BJMS
Borneo Journal of Medical Sciences

EDITORIAL

The Need for a Vaccine Against Hand, Foot, and Mouth Disease in Malaysia

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Received: 17 November 2023

Accepted: 23 December 2023

Published: 31 January 2023

DOI: https://doi.org/10.51200/bjms.v17i1.4285

Keywords: *Vaccine, HFND, Disease Genome, Genotype*

Hand, foot, and mouth disease (HFMD) is a contagious viral infection, which commonly affects young children under five years of age (Yu et al., 2019). HFMD is caused by serotypes of the Enterovirus A species, particularly enterovirus 71 (EV71) and coxsackievirus A16 (CVA16), in the genus Enterovirus (Takahashi et al., 2016). Symptoms of HFMD usually include fever, sore throat and maculopapular or vesicular rashes on hands, feet and mouth, which resolve spontaneously. On the other hand, severe HFMD, which is often associated with EV71 infection, can lead to life-threatening cardiopulmonary and neurologic complications (Xu et al., 2015).

Both EV71 and CVA16 are non-enveloped viruses, containing a genome of single-stranded, positive-sense RNA with a single open reading frame (ORF) encoding a polyprotein. This polyprotein is further cleaved to form four structural proteins (VP1-VP4) and seven non-structural proteins (2A-2C, 3A-3D) (Guo et al., 2019). VP1 region is the main neutralising antigenic site and has higher genetic variability than the other capsid proteins, making it desirable for genotyping of enterovirus (Noisumdaeng et al., 2019). Based on the genetic diversity of the VP1 gene, EV71 is classified into seven genogroups (A-G), where genogroups B and C are more widely circulated throughout the world and consist of 11 genotypes, B0-B5 and C1-C5; and two subgenotypes, C4a and C4b (van der Sanden et al., 2016). Meanwhile, CVA16 is classified into two genogroups (A and B), where B is the predominant genogroup

circulating worldwide. Genogroup B is further classified into two genotypes, B1 and B2; and three subgenotypes, B1a-B1c (Zhou et al., 2021).

Studies have shown distinct geographic distribution for these enteroviruses and many genotypes emerge progressively with uneven global distribution. For instance, EV71 genogroups D, G and H were only circulating in South Asia, while genogroups E and F were only found in Africa (Xu et al., 2021). Even within the same region, such as Malaysia and Singapore, the circulating genotypes were different between these countries (Xu et al., 2021). Besides, the predominance of the genotype circulating in a country changes over time. Genotype B3 was the predominant type that was associated with fatal cases in the 1997 HFMD outbreak in Malaysia. Later in 2000, B4 emerged as the predominant genotype and from 2003 onwards, HFMD in Malaysia was mainly caused by genotype B5 (Fong et al., 2021). Genotype changes are also observed in CVA16. Between 1997 and 2014, the predominant genotype of CVA16 found in Malaysia was B2. However, a recent outbreak in Sabah in 2018 witnessed the emergence of subgenotype B1a as the predominant type, which has never been reported in Malaysia (Fong et al., 2021). Apart from that, a study by Ling et al. (2014) found another serotype of enterovirus, namely CVA6, to be the main type that caused HFMD in Seri Kembangan, Malaysia between 2012 and 2013.

Currently, there is no treatment for HFMD and no vaccine is available in Malaysia. Even though HFMD is usually mild and self-limiting, severe HFMD can be an economic burden to the country, society and families of patients. Moreover, the significant rise in HFMD cases in Malaysia (Fong et al., 2021; Fong, 2022; Kaos Jr et al., 2022) can further increase this burden. To date, the world's only EV71 vaccines are China's three inactivated monovalent EV71 vaccines, which are based on the prominent genotype, C4 in the country (Li et al., 2021). Although the vaccine strain belongs to genotype C4, studies have found good cross-neutralisation against other major genotypes (Li et al., 2021), suggesting that China's vaccines can protect people globally against HFMD caused by EV71. However, it was also reported that the three vaccines were not effective against non-EV71 serotypes (Tong et al., 2021). This is a concern since there is an increase in the emergence of non-EV71 serotypes, such as CVA6, CV10 and CVA16, as the main causative pathogens for HFMD. The ultimate goal is to have a globally representative HFMD vaccine that can protect against all major genogroups and genotypes of each enterovirus serotype. Efforts from local governments, international organisations and the pharmaceutical industry are needed to achieve this ultimate goal. Considering the changing epidemiology of HFMD, epidemiological studies are necessary to provide updated information on the current circulating strains, which is crucial for the development of multivalent vaccines.

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