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REVIEW

Hand, foot and mouth disease (HFMD): emerging epidemiology and the need for a vaccine strategy

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Abstract Hand, foot, and mouth disease (HFMD) is a contagious viral disease and mainly affects infants and young children. The main manifestations are fever, vesicular rashes on hand, feet and buttocks and ulcers in the oral mucosa. Usually, HFMD is self-limiting, but a small proportion of children may experience severe complications such as meningitis, encephalitis, acute flaccid paralysis and neurorespiratory syndrome. Historically, outbreaks of HFMD were mainly caused by two enteroviruses: the coxsackievirus A16 (CV-A16) and the enterovirus 71 (EV-A71). In the recent years, coxsackievirus A6 and coxsackievirus A10 have been widely associated with both sporadic cases and outbreaks of HFMD worldwide, particularly in India, South East Asia and Europe with an increased frequency of neurological complications as well as mortality. Currently, there is no pharmacological intervention or vaccine available for HFMD. A formalin-inactivated EV-A71 vaccine has completed clinical trial in several Asian countries. However, this vaccine cannot protect against other major emerging etiologies of HFMD such as CV-A16, CV-A6 and CV-A10. Therefore, the development of a globally representative multivalent HFMD vaccine could be the best strategy.

Keywords HFMD · Enteroviruses · Vaccine · Epidemiology

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Introduction

Hand, foot, and mouth disease (HFMD) is a common contagious disease, affecting mainly children under the age of 10 and adults too, sometimes. The main manifestations are fever, vesicular rashes on hands, feet and buttocks and ulcers in the oral mucosa. Usually, HFMD is self-limiting, but a small proportion of children may experience severe complications such as meningitis, encephalitis, acute flaccid paralysis (AFP) and neurorespiratory syndrome. Therefore, HFMD poses a serious threat to public health mainly in WPRO region [1].

HFMD is caused by enteroviruses (27–30 nm in size) consisting of single-stranded, positive-sense RNA. These viruses belong to the *Picornaviridae* family. Traditionally, human enteroviruses were classified into many groups, based on pathogenicity in humans and laboratory animals and cytopathic effects. Subgroups are polioviruses (3 serotypes), coxsackievirus A viruses (23 serotypes), coxsackievirus B viruses (6 serotypes), echoviruses (28 serotypes) and other enteroviruses [2]. Based on phylogenetic data, human enteroviruses are currently grouped into seven species (human enterovirus A–D and human rhinovirus A–C) encompassing more than 250 serologically distinct viruses [3, 4]. They can manifest themselves in a wide range of diseases, such as cutaneous, visceral and neurological diseases. These viruses can be transmitted by nasal and throat secretions (saliva, sputum, or nasal mucus), blister fluid or stool of infected individuals. The virus can be detected from the stool and pharynx several days before the onset of the illness and continues to shed through the stool for several weeks [5].

The most known HFMD-associated viruses are EV-A71 and CV-A16; however, increasing cases of HFMD due

to other viruses such as CV-A6 and CV-A10 have been reported recently [6–10]. Most of the clinical signs are self-limited and mild with a short incubation period of 3–6 days. Early symptoms are low-grade fever, cough and sore throat progressing gradually to malaise and loss of appetite. After the initial symptoms, the exanthema begins as a papule with blisters and finally becomes an ulcer. The lesion commonly develops inside the mouth including buccal mucosa, hard palate, the surface of the cheeks, gums and tongue, palms and soles of the feet. Occasionally, lesions may appear on buttocks and genital areas also [11].

Even if clinical features are similar during HFMD, some specific aspects have been often associated with particular viruses [12, 13]. The rashes associated with CV-A16 usually appear as large vesicles. In EV-A71 infection, the rashes are petechial and/or papular in nature, mainly on the trunk and limbs. Coxsackievirus A6 infection has a wide range of manifestations including severe or atypical HFMD, and nail shedding during convalescence period [14]. HFMD can cause severe complications including myoclonic seizure, tremor, nystagmus, brainstem encephalitis and polio-like paralytic disease. In some cases, tachycardia, pulmonary edema/hemorrhage and immediate death due to cardiopulmonary failure are also observed [15, 16].

