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Correspondence

Hand-foot-and-mouth disease (HFMD) in children. Current scenario, and advancements in developing vaccines and therapeutics: An update – Correspondence

Dear Editor,

Hand, foot, and mouth disease (HFMD) is a highly contagious disease caused by viruses of the genus *Enterovirus*, family *Picornaviridae*, especially serotypes coxackivirus A16 (CVA16), A6 (CVA6) and enterovirus 71 (EV71). The disease was first recognized in New Zealand in 1956 and afterwards spread widely. Currently, HFMD outbreaks occur frequently in Asia-Pacific region including Australia, Cambodia, China, Japan, India, Malaysia, Taiwan, Singapore, Thailand and Vietnam [1,2]. In recent times, cases of HFMD have been reported to be increasing. In 2008, China categorized HFMD as a class C infectious disease [3,4]. Although the causative virus may infect human of all ages, the disease mainly occurs in infants and young children (under five). For example, in the HFMD outbreak in Malaysia as of June 2022, 90% of 74,841 cases were children of 6 years and less, 8% (6520 cases) were 7–12 years old, and 2% (1485 cases) were above 12 years (https://www.malaysianow.com/news/2022/06/07/over-82800-hfmd-cases-reported-as-of-june-4/).

This disease is usually most contagious during the first week of infection. It is common in summer, but children may get it any time of the year. HFMD outbreaks usually start in a kindergarten or daycare center. Common clinical manifestations include mild fever, malaise, rashes/blisters on skin especially the buttock region, hands, legs, feet, around the mouth, and particularly on oral and throat mucosae and tongue which cause painful sores in the mouth and throat. Sores in the mouth often ulcerate. In most cases, the disease resolves spontaneously within 7–10 days after symptomatic treatment. Complications of HFMD are rare, including dehydration, viral meningitis, loss of fingernail or toenail, encephalitis (swelling of the brain), and paralysis [5,6]. However, EV71 infections may be complicated by severe neurological (encephalitis, polio-like syndrome, Guillain-Barre syndrome, acute transverse myelitis, and acute cerebellar ataxia), cardiovascular and respiratory symptoms which are life-threatening [7,8]. The HFMD-causing viruses spread easily through person-to-person contact, respiratory droplets, blister fluid/scabs, feces, and fomites [5]. There is no direct-acting anti-enterovirus drug to treat HFMD infection or EV71-associated severe manifestations [3,5]. Frequent hand washing with soap may prevent/minimize virus spread after dealing with infected children and contaminated materials.

Annotated epidemiological data indicates that HFMD seems to affect slightly more males than females. There lies differences in transmissibility of HFMD as is evident at county levels in the Jiangsu province, China. Such differences may be associated with weather and climate change, virus subtypes, demographic features, background immunity/health conditions, sanitary measures and other infectious diseases prevailing in the environment [1]. Outbreaks with case fatalities have been reported from many countries, e.g., Malaysia (1997), Taiwan (1998), Singapore and Maldives (2007), China (2008) (https://ncdc.gov.in/WriteReadData/linkimages/July08475966895.pdf). HFMD outbreaks have also been reported in Spain during 2010–2012, wherein all the EV71 strains belonged to subgenogroup C2. It was concluded that the emergence of HFMD in European countries, including Spain, was due to a greater incidence of CVA6 and CVA16 circulation along with exposure to newer variants of such viruses [9]. CVA16 is the most common cause for HFMD as compared to CA6 [5]. In India, during 2012–2014, HFMD was reported in states of Gujarat and Maharashtra. Genetic analysis revealed predominantly CVA16 subgenotype B1c, CVA6 sub-lineage E2, and EV71 subgenotype C1 [10]. There is a report on emergence of CVA6 and CVA10 in outbreaks and sporadic infections in the recent past, especially in India and Southeast Asia apart from Europe [11]. Recently in the United States and various parts of the world, CVA6 has emerged as the main cause of HFMD outbreaks [12]. In April and May 2022, an HFMD outbreak was observed in several provinces of India, such as Kerala, Maharashtra, and Odisha (the disease was initially called "Tomato Fever or Tomato Flu" (https://www.thehindu.com/news/national/kerala/hfmd-alert-issued-in-kollam/article65391685.Ece). In the outbreak in Orissa, 26 children (1–9 years old) were infected (https://economictimes.indiatimes.com/news/india/26-tomato-flu-cases-in-odisha/articleshow/91767727.cms).

