

# Enterovirus Vaccines for an Emerging Cause of Brain-Stem Encephalitis

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Hand, foot, and mouth disease is a common childhood exanthem caused by enteroviruses that belong to the human enterovirus A species of the family Picornaviridae — most commonly, human enterovirus 71 (EV71) and coxsackievirus A16. Although the clinical signs of hand, foot, and mouth disease associated with various enteroviruses are indistinguishable, EV71 epidemics are a cause for public health concern because they place young children (<5 years of age) at increased risk for severe neurologic disease.<sup>1</sup>

EV71 was first identified in the United States in 1969.<sup>1</sup> Despite causing epidemics of severe neurologic disease in Bulgaria in 1975 and in Hungary in 1978, EV71 was generally associated with relatively minor and infrequent epidemics of hand, foot, and mouth disease until 1997, when 41 children died of acute EV71 infection in Malaysia; the

following year, there was a large epidemic, including 78 fatal cases, in Taiwan.<sup>2</sup> Since 1997, large EV71 epidemics involving fatal cases have been reported in Singapore, Brunei, Japan, Vietnam, Hong Kong, South Korea, Thailand, Cambodia, the Philippines, France, and (annually since 2008) China. Over the past decade, it's been estimated, there have been more than 6 million cases of EV71 infection worldwide, and more than 2000 of them have been fatal.<sup>3</sup>

On the basis of the nucleotide sequence of the variable VP1 structural protein gene, EV71 isolates have been classified into four genetic lineages — A, B, C, and D.<sup>1</sup> Recent epidemics in the Asia-Pacific region have been caused by newly emerged genetic lineages B3, B4, B5, C3, C4, and C5. Although no particular lineage has been linked to increased disease severity, large epidemics have frequently been associated with lineage replacement. Newly emerged genetic lineages of EV71 appear to circulate without being detected by clinical or virologic surveillance for as long as 5 years before causing major epidemics. Furthermore, recombinant strains frequently predominate in epidemics, which suggests that recombination among EV71 strains may also lead to increased viral diversity and reemergence.

The clinical manifestations of EV71 infection vary considerably in presentation and severity.<sup>3</sup> The majority of EV71-infected persons

have asymptomatic infection, and mild cases manifest most commonly as upper respiratory infection, herpangina, or hand, foot, and mouth disease. The vesicular lesions of hand, foot, and mouth disease occur typically on the palms of the hands (see photo), the soles of the feet, and the buttocks and within the oral cavity, where they often ulcerate.

The neurologic complications of EV71 infection, which include brain-stem encephalitis (see scan), acute flaccid paralysis, and aseptic meningitis, are of greater clinical significance and can occur in the absence of the more commonly encountered cutaneous manifestations. Patients with EV71-associated aseptic meningitis usually recover completely. Although cases of acute flaccid paralysis represent only a small subset of cases of EV71-associated acute neurologic disease, this condition is of particular concern because it mimics poliomyelitis and generally results in permanent paralysis. Furthermore, radiologic and histopathological evidence suggests that, as in poliovirus infection, acute flaccid paralysis occurs when EV71 establishes a lytic infection in anterior horn motor neurons of the spinal cord.<sup>3</sup>

The most severe neurologic manifestation of EV71 infection is brain-stem encephalitis, in which extensive inflammation develops in the hypothalamus, brain stem, spinal cord, and cerebellar dentate nucleus. Histologic evidence



Palmar Lesions of Uncomplicated Hand, Foot, and Mouth Disease Due to Enterovirus 71 (EV71).



#### EV71-Related Brain-Stem Encephalitis.

Midsagittal T<sub>2</sub>-weighted magnetic resonance imaging revealed a high-signal lesion (arrows) from the mid-medulla to the spinal cord at the level of T9 (outside the image).

identifying the EV71 antigen in nervous tissue indicates that this disease is due to direct EV71 infection of specific central nervous system structures. Children with brain-stem encephalitis usually present with myoclonus, tremor, ataxia, nystagmus, and cranial-nerve palsies. Children occasionally recover fully from brain-stem encephalitis; however, the development of permanent neurologic sequelae is far more common. The onset of brain-stem encephalitis is rapid and characterized by the sudden onset of neurogenic pulmonary edema that can mimic acute myocarditis. Histologic and neuroradiologic evidence of brain-stem disease indicates

that the pulmonary edema is neurogenic.

EV71-associated neurogenic pulmonary edema progresses rapidly (over a period of 24 to 36 hours) and is associated with high mortality. Although mortality can be reduced by pediatric intensive care support, including the use of milrinone, intravenous immune globulin, and extracorporeal membrane oxygenation,<sup>3</sup> most survivors are left with clinically significant neurologic sequelae. Serious complications are more common in children younger than 2 years of age.