Despite the impact of HFMD on the healthcare system, and HFMD-associated complications during epidemics, there is currently no treatment or effective vaccination. Therefore, developing prophylactic and therapeutic measures for efficient containment of HFMD has become a national priority in many Asia–Pacific countries [17–19]. Based on the global success of poliovirus vaccine, several vaccine researches in the direction of HFMD are in progress, with most of the strategies focusing on a single causative agent [20, 21].

In this review, the time-defined epidemiological dynamics of HFMD is projected, and the vaccine strategies are discussed, with a particular emphasis on the ins and outs of an overall response against HFMD-related agents.

Epidemiology

HFMD was initially reported from New Zealand in 1957 [22]. Since the 1970s, many small and large outbreaks of HFMD have been occurring throughout the world. Based on the surveillance data, CV-A16 was the virus frequently associated with HFMD during the 1970s and 1980s, whereas in the 1990s, it was replaced by EV-A71 [1, 23]. The majority of HFMD outbreaks and deaths were reported from the Asia–Pacific region, including Malaysia, Vietnam, China, Cambodia, India [19]. The first largest comprehensive population-based study on the epidemiology of HFMD was carried out in china [24].

Besides the most common agents, CV-A6 and CV-A10 have also emerged in recent years as important agents of HFMD and complications. CV-A6 and CV-A10 have been widely associated with sporadic cases of HFMD and outbreaks worldwide with increasing number of neurological complications and deaths [9, 25–27]. Even though there are HFMD outbreaks throughout the world, it constitutes a major public health issue especially in Asia–Pacific countries because of its magnitude and severity [1]. Usually, every Asian country experiences at least one HFMD outbreak annually [28].

This part will focus on the epidemiology of HFMD outbreaks due to different viruses with respect to different geographic areas and provide a better understanding of vaccination policies and other control measures.

EV-A71-related HFMD

EV-A71-related HFMD was first detected in Japan during the 1973 and 1978 outbreaks [29]. Since then, outbreaks have been reported worldwide [30]. Larger outbreaks have been reported from several Asia–Pacific countries, Europe and North America [31–35]. Based on the capsid protein VP1, EV-A71 was classified into two major genogroups with different subgenogroups (B0–B5, C1–C5) [30, 36]. Recombination events and virus evolution resulted in identification of new genotypes (D–G), as well as proposed subgenogroups (C6, C7 and B6) [37, 38]. The outbreaks in the Asia–Pacific region were mainly due to B3–B5 and C2–C5 subgenotypes [39]. Most of the cases usually presented as typical HFMD manifestations [1]. Compared to the other agents, complications were more frequently observed [40]. Neurological complications including acute flaccid paralysis were reported during outbreaks [41–46]. The period between 1970 and 2000 saw a large number of EV-A71-associated HFMD outbreaks [47]. China was one of the most affected countries with many outbreaks reported since its first case in 1987 [48]. A severe outbreak also took place in Taiwan in 1998, affecting around 130, 000 children over a period of 8 months [49]. Approximately 6000 children were infected over a period of 6 months in the Perth outbreak, Australia [50]. Large outbreaks or sporadic cases were also reported after 2000 from Singapore, Taiwan, Malaysia, Australia, China and some Asia–Pacific [6, 51–57].

Knowledge regarding the activity of EV-A71-related HFMD outside the Asia–Pacific region is limited. C1, C2 and C4 subgenotypes were mainly associated with HFMD outbreaks in Europe [30]. Most of the EV-A71 infection reports in Europe were severe, with less classical HFMD. The first epidemic was reported in Bulgaria in 1975, with a high rate of paralytic cases and mortality incidents [42].

