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Review

Considerations for developing an immunization strategy with enterovirus 71 vaccine

Li Li[a,1], Hongzhang Yin[b,1], Zhijie An[a,1], Zijian Feng[a,*]

[a] Chinese Center for Disease Control and Prevention, Beijing 100050, China
[b] The Center for Drug Evaluation, China Food and Drug Administration, Beijing 100050, China

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ABSTRACT

Enterovirus 71 (EV71) is a common pathogen for hand, foot, and mouth disease (HFMD), which has significant morbidity and mortality, and for which children aged 6–59 months age are at highest risk. Due to lack of effective treatment options, control of EV71 epidemics has mainly focused on development of EV71 vaccines. Clinical trials have been completed on 3 EV71 vaccines, with trial results demonstrating good vaccine efficacy and safety. When EV71 vaccine is approved by China's national regulatory authority, an evidence-based strategy should be developed to optimize impact and safety. An immunization strategy for EV71 vaccine should consider several factors, including the target population age group, the number of doses for primary immunization, the need for a booster dose, concomitant administration of other vaccines, economic value, program capacity and logistics, and public acceptance. Once EV71 vaccines are in use, vaccine effectiveness and safety must be monitored in large populations, and the epidemiology of HFMD must be evaluated to assure a match between vaccination strategy and epidemiology. Evaluation in China is especially important because there are no other EV71 vaccines globally.

1. Introduction

Hand, foot, and mouth disease (HFMD) is a common enteroviral infection, most frequently caused by coxsackievirus A16 (CV A16) and enterovirus 71 (EV71) [1,2]. Most patients show mild and self-limiting illness, but some patients rapidly develop central nervous system (CNS) complications that can be fatal—especially HFMD caused by EV71 virus. Young children <3 years old are the most susceptible to EV71 infection and have the highest risk CNS involvement, which is why the pathogen has captured much attention [3–5].

The relatively high incidence of disease caused by EV71 is recognized as a serious public health problem. Due to lack of effective treatment options, control of EV71 epidemics has mainly focused on development of EV71 vaccines. Three manufactures in mainland China have recently completed phase III trials for EV71 vaccines and have applied for licensure approval from the China Food and Drug Administration (CFDA).

As human EV71 vaccines move closer to the China market, it is necessary for policy makers, public health officials, clinicians, and other government vaccination program decision makers to consider how to use such a vaccine. Introduction of EV71 vaccine will have unique challenges. EV71 vaccine, if licensed and recommended, will be the first vaccine introduced in China without experience in other countries. Thus, developing a robust, evidence-based immunization policy may be difficult. Introduction of this vaccine may change EV71 disease epidemiology, and so potential risks related to a changing epidemiology must be considered prior to introduction. In this article we discuss considerations for the development of an immunization strategy for this vaccine.

2. Methods

A working group from the national immunization program (NIP) of the Chinese Center for Disease Control and Prevention (CCDC) and the Center for Drug Evaluation (CDE) of the China Food and Drug Administration (CFDA), reviewed information relevant to the development of an EV71 immunization strategy. We reviewed literature published before March of 2014 on the epidemiology of HFMD and EV71 infection in mainland China, clinical data (including efficacy, safety, immunogenicity, and immune persistence) of EV71 vaccines in Chinese children, the economic value of EV71 vaccines, potential immunization schedules for EV71 vaccines, public acceptance and willingness-to-pay for an EV71 vaccine, and challenges of EV71 vaccine policy.

* Corresponding author. Tel.: +86 01 58900309.
E-mail addresses: fengzj@chinacdc.cn, anzhj@139.com (Z. Feng).
[1] Drs. L. Li, H. Yin and Z. An contributed equally to this article.

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3. Epidemiology and disease burden

3.1. Epidemiology and seroepidemiology of EV71 and HFMD

The first EV71 case was reported in the United States in 1969. Since 1998, there has been a continually increasing trend of EV71 infection-related epidemics in the Western Pacific Region of the World Health Organization, including in mainland China [5–9], Malaysia [10,11], Vietnam [12], Singapore [13,14], Thailand [15], Hong Kong (China) [16], and Taiwan (China) [17,18]. In Taiwan (China), after the largest EV71 epidemic, which happened in 1998 and caused 405 serious neurological complications and 78 deaths, EV71 caused additional epidemics: in 2000–2001, 2004–2005, and 2008–2009 [18,19]. The country of Malaysia experienced 5 outbreaks HFMD caused by EV71 since its first recorded emergence there in 1997 [10,11]. In Vietnam, EV71 was first isolated in 2003, and an outbreak of HFMD caused by EV71 was reported in 2005. Between February 2011 and July 2012, Vietnam reported a total of 174,677 cases and 200 deaths [12]. In Singapore, recent EV71-associated HFMD epidemics (140,000 cases and 8 deaths) occurred in 2006 and 2008, with the 2008 outbreak being the largest known HFMD outbreak [13,14]. Thailand first reported a large-scale HFMD outbreak caused by EV71 in 2012 that included 39,000 cases and led to 3 deaths [15]. Due to its significant public health and social implications, EV71 infection has been a statutorily-notifiable disease in Hong Kong since March 2009 [20].