Samples collected from patients' throats, blisters and feces are used for HFMD diagnosis (https://www.cdc.gov/hand-foot-mouth/about/signs-symptoms.html). The HFMD-causing virus is detected in stool about six weeks post infection. Virus isolation/detection may be carried out using confluent monolayer of Vero, rhabdomyosarcoma (RD) or MRC5 cells. Cytopathic effects (CPE) caused by enteroviruses are cell rounding, clumping, and/or detaching. An immunofluorescence test can serve as a confirmatory test (https://ncdc.gov.in/WriteReadData/linkimages/July08475966895.pdf). Light microscopy of biopsies or vesicle scrapings is used to differentiate HFMD-causing viruses from herpes simplex and varicella zoster viruses [12,13]. Antibody detection is not adequate to diagnose HFMD, but may be used to differentiate EV71 from coxsackieviruses due to prognostic significance. However, IgG levels may be used to monitor recovery. Real-time PCRs have been used for diagnosis of HFMD, and along with sequencing of a particular gene segment (*viz.*, VP1–2C region of Coxsackie virus) and dendrogram studies have effectively helped in identification of the virus responsible for the disease [8].

To control a HFMD outbreak, patients need to be isolated at the early stage of case detection. Also, frequent hand washing and better ventilation are essential [14]. Development of vaccines and specific medical treatment options are presently being explored against HFMD [5]. Currently, inactivated EV71 vaccines licensed by the Chinese Food and Drug Administration are available [15] but they are effective against

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only EV71 infections and elicited no protection against the other HFMD-causing enteroviruses [16]. In various Asian countries, clinical trials of a formalin inactivated EV71 vaccine have been conducted. The vaccine was shown to be unprotective against the heterologous CAV16, CVA6 and CVA10. Based on the most widely circulated strains in specific regions, alum adjuvanted-inactivated whole virus vaccines have been prepared with EV71C4a (China), B3 (Singapore), and B4 (Taiwan) strains. Clinical randomized trials of these vaccines conducted on thousands of infants suggested that two doses of such vaccines at 28 days-intervals could provide protection, which can be prolonged for a minimum period of 2 years by administering a third dose. The immune response generated by the EV71 strain C4a-based vaccine can provide cross-protection against subgenotypes B and C, but not against the subgenotype A strains. Moreover, the efficacy of these vaccines against the subgenotypes of EV71 circulating in India and Africa is questionable [17]. In countries of the Asia-Pacific region, immunization with EV71 inactivated vaccine faces considerable hindrances in terms of standardization and vaccine registration, cost, and harmonizing infectious agent measurements as well as surveillance [18].

Several new vaccines for HFMD including DNA-/recombinant vector-, synthetic peptide-/recombinant protein-, live attenuated-, and virus-like particle (VLP)- based vaccines have all been investigated. Live attenuated virus vaccines elicit long-lasting cellular and humoral immunity. However, proper knowledge of virulence factors is required to sufficiently attenuate the vaccine strains to avoid the danger of severe adverse events in the vaccinees. Several attempts have been undertaken in this direction, and it is likely that in the future, strains with adequate attenuation and stability will be accessible for vaccine formulation. The VLP vaccines are in advanced developmental phases [19]. A broadly effective vaccine against enterovirus infection is existentially needed [11]. Further, to prevent diseases caused by two viruses, multiple virus genotypes, development of bivalent and/or multipotent vaccines are required [14]. These can be achieved by altering the virus genome via genetic recombination of the circulating genotypes and subgenotypes that cause HFMD. The viral genome can also be altered to impair the virus spreading ability [6]. Large changes in genetics of circulating HFMD-causing viruses, including antigenic evolution and mutations, should be explored because these can continually alter vaccine efficacy via the immune escape mechanism, resulting in inadequate protection against the sub-genotype contained in the vaccination, and, in particular, against distinct sub-genotype strains. It is possible to address this problem in part by using vaccines that contain a variety of viruses. There is, however, no definitive answer as to which combination is best. Further research is also needed to develop an effective universal vaccine that confer long-term immunity. Current use of vaccination should have numerous elements which are better characterized to determine appropriate administration schedule, correlate protection, determine true duration of induced protection and whether a combination of several viruses creates immunologic interference (antigenic competition) among themselves or vaccines against other diseases [19,20].