In 1978, a similar pattern was also observed in Hungary [58]. Recently, Denmark also reported EV-A71 association with HFMD and other complications such as meningitis, encephalitis and sepsis-like illness [59]. EV-A71-associated HFMD is not a major problem in the USA, with only a few reports published so far [60].

HFMD due to coxsackievirus A16

Coxsackievirus A16 was first isolated from South Africa in 1951 [61]. CV-A16 is another important HFMD agent, often circulating alternatively or together with EV-A71. Studies indicated that EV-A71 and CV-A16 coinfection increased the severity of the disease [62]. Usually, the disease associated with CV-A16 is mild, even though severe and complicated HFMD including neurological complications has been also reported globally [63–66]. Molecular epidemiology of CV-A16 has not been well described. CV-A16 has been classified into two genotypes [genotypes A and B] based on the VP1 nucleotide sequence. Genotype B was divided into B1 and B2 and again subdivided into B1a, B1b, B1c, B2a, B2b and B2c [62]. B1a and B1b have reported the predominant genotypes in mainland China and neighboring regions, including Taiwan, Japan, Vietnam, Thailand, Malaysia and Australia [67].

The first HFMD outbreak due to CV-A16 was reported in Toronto in 1957 [68]. Once again, mainland China is the most affected part of the world with more than ten outbreaks of CV-A16 described since 1999 [62]. England and Wales faced a devastating impact of HFMD due to CV-A16 in 1994 [69]. A larger and prolonged morbidity due to HFMD occurred in Taiwan spanning from the year 1999 to 2006 [62]. Other outbreaks were reported in Australia, Thailand, Singapore, Vietnam, India and Japan [70–75].

HFMD due to emerging pathogens CV-A6 and CV-A10

For many decades, HFMD surveillance mainly focused on EV-A71 and CV-A16, but recently CV-A10 and CV-A6 emerged as important HFMD agents worldwide [8] (Table 1).

The first outbreak of CV-A6-associated HFMD was reported in Finland in 2008 [76]. Since then, other reports from Europe including France, the UK, Spain and Finland have been published [10, 12, 77–81].

Many CV-A6 cases have also been reported from the Asia–Pacific region where HFMD is a major public health concern, previously caused by EV-A71 and CV-A16. Indeed, several CV-A6 outbreaks have been noticed in China, India, Singapore, Taiwan, Japan, Thailand and Israel [7, 8, 25, 52, 74, 82–91]. Other parts of the world such as the USA, New Zealand and Cuba were also affected [92–96].

CV-A6 strains isolated from the Shenzhen epidemic, between 2008 and 2012, were classified into seven Clusters; A–F. Predominant strains were D and C, which were the same strain responsible for other outbreaks around the world [97].

In a few patients, including children and adults, the CV-A6-associated HFMD was atypical. The features presented as widespread exanthematous rashes, which can extend to the perioral region, buttocks, trunk, knees, elbows, dorsal and lateral surface of hands and feet and perianal area [12, 25, 82, 83, 92, 98].

In addition, few more atypical clinical features have been frequently described including widespread mucocutaneous bullous reactions mimicking drug adverse reactions, vesiculobullous erosive eruption, severe vasculitis-like rash, rashes similar to eczema herpeticum or chickenpox, or rashes resembling primary immunobullous disease [14, 81, 82, 96, 99]. Most of the CV-A6-related HFMD patients also presented onychomadesis (periodic shedding of the nails) a few weeks after the onset of the disease, followed by desquamation of palms and soles [7, 14, 92, 94, 100]. It can also present as a widespread papular or vesicular eruption with exacerbation in areas of dermatitis in atopic patients [79]. Severe complications such as aseptic meningitis, encephalitis or other neurological complications, and epididymitis have been also associated with CV-A6-related HFMD [25, 87, 101].

