Enterovirus EV-A71 Vaccine Licensure: What's next?

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Opinion

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Enteroviruses (EVs) serotypes are non-enveloped, positive-sense, single-stranded RNA viruses within the *Picornaviridae* family. More than one hundred serotypes including polioviruses, coxsackieviruses A (CV-A) and B (CV-B), echoviruses (E) and numbered enterovirus serotypes (EV) are responsible for a spectrum of various clinical manifestations, including severe neurological complications and cardiopulmonary diseases in young children [1-5]. In the past two decades, coxsackievirus A16 (CV-A16) and enterovirus 71 (EV-A71) have been the predominant etiologic agents of herpangina (HA) and hand, foot and mouth disease (HFMD) epidemics [5-7]. Several other enterovirus serotypes frequently co-circulate with EV-A71 and CV-A16 in sporadic and large epidemics [5]. HFMD has become a major health issue and a substantial economic burden throughout the AsiaPacific region [4,5,7]. Following the near complete eradication of poliovirus, EV-A71 has emerged as a major neurotropic virus responsible for severe neurological complications and fatal outcomes and has been recognized by WHO as a rising health threat in Asia. In the absence of approved antiviral treatment, the development of an efficacious prophylactic vaccine against EV-A71 was urgently needed.

Enterovirus EV-A71 predominantly infects infants and young children below 5 years of age. The disease is typically characterized by a papulovesicular or maculopapular rash, blisters of the hands, soles, and buttocks associated with painful ulcerative lesions of the mouth but most infectees remain asymptomatic [5]. Highly contagious, the virus is responsible for severe neurological complications including aseptic meningitis, cerebella ataxia, poliomyelitis-like paralysis, Guillain-Barré syndrome, acute brainstem encephalitis, and fulminant neurogenic pulmonary edema/hemorrhage associated with high mortality. Survivors from brain stem encephalitis are at risk of severe neurological sequelae [4,5].

There is only one EV-A71 serotype but there are seven EV-A71 genotypes, A to G. Genotypes B and C have been further subdivided into B0-B5 and C1-C5 subgenotypes, respectively. The VP1 capsid protein contains the major neutralization epitopes and is used for strain identification and evolutionary analyses. Since its isolation in California in 1969, EV-A71 has been the cause of large life-threatening epidemics worldwide, in North America, Europe, Australia, and Asia [4,5,8,9]. In the past decade, cyclic outbreaks of co-circulating or alternating EV-A71 and CV-A16 infections have become a major health problem in particular in the Asia-Pacific region. The nature of EV-A71 genotypes responsible for these epidemics is unpredictable and the co-circulation of different genotypes may lead to recombinant variants with altered virulence and biological properties. Severe EV-A71 outbreaks were earlier reported in the USA, France, Hungary, Greece, Netherlands, Norway, and UK [4,5] and the large epidemics in Malaysia (1997, 2005 and 2008), Singapore (2006, 2008), Taiwan (1998, 2008), southern Vietnam (2005), Ho Chi Minh City (2011) and Cambodia (2012) were associated with severe neurological complications and fatal outcomes. In response to a significant increase in HFMD outbreaks during the last 5 years in Mainland China [10,11], HFMD was declared a class C notifiable infectious disease by the Ministry of Health of China and a national surveillance system was established in 2008 [12]. The dominant epidemic EV-A71 genotype varied depending on the outbreak and the country but C4 has always been the prevalent genotype in Mainland China. No correlation could be established between genotype and disease severity. During the past decade, at least 13 million HFMD cases in mainland China and more than 3,000 deaths were reported [China Center for Disease Control and Prevention, 2016, Available from:

http://www.nhfpc.gov.cn/zhuzhan/yqxx/lists.shtml]. EV-A71 has been the pathogen responsible for the majority of severe cases of neurological HFMD and for 90.2% of the fatal outcomes [7].

Several monovalent candidate EV-A71 vaccines including peptide-, subunit-, DNA-, vector-based vaccines have been in development, but chemically inactivated virions have emerged as the most efficacious and cost-effective vaccines [13]. Although the first cross-neutralizing B4-based vaccine currently in Phase II trial was produced in Taiwan [14,15], three Chinese companies [Vigoo Biological, Sinovac Biotech, and the Institute of Medical Biology, Chinese Academy of Medical Sciences (CAM)] have manufactured C4-based EV-A71 vaccines adjuvanted in alum that were tested in large efficacy trials [12,16-19]. All vaccines were shown to be safe and well tolerated. They were more than 90% efficacious and protected vaccinees against herpangina and EV-A71-related

hospitalization. A 1/16-1/32 neutralizing antibody titer was found to correlate with 50% protection [12]. The Chinese Academy of Medical Sciences (CAMS) and Sinovac Biotech vaccines have been approved by China Food and Drug Administration (CFDA) [1,2,9]. Immune sera from subjects immunized with Vigoo's and Sinovac's vaccines were shown to cross-neutralize recently circulating EV-A71 genotypes/subgenotypes [20]. However, neutralizing antibody titers waned after six months and the vaccines did not protect against CV-A16 infection.