It is important to treat symptoms and prevent dehydration by drinking enough liquid while a child is sick. If the immune system of the child is weak, symptoms can be severe and do not improve after ten days, then the parents should contact healthcare providers. Intravenous immunoglobulins (IVIG) have been used for treatment of serious cases of HFMD. It reduces inflammatory response in the disease-associated central nervous system. IVIG has been shown to be particularly beneficial in children with EV71-related encephalitis which involves brain stem along with complications like autonomic nervous system dysfunction and lung edema. This is due to reduced levels of plasma pro-inflammatory cytokines/chemokines (e.g., IFN-γ, IL-6, IL-8, IL-10, IL-13). Unfortunately, the use of IVIG is complicated by antibody-dependent enhancement (ADE), as the IgG3 fraction is not having a neutralizing function; instead, it enhances cellular entry of the EV71 [19,21]. Recently, human single-chain antibodies (devoid of Fc portion) specific to VP4 protein of enteroviruses that prevent virus entry/genome uncoating have been offered as a broadly effective direct-acting anti--enterovirus agent [16]. In children with severe HFMD, dysphagia is a discomforting complication and this can be treated effectively by acupuncture to improve the swallowing process and nutritional level/-status. A liquid mixture of ibuprofen and diphenhydramine may be used to gargle [22,23]. Ribavirin, quinacrine, and amantadine can treat severe cases of EV71 induced HFMD. Pleconaril has also shown promising effects in treating EV71 infection [24]. The prompt medication/IVIG administration with mechanical ventilation are the two key measures to reduce fatality in severe HFMD cases [25]. Infants and children (≤5 years), and especially boys, have been found more susceptible to HFMD, and it is highly recommended to take care of their vulnerability of HFMD [26].

Even though the world battles with COVID -19, some countries also surprisingly recorded fresh outbreaks of new diseases, alerting researchers, health experts, and medical community. From the beginning of this COVID-19 pandemic, children have been additionally stressed as they missed out on an essential part of their lives, that is, playing in the open with their peers, and they have to remain behind closed doors with little scope for socialization which influenced their behavioral pattern greatly [27]. So, this pandemic has adversely affected the future generation and their education and social lives, particularly students in countries with the highest infection rates are the most affected. Amid the ongoing COVID-19 pandemic, HFMD cases in children need to be paid due attention and be tackled by adopting adequate prevention and control measures.

Ethical approval

The authors declare no involvement of animal studies or human participants in the study as it is a compiled letter article.

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Author contribution

RKM, DC: designed the study. SC: made the first draft. RKM, DC, RR, FN, CC: updated the manuscript. KD and WC: reviewed the final draft and edited final. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. Please note that providing a guarantor is compulsory.

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Sandip Chakraborty
Department of Veterinary Microbiology, College of Veterinary Sciences and Animal Husbandry, R.K. Nagar, West Tripura, Tripura, 799008, India

Ranjan K. Mohapatra*
Department of Chemistry, Government College of Engineering, Keonjhar, 758002, Odisha, India

Deepak Chandran
Department of Veterinary Sciences and Animal Husbandry, Amrita School of Agricultural Sciences, Amrita Vishwa Vidyapeetham University, Coimbatore, 642109, Tamil Nadu, India

Rashmi Rana
Department of Research, Sir Ganga Ram Hospital, Delhi, 110060, India

Firzan Nainu
Department of Pharmacy, Faculty of Pharmacy, Hasanuddin University, Makassar, 90245, Indonesia

Chiranjib Chakraborty
Department of Biotechnology, School of Life Science and Biotechnology, Adamas University, Kolkata, West Bengal, India

Wanpen Chaicumpa
Center of Research Excellence in Therapeutic Proteins and Antibody Engineering, Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, 10700, Thailand

Kuldeep Dhama**
Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly, Izatnagar, Uttar Pradesh, 243122, India

* Corresponding author.

** Corresponding author.
E-mail address: ranjank_mohapatra@yahoo.com (R.K. Mohapatra).
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