The reasons behind this global emergence and these unusual presentations are still unclear. However, viral-specific factors and host factors may play a role [27]. Since the Finnish outbreak in 2008, all the CV-A6 strains reported throughout the world showed high sequence similarities, based on the VP1 region [25, 91, 99]. A detailed genetic analysis of the outbreak in Edinburgh revealed that CV-A6 variants associated with atypical presentations (eczema herpeticum) were genetically distinct from those reported previously in Edinburg and worldwide. Authors found multiple recombinations between structural genes and other parts of the genome [27]. The emergence of recombinant CV-A6 has also been reported in China, where it was shown that recombinant CV-A6 can cause widespread lesions leading to severe disease, thereby acquiring a public health threat status [102]. Nevertheless, a global molecular study is needed to identify genetic variability in CV-A6, which can explain these atypical presentations.

CV-A10 is another enterovirus also considered as an emerging agent of HFMD [103]. Globally, the activity of CV-A10 is observed along with other enteroviruses such as CV-A6 and CV-B3 [8, 10, 104–106]. Circulating genotype of CV-A10 strain varies according to the geography

Table 1 Major reports of CV-A6 from different part of the world

Country/place	Year	Population affected (age in years)	Trend	References
Finland	2008	Pediatric age (10 or below 10 years old)	CV-A6 was found as major pathogen responsible for HFMD during the nationwide outbreak in Finland	[76]
France	2010	2.4 (5 weeks to 14 years old)	The major presentation was herpangina with classical signs of HFMD. CV-A10 and CV-A6 were the major serotypes	[10]
Spain	2010–2012	11 days to 34 years old	CV-A6 was the major agent for outbreaks and sporadic cases of HFMD during this period	[78]
UK	2014	Below 2 years old	All CV-A6 cases associated with atypical HFMD resembling eczema herpeticum or chickenpox	[81]
Orissa, West Bengal, Tamil Nadu and Kerala [India]	2009–2010	4 months to 10 years old	CV-A16 and CV-A6 were found as major agents of HFMD along with rare viral pathogens such as CV-A10, EV-71 and E-9	[84]
Taiwan	2009–2010	<3 years old	CV-A6 clinical symptoms were Herpangina/HFMD with rash beyond the typical site of HFMD	[141]
Singapore	2008–2009	Below 5 years old	CV-A6, CV-A10 and EV-A71 were the major serotypes	[88]
Taiwan	2010	Mean age 2 years old	Coxsackie A6 infection affecting a wide spectrum of skin sites, nail abnormalities and more tissue damage	[7]
China	2010–2012	1–2 years old	Main symptoms of CV-A6-associated HFMD were, fever, maculo-papular/vesicular rash in the perioral, intraoral, buttocks, trunk and knee area	[83]
Thailand	2012	1 month to 38 years old	Majority were coxsackievirus A6-associated HFMD: 32.9 % were caused by coxsackievirus A6, 9.2 % by enterovirus 71, 9.2 % by Coxsackievirus A16 and 17 % by untyped enteroviruses	[98]
California	Nov 2011–Feb 2012	≤18 years old	Coxsackievirus A6 was detected in most of the cases [74 %]. Nail shedding was often associated with HFMD	[142]
North America	2011–2012	1.5 years old (4 months to 16 years old)	CV-A6-associated disease exhibited unusual presentation like a vesiculobullous and erosive eruption. Exanthematous rashes also are seen in the trunk and the perioral region	[96]

of the epidemic, although genotypes B and C were the most common genotype of CV-A10 isolated from mainland China during epidemics [97]. CV-A10 is usually associated with HFMD/herpangina and sometimes with post-HFMD onychomadesis [107]. It can also cause severe forms of HFMD [8].

