HHS Public Access

Author manuscript

Lancet. Author manuscript; available in PMC 2024 August 19.

Published in final edited form as:

Lancet. 2013 March 23; 381(9871): 976–977. doi:10.1016/S0140-6736(13)60286-X.

Enterovirus 71 encephalitis: a new vaccine on the horizon?

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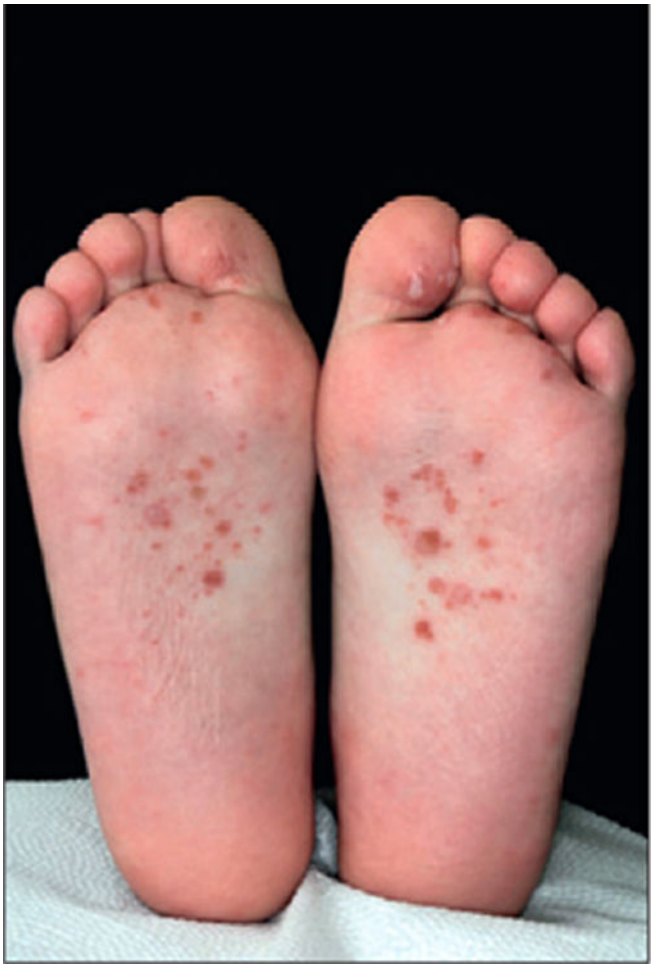
GRAPHICAL ABSTRACT



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Since its discovery in 1969, enterovirus 71 (EV71) has been associated with outbreaks of severe neurological disease and mild hand, foot, and mouth disease.[1] The virus circulates

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We declare that we have no conflicts of interest. The opinions and conclusions in this Comment are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

worldwide and caused several outbreaks of poliomyelitis-like paralysis and brainstem encephalitis in eastern Europe during the 1970s, with few associated outbreaks of hand, foot, and mouth disease. Yet in Europe and North America, EV71 is a common cause (as are several other enteroviruses) of hand, foot, and mouth disease—a common illness of young children—although few cases are regarded as serious in these regions.

In 1997, EV71 was implicated in the deaths of 34 children due to neurogenic cardiopulmonary failure during a hand, foot, and mouth disease outbreak in Sarawak, Malaysia.[1,2] Since then, hundreds of deaths have been attributed to EV71 infection during large disease outbreaks throughout the Asia-Pacific region, including in Taiwan, Malaysia, China, Vietnam, and Cambodia.[3] In 2009, China reported more than 1·1 million hand, foot, and mouth disease cases, more than 13 000 of which were classed as severe, and 353 deaths were reported. During this period, EV71 was also circulating in Europe, North America, and Africa, but led to few severe cases and deaths.

The large number of deaths in Asia has caused substantial public concern, and each outbreak brings anxiety to parents of young children. As a result, several Asian countries have established sentinel surveillance systems for hand, foot, and mouth disease and associated severe sequelae.[4,5] Malaysia's Sarawak state uses private and government clinics to treat young children.[4] The WHO Western Pacific Regional Office has published a guide for clinical management and public health response for hand, foot, and mouth disease.[3]

In *The Lancet*, Feng-Cai Zhu and colleagues[6] report results of a phase 2 clinical trial of an inactivated EV71 vaccine that could prevent severe outcomes of EV71 infection in young children.[6] The approach taken to develop this vaccine followed that of the inactivated polio vaccine—ie, chemical treatment of purified virus to render it non-infectious yet still antigenic. Although enteroviruses share many similarities, there is always uncertainty as to whether immunogenicity reported in animal experiments will be noted when the inactivated virus is presented to the human immune system. 1200 children were enrolled in total, with 120 randomly assigned to each of ten treatment groups according to age and allocation of vaccine (with or without adjuvant) or placebo. Zhu and colleagues report that the vaccine does elicit a significantly higher antibody response (measured by anti-EV71 neutralising antibody geometric mean titres 56 days after the first injection) in both infants (aged 6–11 months) and young children (aged 12–36 months) than in those who received a placebo ($p<0·0001$).[6]

The investigators omitted a planned follow-up at 14 months because they were concerned that an EV71 outbreak, which occurred towards the end of the study, would confound the seroconversion data; however, the investigators might have missed an opportunity to collect some preliminary efficacy data from the study participants for hand, foot, and mouth disease symptoms, and this decision restricted the time they could have used to measure antibody waning. This limitation emphasises the challenges associated with undertaking clinical trials in a population naturally exposed to the same virus as contained within the vaccine. The small size of the placebo group would have reduced the ability to measure this exposure, leading to potential overestimation of the immunogenicity of the vaccine and underestimation of the extent of antibody waning, as Zhu and colleagues note.

Although the results show that the vaccine is immunogenic, several steps remain before the vaccine will be ready for the clinic. Even though the investigators and sponsors have made decisions about how to proceed with the next clinical trial, the usual issues of antigen content, need for adjuvant, and immunisation schedule could still be improved. Practical issues surrounding optimisation of production will affect production costs and scalability of production. These early trials are encouraging, and the precedent set by the inactivated polio vaccine provides hope that an antibody response will indeed equate with protection from the severe effects of infection, but a clinical trial showing that the vaccine protects recipients from disease will be the most important test.

EV71 has several epidemiological characteristics that are poorly understood, and investigators still do not completely understand why it is largely a regional problem. Advances in virological surveillance have shown that the virus is present in all continents and probably exists in most countries, as do other enteroviruses. The viruses causing the current outbreaks in the Asia-Pacific region had been detected in Europe and North America previously. The magnitude of outbreaks outside of the Asia-Pacific region is hard to assess, since hand, foot, and mouth disease is a ubiquitous childhood illness for which the cause is almost never established. In the absence of severe disease, infection with EV71 is largely ignored.

If this and other attempts to develop EV71 vaccines continue to succeed, substantial public health decisions will need to be made. The very large outbreaks of EV71 in many Asia-Pacific countries and the young age at which severe disease occurs suggest that EV71 immunisation would need to become part of routine childhood vaccination schedules. Discussions will then need to focus on efficacy, schedule, and cost. The issue of an additional injection, particularly in an infant population if necessary, will also need to be addressed, because the development of combination vaccines will take several years. Countries with the most severe outbreaks of EV71 will most likely lead these discussions, but the effect that the outcome of these discussions will have on decisions about vaccine use in other regions that are not as severely affected is unclear. Zhu and colleagues' study provides encouragement that an intervention might be within sight. But results of the phase 3 efficacy trial—a necessary and crucial step to turn this experimental vaccine into a practical intervention—are eagerly awaited.

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