Editorial

Sinovac EV71 vaccine: the silver bullet for hand, foot and mouth disease—or not?

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With the imminent eradication of Polio worldwide (1), non-polio enteroviruses have gained traction as a major public health threat during the recent two decades (2-4), commonly manifesting as the hand, foot and mouth disease (HFMD). Associated with infections by a plethora of human enteroviruses (5-9), HFMD is a highly infectious and common childhood affliction in many countries. Endemic countries, particularly in the Asia-Pacific, experience outbreaks of HFMD every 2 to 3 years or even yearly (9-12). These periodic outbreaks have put a strain on the public healthcare infrastructure with increased patient visitation and inconvenience from childcare facility closures, in a bid to contain localized outbreaks.

In the continued absence of an effective antiviral to treat afflicted patients, much effort has been devoted to the development of a vaccine to Enterovirus 71 (EV71), a HFMD-associated serotype that has been linked to more severe disease outcomes (13,14).

An extended vaccine efficacy study on the China FDA-approved Sinovac EV71 vaccine, 'Two-year efficacy and immunogenicity of Sinovac EV71 vaccine against hand, foot and mouth disease in children', had been published in 2015. In this study, robust vaccine-induced protection against EV71 had been demonstrated by the formalin-inactivate EV71 vaccine, following a 2-dose immunization protocol, up to 25 months post-immunization.

Focusing on the per-protocol population results (i.e., participants who received 2 doses of the vaccine) for simplicity, the vaccine consistently protected the vaccine group participants from EV71-associated HFMD compared to the placebo group, albeit with a gradual decrease in efficacy over time (15). This decrease is likely negligible since the overall vaccine efficacy stayed high at 94.7%. Overall, the disparity between the total numbers of EV71-associated HFMD cases reported for the vaccine and placebo groups during the entire study is significant enough to demonstrate the efficacy of the vaccine. The much lower numbers reported in the second year (1 case in vaccine group *vs.* 20 in placebo group) made it difficult to ascertain if the vaccine is truly as efficacious during the second year of the study.

While the protective efficacy seemed to have remained as high during the extended follow-up period, immune persistence of the vaccine did not seem to fare as well, with the geometric mean titer (GMT) of EV71-neutralizing antibodies showing a gradual, downward trend. The waning of immune persistence appeared to be inconsequential since the vaccine remained efficacious throughout the study. It is however noted that the GMTs of the placebo group increased consistently through the study, presumably due to sub-clinical exposure to circulating EV71 by the participants. This may imply that the decline of vaccine-induced immunity could be much higher than expected.

In terms of safety, the Sinovac inactivated-EV71 vaccine has demonstrated a good safety profile in infants and young children below 2 years of age. As there is no significant difference in severe adverse events reported between the

vaccine and placebo groups, the vaccine appears to be very safe for large scale immunization programs since most vaccine-induced adverse events would likely occur in the immediate period post-immunization.

The results presented by the extended study has validated the findings from the initial phase 3 clinical trial and demonstrated the durability of vaccine-induced protection against EV71-associated HFMD. While the Sinovac EV71 vaccine proved to be highly efficacious during the extended follow-up, this vaccine alone is no silver bullet for HFMD. There are several limitations of the study which had been discussed by the authors. Firstly, the protective efficacy of the Sinovac EV71 vaccine, based on the C4a genotype prevalent in China, against genotypes dominant in other countries remains to be confirmed. In this respect, research on post-infection serum samples from volunteers has demonstrated cross-neutralizing activity of antibodies induced by different EV71 genotypes, implying that an EV71 vaccine of a certain genotype is likely to confer broad spectrum protection against all EV71 genotypes (16).

Next, the study had not been designed to detect asymptomatic cases, which are a bane to outbreak management since all infected individuals can contribute to transmission, even in the absence of symptoms. An extension of this issue, in our opinion, would be the need for inclusion of all EV71-associated diseases in the evaluation of vaccine efficacy, even though HFMD may have been the most common manifestation of EV71 infections. Since the vaccine had not been fully characterized in the modulation of disease manifestation, in the likelihood of a reduction of disease severity due to vaccine-induced immunity, EV71-infected participants may present mild or atypical symptoms, which may not be reported as HFMD. It would take a much greater effort however, to address this issue as much more resources would be required to have many more participants tested for EV71 infection.

The third issue discussed by the authors is the fact that this study was conducted in a community with high incidence of HFMD, resulting in a high background immunity elicited by natural exposure to EV71. We however did not feel this has diminished the impact of the study, although it did cast some doubt on the durability of vaccine-induced immunity against EV71.

In addition to the above issues raised by the authors, it was unfortunate that there were much lesser cases of EV71-associated HFMD reported in the second year of the study, affecting the significance of the results with regards to the persistence of vaccine-induced immunity. Also, we feel that the true test of the vaccine's efficacy would be a documentation of its protective efficiency during an outbreak, during which the infection challenge would likely be more intense. This however, would likely require a large scale application of vaccinations across the country.

Next, it was surprising to note that there had been much more HFMD cases associated with CA16 (584 cases) and other enteroviruses (565 cases) than EV71 (116 cases) for the entire duration of the 26-month study. While the dominant enterovirus serotypes in circulation is beyond control, the effectiveness of vaccinating a population against HFMD using an EV71 vaccine had been diminished as a result of having less than 10% of HFMD cases reported contributed by EV71.

Lastly, it has been confirmed in multiple trials, vaccines based on EV71 cannot confer protection against Coxsackievirus A16 (CA16), a closely related and very common aetiologic agent for HFMD. Although EV71 and CA16 are the most commonly circulated serotypes globally, co-circulation with other Coxsackievirus serotypes, e.g., Coxsackievirus A6 (CA6) and A10 (CA10) occur in a sizable population, evident in the aetiology of HFMD reported by this study and epidemiological data collected by agencies in respective countries. In addition, type B Coxsackieviruses and Echoviruses (6-8) that can cause HFMD are also in co-circulation, albeit to a smaller extent. This is an important issue that needs to be addressed before a vaccine can be adopted on a large scale as the question of how the vaccination against EV71 alone will drive the emergence of other serotypes to overtake EV71 as the leading cause of HFMD, thereby rendering the vaccine ineffective against HFMD in the future remains to be answered.

Despite the fact that there remain issues to be addressed on the effectiveness and longevity of the Sinovac EV71 vaccine, it is still a valuable addition to the arsenal of anti-HFMD treatments, particularly in the prevention of severe HFMD, commonly associated with EV71 infections.

The highly contagious nature of enteroviruses and high international traffic calls for the need of a vaccine that can efficiently protect against HFMD on general and not just EV71-associated HFMD. In conclusion, the Sinovac EV71 vaccine can reduce the severity of EV71-associated HFMD, but the reduction of socioeconomic impact of HFMD can only be achieved with a vaccine that can protect against most serotypes of HFMD-associated enteroviruses. The adoption of this EV71 vaccine for any large scale vaccination programs should be carefully considered with the dominant serotypes in circulation in mind.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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