In conclusion, the epidemiology of HFMD has considerably changed over the last decade, with the emergence of new causative agents. Additionally, coinfection with multiple enteroviruses, recombination events and the lack of effective vaccination could explain the spread of the disease worldwide and the frequent atypical presentations. These unusual clinical features can lead to an incorrect diagnosis by the clinicians. Therefore, effective enterovirus detection and typing methods can be helpful to manage and prevent the disease. An enhanced worldwide epidemiological and laboratory-based surveillance for HFMD is useful to predict the possible outbreak and thus prevent severity and complications.

Prevention and control

Currently, there is no pharmacological intervention or vaccine available for HFMD. The major point for prevention and control is to block viral transmission and prevent severe complications and death. WHO's guidelines on HFMD summarize the prevention and control measures into the following eight items: establishing and strengthening surveillance, conducting educational campaigns on good personal hygiene, providing assistance to childcare organizations during outbreaks, enhancing infection control measures in both healthcare facilities and the community, upgrading the equipment of severe disease's medication and care, regional preparedness and response information exchange during outbreaks, establishing administrative framework beneficial to promoting prevention and control measures, evaluation and monitoring [1].

The development of vaccine or anti-virals against viruses could prove to be one of the effective ways to control and prevent HFMD [108–110]. Several vaccine-related researches are ongoing considering the impact of HFMD on public health.

Ongoing vaccine research on HFMD

Vaccine toward EV-A71

Considering the public health significance of EV-A71, a wide range of experimental EV-A71 vaccine approaches have been studied including formaldehyde-inactivated virus, EV-A71 virus-like particles (VLP), VP1 recombinant protein, VP1 DNA vaccine, vaccine targeting the neutralizing domain, bacterial or viral vector expressing VP1, Vero cell-adapted live attenuated virus and passive immunization with sera from infected individuals [18, 97, 106, 111–116]. Among these, formalin-inactivated EV-A71 virus was found to be more immunogenic [97].

Research and development of the EV-A71 vaccine were carried out in several Asian countries. Based on the success of the inactivated poliovirus vaccine, five EV-A71-inactivated vaccines have also entered into clinical trials. Among them, three companies in mainland China have completed phase III of the clinical trials and two other companies in Taiwan and Singapore have completed phase I of the clinical trials [117–121]. The results from these clinical trials have indicated the EV-A71 vaccine has a high level of safety and immunogenicity. Protective efficacies were over 90 % on EV-A71-associated HFMD and over 80 % on other EV-A71-associated diseases. Two vaccines have received regulatory approval for scaled-up manufacturing and marketing in China. The vaccine manufacturers are also working on developing a standard protocol to facilitate the comparison of the potency and immunogenicity of vaccine candidates [122].

Some of the major challenges for the EV-A71 vaccine are the cross-neutralizing ability of the EV-A71 vaccine and the selection of appropriate vaccine strain. The EV-A71 genotypes and subgenotypes share some common neutralizing epitopes. However, the degree of cross-neutralization depends on the vaccine strain [17]. Moreover, intra- and intertypic recombination is increasingly reported in EV-A71, which may lead to the emergence of a novel genotype that can escape the current vaccine formulations [123].

Another challenge is the durability of neutralizing antibodies induced by the EV-A71 vaccine. The recent clinical trials showed that neutralizing antibody levels declined after 6 months. A booster injection 1 year after vaccination and a third dose at 18 months are highly recommended for long-lasting protection against EV-A71 [17].

Bivalent EV-A71/CV-A16 vaccine

A wide range of vaccine approach has been tried against coxsackievirus A16 infection, including infectious cDNA clone of CV-A16, inactivated whole virus vaccine and CV-A16 virus-Like particle [55, 124, 125]. Most studies succeeded in inducing neutralizing antibodies in experimental animals.

Although a monovalent vaccine containing either EV-A71 or CV-A16 has a protective efficacy over 90 % for EV-A71-associated cases, a bivalent vaccine (EV-A71/CV-A16) has a better chance and could be the preferred choice. This is considering the fact that an HFMD outbreak

can present association with either of the two viruses, EV-A71 or CV-A16. Moreover, there are reports supporting the efficacy of the bivalent vaccine in inducing strong neutralizing antibodies against both the viruses in animals [126]. However, one of the limitations of bivalent vaccine is that it failed to neutralize other HFMD agents such as CV-A6 and CV-A10.