The licensure of EV-A71 vaccines represents a major breakthrough in the prevention of life-threatening HFMD. However, several issues must be given consideration. International efficacy trials need be performed to firmly assess the breadth of the cross-protective ability of the C4-based vaccines against other genotypes and subgeno types circulating in the world in particular in India and Africa where the D, E and F are the predominant genotypes. Although the Sinovac's vaccine has shown an overall efficacy of more than 90% over two years [12], the durability of the protective immune response needs to be further addressed in extended follow-up studies. In this regard, the availability of a correlate of protection from the previous Phase III trials will be most convenient [21]. Results from phase IV studies will help determine whether booster injections are necessary for long-term protection. The production of inactivated whole virions is relatively expensive and difficult to scale-up for mass-immunization. Improvement in downstream processes will be necessary for large-scale vaccine production and to improve cost-effectiveness [5]. However, vaccination at a cost below US$ 12.0-18.0 would be economically cost-effective in China [22]. Virus-like particles (VLPs) are very immunogenic and easier to manufacture in large quantities using yeast expression systems. They have been successfully used to produce commercial hepatitis B virus and human papilloma virus vaccines and they hold promises for the development of the next generations of EV-A71 vaccines.

Because of the high efficacy of the EV-A71 vaccines, recent modeling epidemic dynamics studies of enterovirus genotypes suggest that mass EV-A71 vaccination programs could provide significant benefits in terms of a reduction in the overall HFMD burden [23]. However, HFMD is also caused by cocksackievirus CV-A16 in more than 40% of cases [5,8] and by several other enteroviruses including coxsackieviruses A CV-A2, CV-A3, CV-A4, CV-A5, CV-A6, CV-A8, CV-A9, CV-A10, CV-A12, CV-A14, coxsackieviruses B CV-B1 to CV-B6 and echoviruses E-4, E-5, E-6, E-7, E-9, E-11, E-18, E-25, E-30 [5]. In spite of an effective EV-A71vaccination, HFMD may not be perceived by the public as being controlled and the efficacy of the vaccine may be questioned by parents whose children below the age of six months would need to be vaccinated.

Coxsackievirus A16 is the other major cause of herpangina and HFMD. Although it is usually associated with mild disease, it can be responsible in some outbreaks for severe neurological complications, myocarditis and pneumonia and high morbidity [5,6]. Thus the next objective in enterovirus vaccines research is the development of a bivalent EV-A71/CV-A16 vaccine. Significant efforts have recently focused on the production of bivalent inactivated virions, VLPs or recombinant hybrid EV71/CV-A16 particles. These candidate bivalent vaccines have induced cross-neutralizing immune responses against both viruses and have conferred protection in the mouse model [5].

Recently, CV-A6 and CV-A10 have emerged as prevalent pathogens in a number of HFMD outbreaks and were responsible for severe clinical manifestations [5,6]. Other co-circulating life-threatening enteroviruses such as CV-B3, CV-B5 and E-30 that are associated with HFMD expose children to aseptic meningitis and acute myocarditis due to their neurotropism and cardiovirulence [5].

We were the first to propose that the ultimate goal in enterovirus vaccine development is to produce a multivalent HFMD vaccine combining EV-A71, Coxsackieviruses CV-A16, CV-A6, CV-A10, CV-B3, CV-B5 and Echovirus E30 [5,24,25]. This is a challenging task due to a number of hurdles to overcome. Extensive surveillance and epidemiological studies will have to be conducted at both the national and international levels and will require standardized reagents and harmonized protocols to monitor the emergence of new serotypes, genetic drifts and antigenic variations. The second difficulty is to establish reliable animal challenge models for viruses that use different cell entry receptors. Although current commercial multivalent vaccines contain 3, 8 and 13 different components, multivalent HFMD combination vaccines may be faced with physico-chemical instability and antigenic interference problems. Although the selection of VLPs as immunogens might be the most cost-effective approach for making such a vaccine, significant investments in large scale-up infrastructures will be required, downstream processes will have to be optimized and comprehensive analyses will need to be performed to ensure its economic viability. A close collaboration between Governments, Public Health organizations, research institutions and the vaccine industry will be necessary to give such a project a chance of success [26].

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