The increasing burden of EV71 acute neurologic disease, especially in the Asia-Pacific region, together with the lack of effective antiviral or other treatments for severe EV71 infection, make disease prevention a public health priority. EV71 is most commonly transmitted by close personal contact through the fecal-oral route, but the majority of EV71 infections are asymptomatic or result in mild disease, which limits the effectiveness of public health interventions such as hand washing, disinfection, and social distancing during epidemics. Indeed, these practices have been largely ineffective in containing EV71 epidemics. Thus, the development of a vaccine is likely to provide the best means of controlling or even eradicating EV71 infection within affected populations — just as poliovirus has nearly been eradicated by vaccination.

The rapid development of potential EV71 vaccines has been driven by an overwhelming public health need and strong market demand in upper-middle-income and high-income Asian countries.

Strategies that have been applied to the development of EV71 vaccines include the inactivation of whole virus, the development of viruslike particles, the selection of live attenuated EV71 strains, and the expression of cloned subunit vaccines, especially of the immunodominant VP1 structural protein.<sup>1</sup>

Not surprisingly, the development of inactivated whole-virus vaccines has proceeded most rapidly, thanks to the application of existing technology for vaccine manufacture. A phase 3 clinical trial of an inactivated EV71 vaccine was completed in 2013.<sup>4</sup> The results of two further phase 3 trials of vaccines are reported in this issue of the *Journal* (see Zhu et al., pages 818–828, and Li et al., pages 829–837). All three vaccines were manufactured in China with the use of the C4A genetic lineage that has predominated in China since 2008.<sup>1</sup>

None of the three candidate vaccines has raised obvious safety concerns in the studies to date, and all three appear to be effective in preventing hand, foot, and mouth disease, herpangina, or both in the target populations (children 6 months to 6 years of age) for periods of 11 to 13 months after the intramuscular administration of two doses of vaccine. The vaccines also generate immunity in more than 98.8% of children after two doses. In addition, Zhu et al. found that a neutralizing antibody titer of at least 1:16 is associated with protection against EV71-associated hand, foot, and mouth disease or herpangina. None of the studies were able to show vaccine efficacy against EV71-associated neurologic disease. Indeed, it is un-

likely that such efficacy will be shown until the vaccines are licensed and postmarketing surveillance commences.

Recent evidence suggests that EV71 vaccines do not provide cross-protection against all circulating genetic lineages of EV71 or against coxsackievirus A16.<sup>5</sup> Thus, the Chinese C4A-based vaccines may not generate protective immunity against EV71 in regions where other extant or newly emerged lineages circulate. Consequently, it may be necessary to develop multivalent vaccines to ensure that protection is provided against all EV71 strains.

Nevertheless, this is an exciting development in the global response to the emergence of EV71 as a cause of severe neurologic disease. It is also worth noting

that in the past 17 years, EV71 research and vaccine development have been primarily centered in Asia — a fact that not only reflects the predominance of EV71 epidemics in this region but also underscores the increasing importance of Asia as a center of medical research. Finally, if these vaccines prove to be effective in preventing EV71-associated neurologic disease, an important tool for controlling, or even eradicating, EV71 infection in regions where it is endemic may have been developed. If its promise is realized, a priceless gift will have been given to the children of the Asia-Pacific region and to the rest of the world.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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## Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

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With approximately 25.8 million diabetic patients in the United States and 33 million in the European Union alone, the growing prevalence of diabetes worldwide poses a major public health challenge. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are committed to ensuring the safety of drug products marketed for the treatment of diabetes, and postmarketing reports of pancreatitis and pancreatic cancer in patients taking certain antidiabetic

medications have been of concern to both agencies. Working in parallel, the agencies have reviewed nonclinical toxicology studies, clinical trial data, and epidemiologic data pertaining to blood glucose-lowering drug products (e.g., exenatide and sitagliptin) that stimulate postprandial insulin release by potentiating the incretin hormone pathways.

In keeping with the pathophysiological complexity of diabetes, several classes of blood glucose-lowering drugs, encompassing diverse mechanisms of

action, have been developed to treat the disease. The incretins (i.e., glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide) are intestinal hormones that stimulate the postprandial production of insulin and glucagon by the pancreas. In the past decade, drugs that act as incretin receptor agonists (e.g., exenatide) or that inhibit the proteolytic degradation of incretins (e.g., sitagliptin) have been approved by both the FDA and the EMA (see table), in part on the basis of clinical data establishing