Multivalent HFMD vaccine: between dream and reality

The idea of a multivalent vaccine is the current trend, and the component viruses of such a vaccine should likely be the ones circulating in the community. Therefore, these viruses which are commonly circulating may be considered as a constituent of the upcoming multivalent vaccine preparations. However, in future looking at the epidemiological trends of the HFMD causing viruses, several other multivalent vaccine preparations with varying virus composition can be thought of. During the last decade, most of the HFMD cases across the world are caused by the four major viruses: EV-A71, CV-A16, CV-A6 and CV-A10. Even though ongoing vaccine studies are promising, most current strategies are targeted at only one/two viruses. Unfortunately, as described above, a significant cross-protection was not observed between the viruses. Therefore, a global prevention strategy based on a multivalent vaccine, encompassing all these four viruses, should be introduced. However, several challenges confront the idea of an effective multivalent HFMD vaccine.

Epidemiological challenges

HFMD-related viruses include many genotypes and subgenotypes emerge over time with uneven global distribution. An ideal vaccine should protect against all the major genotypes and subgenotypes of each virus that constitutes the vaccine formulation. The appropriate selection of strains to be included in a vaccine is crucial. Selection should be based on the current epidemiological information available for each virus. For EV-A71, C4 strain could be the best candidate as it showed a high degree of cross-neutralization against all major EV-A71 genotypes and subgenotypes in clinical trials [127]. In addition, C4 is a world prevalent EV-A71 genotype compared to other subgenotypes [2, 128, 129]. Preclinical trials with B genotype of coxsackievirus A16 elicited cross-neutralizing activity against genotypes A and B and could be a possible candidate for multivalent vaccine [130]. The detailed molecular epidemiological study is required to find the circulating genotype for CV-A6 and CV-A10. According to the current epidemiological surveillance data, CV-A6 –C/D and CV-A10 –B/C are possible candidates that could be incorporated in a multivalent vaccine.

However, global epidemiological influenza-like surveillance could also probably be required in case of HFMD in order to update the changing trend, various recombination patterns and the emergence of new variants with more virulence, toward identifying the most appropriate strains for vaccine formulation.

Technical challenges

In order to develop a global multivalent vaccine, it is necessary to establish rapid diagnostic tool and typing methods to identify the HFMD strains circulating in different regions and countries. Moreover, international harmonization of vaccine efficacy testing should also be implemented.

A technologically advanced platform for optimal virus antigen preparation needs to be established. In previous studies, an inactivated virus showed higher immunogenicity in monovalent EV-A71 and monovalent CV-A16 vaccine trials, whereas VLP-based system yielded a better response than an inactivated virus in EV-A71/CV-A16 bivalent vaccine trial without any risk of cross-antibody enhancement [131–133]. Large-scale production of an inactivated virus is more technically challenging and requires improvement in the manufacturing processes including production and downstream purification. The VLP-based strategy remains a good alternative, as successfully implemented for HPV or HBV vaccine [134].

An appropriate animal model for evaluating the vaccine potency is yet another challenge in the development of multivalent vaccine [17]. Several experimental murine and non-human primate models have been developed for HFMD vaccine research [135]. Each of these models has its own advantages and disadvantages. Several mouse models including neonatal suckling mice, virus adapted mice and immunodeficient mice have been used for both CV-A16 and EV-A71, but they did not mimic the human infection [17, 130, 132, 135]. Non-human primate models including cynomolgus, rhesus and green monkeys are susceptible to EV-A71 infection. These species are not suitable for evaluating the neurovirulence and cardiopulmonary complications associated with HFMD. Moreover, ethical issues associated with these models should also be considered [17]. Recent research on a transgenic mouse model, carrying the human SCARB2 receptor, showed promising result during evaluation of the EV-A71 and CV-A16 vaccine. However, CV-A6 and CV-A10 use SCARB2-independent pathway for infection [136]. In future, the transgenic system could be a promising model for the multivalent vaccine, providing a detailed study on HEV–A receptors and coreceptors.

