiao, "Relationship between polymorphism of receptor SCARB2 gene and clinical severity of enterovirus-71 associated hand-foot-mouth disease," *Virology Journal*, vol. 18, no. 132, pp. 1–10, 2021.

[51] G. P. Chen, K. Xiang, L. Sun, Y. L. Shi, C. Meng, L. Song, *et al.*, "TLR3 polymorphisms are associated with the severity of hand, foot, and mouth disease caused by enterovirus A71 in a Chinese children population," *Journal of Medical Virology*, vol. 93, no. 11, pp. 6172–6179, 2021.

[52] M. Li, Y. P. Li, H. L. Deng, M. Q. Wang, Y. Chen, Y. F. Zhang, *et al.*, "DNA methylation and SNP in IFITM3 are correlated with hand, foot and mouth disease caused by enterovirus 71," *International Journal of Infectious Diseases*, vol. 105, pp. 199–208, 2021.

[53] G. Liu, Y. Xu, X. Wang, X. Zhuang, H. Liang, Y. Xi, *et al.*, "Developing a machine learning system for identification of severe hand, foot, and mouth disease from electronic medical record data," *Scientific Reports*, vol. 7, no. 16341, pp. 1–9, 2017.

[54] Y. Wang, Z. Cao, D. Zeng, X. Wang, and Q. Wang, "Using deep learning to predict the hand-foot-and-mouth disease of enterovirus A71 subtype in Beijing from 2011 to 2018," *Scientific Reports*, vol. 10, no. 12201, pp. 1–10, 2020.

[55] B. Zhang, X. Wan, F. Ouyang, Y. D. Hao, D. Luo, J. Liu, *et al.*, "Machine Learning Algorithms for Risk Prediction of Severe Hand-Foot-Mouth Disease in Children," *Scientific Reports*, vol. 7, no. 5368, pp. 1–8, 2017.

[56] W. Li, Y. Zhu, Y. Li, M. Shu, Y. Wen, X. Gao, *et al.*, "The gut microbiota of hand, foot and mouth disease patients demonstrates down-regulated butyrate-producing bacteria and up-regulated inflammation-inducing bacteria," *Acta Paediatrica*, vol. 108, no. 6, pp. 1133–1139, 2019.

[57] P. Rahayu, L. Agustina, and R. R. Tjandrawinata, "Tacorin, an extract from Ananas comosus stem, stimulates wound healing by modulating the expression of tumor necrosis factor α, transforming growth factor β and matrix metalloproteinase 2," *FEBS Open Bio*, vol. 7, no. 7, pp. 1017–1025, 2017.

[58] P. Rahayu, F. Marcelline, E. Sulistyaningrum, M. T. Suhartono, and R. R. Tjandrawinata, "Potential effect of striatin (DLBS0333), a bioactive protein fraction isolated from *Channa striata* for wound treatment," *Asian Pacific Journal of Tropical Biomedicine*, vol. 6, no. 12, pp. 1001–1007, 2016.

[59] Y. Yuliana, O. M. Tandrasasmita, and R. R. Tjandrawinata, "Anti-inflammatory effect of predimenol, a bioactive extract from *Phaleria macrocarpa*, through the suppression of NF-κB and COX-2," *Recent Advances in Inflammation & Allergy Drug Discovery*, vol. 15, no. 2, pp. 99–107, 2022.

[60] S. Y. Zhu, Y. Z. Jiang, N. Shen, M. Li, H. J. Yin, and J. B. Qiao, "Changes in the intestinal microbiota of children with hand, foot, and mouth disease under 3 years old," *Medicine (Baltimore),* vol. 102, no. 18, pp. 1–6, 2023.

[61] Y. Zhuang, Y. Lin, H. Sun, Z. Zhang, T. Wang, R. Fan, *et al.*, "Gut microbiota in children with hand foot and mouth disease on 16S rRNA gene sequencing," *Current Microbiology*, vol. 80, no. 159, pp. 1–8, 2023.

[62] R. R. Tjandrawinata, M. Kartawijaya, and A. W. Hartanti, "*In vitro* evaluation of the anti-hypercholesterolemic effect of Lactobacillus isolates from various sources," *Frontiers in Microbiology*, vol. 13, no. 825251, pp. 1–10, 2022.

[63] H. Zhang, L. Zhang, J. Xie, W. Wen, L. Wei, and B. Nie, "Probiotics supplement in children with severe hand, foot, and mouth disease," *Medicine (Baltimore)*, vol. 98, no. 45, pp. 1–3, 2019.