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Commentary

Inactivated enterovirus A71 vaccines and moving forward

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The inactivated poliovirus vaccine (IPV) was introduced in 1955 in the USA for the first time globally, and the excellent efficacy and safety of IPV have been widely accepted worldwide. IPV effectively elicits serum neutralizing antibodies against poliovirus types 1, 2, and 3 by multiple IPV doses and effectively prevents paralytic poliomyelitis.[1] However, vaccines against non-polio enteroviruses (NPEVs) had not been licensed for almost 60 years since the introduction of IPV. In response to the large-scale outbreaks of hand, foot, and mouth disease (HFMD), including cases with severe and fatal neurological complications associated with enterovirus A71 (EV-A71), developing EV-A71 vaccine had been encouraged mainly in countries in the Western Pacific Region (WPR).[2,3] Three inactivated EV-A71 vaccines manufactured by three companies were approved in China from 2015 to 2016 to prevent EV-A71-associated diseases as the world's first NPEV vaccines.[4]

In *The Lancet Regional Health-Western Pacific*, Yan Li and colleagues report results of a multicenter, open-label, non-inferiority, three-group, randomized controlled clinical trial in children aged 6–35 months to compare the immunogenicity and safety of three inactivated EV-A71 vaccines currently available in China.[5] After two doses of one of the EV-A71 vaccines, the seropositivity rate of serum neutralizing antibody against an EV-A71 strain (the EV-A71-523/subgenotype C4 strain) was measured as a surrogate marker for the vaccine efficacy. Four weeks after the second dose of the EV-A71 vaccine, the seroconversion rates were 98.8% or higher for three groups, which was mutually non-inferior in all pairwise comparisons. Additionally, there was no evidence of a difference among the three groups in the incidence of local and systemic adverse events. Regardless of differences among the three vaccines, including the EV-A71 strain, cell culture system for viral amplification, and antigen content (unit/dose), the vaccines are manufactured by formalin-inactivating the purified whole virus particles of the subgenotype C4 strains isolated in China, adjuvanted with aluminum hydroxide. Therefore, the result of the non-inferiority among the three vaccines would be reasonable. Thus, this clinical study will be an important reference for immunization policymakers and public health authorities, especially in China.

To date, NPEV vaccines, including EV-A71 vaccines, are not licensed in the world except China. Accumulating post-market evaluations on the efficacy and safety profiles of current inactivated EV-A71 vaccines in China, including this study, will provide critical insights into the development of next-generation NPEV vaccines in China and other countries. Phylogenetic analysis of EV-A71 strains based on the VP1 region demonstrates that EV-A71 is classified into genotypes A–H, and genotypes B and C are further divided into subgenotypes B0–B5 and C0–C5, respectively.[6] The trend of molecular evolution of EV-A71 in mainland China is unique compared with other WPR countries and at the global level. Among various EV-A71 subgenotypes, C4 has been consistently the predominant subgenotype from 1998 in China for unknown reasons, and the circulation of other subgenotypes has been limited and sporadic.[6,7] It is rather common for the chronological shift in different EV-A71 subgenotypes (B3, B4, B5, C1, C2, and C4) in countries outside China, and the multiple subgenotypes often co-circulate at the same time and in the same region.[7] All three EV-A71 vaccines in China use the subgenotype C4 strains, which is reasonable considering the previous molecular evolution of EV-A71 in China. As the authors pointed out, cross-neutralizing activity induced by the current C4-based vaccines can be expected for neutralizing the other EV-A71 genotypes prevalent in the other countries.[5] However, we cannot exclude the possibility that other (sub)genotypes of EV-A71 with different neutralizing antigenicity become prevalent, dominant, or both even in China in the future. Specifically, for instance, the re-emergence of subgenotype C1 variants with antigenic variation was recently reported in different

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geographical areas in the world, including Taiwan and mainland China.[8,9] If the neutralizing antigenicity of the dominant EV-A71 genotypes is significantly altered, there is room for consideration of changing to or adding an alternative non-C4 antigen for the next-generation EV-A71 vaccine.

As for poliovirus types 1–3, neutralizing antigenicity against NPEVs differs among types, and serum neutralizing antibodies induced by current EV-A71 vaccines do not neutralize other types of NPEVs. Although EV-A71 is more frequently detected from cases with severe neurological infections, the prevalence of EV-A71 from HFMD cases has recently declined in many countries, including China. During the last decade, coxsackievirus A6 (CV-A6) has been implicated in large outbreaks with atypical HFMD cases.[10,11] However, the risk of severe neurological complications due to CV-A6 would be relatively lower than EV-A71. Currently, multivalent vaccines containing different NPEV antigens are being developed in China and other countries, but further vaccine and vaccination strategies need to be established based on the sensitive disease and enterovirus surveillance and careful evaluation of disease burden in the enterovirus-associated diseases.

Declaration of Competing Interest

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