Immunological challenges

The neutralizing antibody levels and duration of protection are critical in vaccine development. In phase III EV-A71 vaccine clinical trials using a formaldehyde-inactivated virus, protection only lasted 6 months after two doses with antibody levels below 1/16 after this period [122]. No data are currently available for enterovirus VLP-based vaccine candidates. Even though VLP vaccines can be highly immunogenic as seen in HPV and HBV, the booster doses are still necessary for long-term protection [137]. An immunization strategy depending on the age and number of doses needs to be optimized. Approximately 50 % of neonates have significant anti-EV-A71 antibody levels at birth, but the maternal protection declines rapidly after 6 months [138]. Therefore, the ideal age for vaccination should be on or before 6 months of age. Considering the duration of protection, the booster doses are necessary to cover the period of maximum HFMD incidence, i.e., between one and 2 years of age. The vaccine might also be coadministered along with other pediatric vaccines such as diphtheria, tetanus, pertussis, poliovirus, hepatitis B, hemophilus influenza B. Studies are needed to understand whether coadministration of multivalent HFMD vaccine can alter the protection of these pediatric vaccines. However, clinical trials with EV-A71 candidate vaccine did not influence preexisting anti-CV-A16 or anti-polio antibody levels [117–119].

Economic aspects

Until recently, HFMD was a public health concern with high burden only in the Asia–Pacific region. Therefore, most of the efforts to develop a preventative solution were focused on that region. Currently, considering the emergence of new HFMD agents such as CV-A6 and CV-A10, and particularly their worldwide spread, including western countries, this disease attracted more attention in terms of preventative strategies. However, the distribution of each HFMD agent is still uneven in different parts of the world and continues to change over time. In such situations, monovalent vaccines no longer seem effective in containing a disease with varied etiological associations, with a wider global presence. The development of multivalent HFMD vaccine could be an economically interesting opportunity for manufacturers since it can target a large market. With the enhancement of technologies in vaccine manufacturing platforms, it is thought that multivalent HFMD vaccine could easily be cost-effective, and in the context of a scaled-up production, the cost per dose would be minimum [139, 140].

Even in developing countries, a cost-effective multivalent vaccine is accessible, and with the partnership of international agencies such as the WHO, such vaccine should be included in the national immunization program in resource-limited areas. With a global market extending beyond the Asia–Pacific region, the vaccine manufacturing companies will be more interested in investing, developing and marketing HFMD vaccine.

Conclusion and perspective

Even after the successful eradication of poliovirus virtually from all countries in the world, the non-polio enteroviruses-related diseases such as HFMD continue to be a public health threat. HFMD can be associated with a higher morbidity rate and can lead to severe complications. This disease was earlier restricted mostly to the Asia–Pacific region but, currently, it is prevalent worldwide, with the involvement of new enterovirus serotypes. Considering the severe complication associated with EV-A71, new available vaccine(s) against EV-A71 should be used and evaluated (impact on the reduction in severe cases) and a possible “replacement” by other enteroviruses (causing severe HFMD) should be monitored over a couple of years.

Given the changing epidemiology of HFMD, a global solution focusing on a multivalent HFMD vaccine, designed to target the major viruses involved, should be the ultimate goal.

Some challenges need to be overcome, but there is hope in the direction of manufacturing and marketing of a multivalent HFMD vaccine. Governments and international health organizations should join their efforts with the vaccine industries to achieve this goal. Epidemiological surveillance of HFMD viruses also needs to be strengthened to allow regular updates with regard to such a multivalent vaccine.

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