CLINICAL INVESTIGATION

Clinical progress for enterovirus 71 vaccines: what does the future hold?

"The decision of whether EV71 vaccine should be added to a national expanded programme of immunization needs further integrated assessment, including cost–effectiveness, feasibility and contextual considerations in different regions."

Keywords: clinical trial • enterovirus 71 vaccine • foot • hand • immunization strategy • mouth disease

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Enterovirus 71 (EV71) had been first identified in California, USA in 1969 [1]. Since then, outbreaks of hand, foot and mouth disease (HFMD) caused by EV71 have been reported worldwide [2]. In the last 15 years, EV71-associated HFMD epidemics have been increasingly reported across the Asia-Pacific region, including Malaysia, Taiwan, Japan, Singapore, Vietnam, mainland China, Hong Kong and Cambodia [3–8]. Recently, three EV71 vaccine candidates developed in mainland China had been tested successfully in Phase III clinical trials [9–11]. All the three EV71 vaccines were alum-adjuvant-inactivated whole-virus vaccines. Although the techniques of the production process of the EV71 vaccines may vary in some aspects, all of them were demonstrated to be highly efficacious against EV71-associated disease in the first year after vaccination [12].

Immunization with EV71 vaccine in realistic conditions

Currently, the EV71 vaccine candidates are undergoing regulatory vetting in China. It is possible that China will become the first country to have vaccines against EV71 available on the market in the near future. Although EV71 vaccine candidates have demonstrated a good safety profile, satisfying immunogenicity and significant efficacy in Phase III trials, the long-term immunogenicity still needs further investigation, especially when massive immunization campaigns with EV71 vaccine are launched after its approval. In the clinical trials, considerable efforts were made to ensure that every aspect of administration with EV71 vaccines were under ideal conditions, therefore data collected in these trials may be better than that in reality. The participants recruited in clinical trials may be healthier children who may present a better immune response to EV71 vaccines or children who may have a cleaner baseline EV71 antibody in serum. Vaccine efficacy could also be influenced by age, nutritional status and co-infection. In addition, programmatic factors such as errors in vaccine storage, preparation or administration and the drop out between the first and second dose can also impair the vaccine efficacy. Therefore, the efficacy of the EV71 vaccine in practical immunization programs in populations may not be as high as that in the controlled clinical studies. If a large-scale immunization with EV71 vaccine is carried out in a population, naive children who receive EV71 vaccines will become seroprotected against EV71. Then, the accumulation of susceptible children to EV71 would be significantly reduced and the epidemic patterns of EV71 could be altered, as the EV71 circulation is suppressed by EV71 vaccines. However, recent studies showed that the neutralizing antibody elicited by EV71 vaccine waned rapidly with time. There is concern that the vaccinated children may become vulnerable to EV71 again as the EV71 neutralizing antibody drops to a very low level as the child ages.

Long-term surveillance on EV71 after the vaccine approval

Epidemiological surveillance could not only provide disease burden data for deciding

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on vaccine licensing, but also enable the collection of data on the impact of the EV71 vaccine after market approval. The dynamic changes of EV71 neutralizing antibody levels as well as the vaccine efficacy in children for a long period of time could provide vital evidence to deploy a booster immunization strategy.

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Although the EV71 vaccines have been assessed in more than 15,000 children in clinical trials and been proven to be fairly safe with a relatively low incidence of adverse reactions, the safety profile of the EV71 vaccine still needs further observation to identify some rare and serious late-onset adverse reactions, in cases where some rare adverse events may not have been captured in clinical trials. There should also be data about the impact on safety and efficacy on other routine vaccines that are given in children at the same time. Besides, strengthening the surveillance systems to identify all the probable EV71-vaccination associated cases is a worthy investment for the vaccine immunization program and controlling of EV71-associated disease or HFMD in the future. However, currently the data from surveillance systems are rarely complete, owing to numerous weaknesses [13]. On the other hand, EV71 is prone to genetic recombination and mutation. Recombination can occur among EV71 strains of different genotypes, and occasionally even between EV71 and other enteroviruses [14]. The implemention of immunization with EV71 vaccines may further promote EV71 to generate new genotypes and serotypes by suppressing the circulation of normal strains of EV71. Although previous studies have shown that EV71 vaccine with a signal genotype could stimulate a wide spectrum of antibodies against other EV71 genotypes, this may not always be the case [12]. In Taiwan, scientists had discovered a C2-like subgenogroup strain of EV71, which showed significantly different antigenicity from other EV71 genotypes [15]. Therefore, surveillance for epidemiological variations in EV71 will be crucial to determine whether the vaccine has ongoing efficacy and if any genotype replacement has occurred.

Development trend of HFMD vaccines in the future

Although the EV71 vaccine is considered an efficient control for HFMD epidemics, EV71 is not the only pathogen that can cause HFMD. If the public expects this EV71 vaccine to eliminate all HFMDs, they will be disappointed. There are several other enteroviruses that could cause a HFMD epidemic, such as Coxsackie virus (CA) and Echoviruses [16]. In Phase III trials, EV71 vaccine has been confirmed to have little cross-protection against CA16 and other non-EV71 enteroviruses [9,11]. Recently, there have been reports of CA16 showing rising epidemics in Singapore, Finland, France, India, Taiwan, mainland China and Japan, which has aroused the concerns worldwide [17]. If EV71 is suppressed by immunization of EV71 vaccines, it is likely that CA16 or other enteroviruses may take EV71's place to become the predominant enterovirus circulating during the HFMD epidemics. As a result, the best strategy to control HFMD is to develop combined CA16–EV71 vaccines or multivalent enteroviruses vaccines that could protect children from EV71, CA16 and other enteroviruses simultaneously. Currently, several combined CA16–EV71 vaccine candidates are under development and they have been shown to provide a balanced protective immunity in animal models [18].

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However, EV71 vaccine is still an important milestone for the HFMD control, as EV71 caused the majority of the severe HFMD cases. The decision of whether EV71 vaccine should be added to a national expanded programme of immunization needs further integrated assessment, including cost–effectiveness, feasibility and contextual considerations in different regions. As any new vaccine first on the market, EV71 vaccine might be produced by a limited number of manufacturers and it might take time for the vaccine market to reach a level of maturity in terms of both supply and price. In China where HFMD morbidity and mortality is relatively high, the expected benefits can far outweigh the risk of adverse effects.

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