In mainland China, significant increases in HFMD morbidity and mortality have caused an enormous burden on the public health system. Nationwide epidemics of HFMD started in 2008, beginning with an outbreak in Anhui province that spread rapidly to other provinces. In total, 488,955 young children suffered in this epidemic that had 1165 severe cases and 126 fatal cases [7]. In response to these large outbreaks, HFMD was listed as a category C notifiable disease in China in May 2008.

A recent study characterized the epidemiology of HFMD in China on the basis of epidemiological, clinical, and laboratory data that were reported to the National Enhanced Surveillance System between 2008 and 2012 [5]. From 2008 to 2012, more than 7.2 million cases of HFMD were reported, with an estimated incidence of 1.2 per 1000 person-years from 2010 to 2012. HFMD has been responsible for 500–900 deaths each year, primarily among young children. Young children less than 5 years old had the highest risk of disease, with the highest incidence and mortality rate among children aged 12 to 23 months (38.2 cases per 1000 and 1.5 deaths per 100,000 in 2012), followed by 6–11 months of age (28.9 cases per 1000 and 1.3 deaths per 100,000 in 2012) and 24–59 months of age (23.1 cases per 1000 and 0.4 deaths per 100,000 in 2012). The incidence has been low among infants younger than 6 months, older children (age 5–14 years) and adults (age $\geq$ 15 years). The median age of reported cases was 27 months (IQR 18–43 months). Median duration from onset to diagnosis was 1.5 days (IQR 0.5–2.5 days) and median duration from onset to death was 3.5 days (2.5–4.5 days).

Each year in June, HFMD peaked in north China, whereas southern China had semiannual outbreaks in May and during September–October. Geographical differences in seasonal patterns were weakly associated with climate and demographic factors, which explained 8–23% and 3–19% of the variance, respectively. As in other countries, EV71 predominated in laboratory-confirmed HFMD cases, accounting for 45% of mild, 80% of severe, and 93% of fatal cases. The case-severity rate of patients with cardiopulmonary or neurological complications was 1.1% (range across years 0.2–1.6%), the case-fatality rate was 0.03% (0.03–0.05%), and the severe case-fatality rate was 3.0% (2.6–10.4%). A predominance of EV71 serotypes was recorded in severe and fatal cases, with a median age of infection at 2.3 years. Consistently across all age groups, EV71 infections were much more severe than were CV A16 infections. Beyond young age and infection with EV71, several risk factors, including rural residence and long onset-to-diagnosis interval, were identified as predictors for mortality.

Previous studies suggested that infants older than 6 months of age would be susceptible to EV71 infection due to waning maternal antibody. A seroepidemiological study in Jiangsu province, China, showed that infants aged 7 to 12 months had the lowest seropositivity against EV71, and the incidence of HFMD remained low until 14 months [21].

3.2. Estimating transmission dynamics of EV71

Vaccination coverage levels required to interrupt transmission can be estimated from strain-specific basic reproductive number (R_0) values. Approximate coverage values for each cohort, P, required to stop transmission may be derived from the relationship, $P > 1 - 1\,R$–0. However, few studies have evaluated transmission dynamics of EV71 outbreaks. Ma et al. reported that the median R_0 for EV71 in Taiwan was 5.48, which is considered moderately infectious compared with other contagious diseases. Given this value, 82% of a birth cohort would have to be immunized through vaccination to stop sustained EV71 transmission in the cohort [22].

3.3. Economic and disease burden of EV71-associated HFMD

EV71-associated HFMD poses a substantial health and economic burden in China. Quantifying this burden is critical to set policy priorities and disease-control strategies.

As described above, millions of cases and thousands of deaths due to HFMD have been reported annually in China since 2008, and EV71 predominates in laboratory—confirmed cases [5]. However, the officially reported cases are considered to reflect only a small proportion of the cases. Medical care may not be sought for clinically mild cases. Many clinicians, especially in rural areas, lack the necessary experience and knowledge required for the identification and diagnosis of severe and fatal cases, in which extremity rashes or oral ulcers appear less frequently. In addition, township-, village- and community- level health facilities are unable to carry out etiological diagnosis, such as serotyping and genetic sequencing, due to lack of laboratory capacity.

Although specific studies of the economic burden of EV71-associated HFMD are not yet available, costs could be estimated using data from cost-burden studies of HFMD [23]. We obtained an average direct and indirect cost of US $129 (≈800 RMB) for an outpatient, $484 (≈3000 RMB) for an inpatient, and $1936 (≈12,000 RMB) for a severe inpatient, respectively. If the proportion of EV71 infections for severe HFMD cases is assumed to be 80%, the annual cost of severe EV71-associated HFMD would be about $29 million (≈180 million RMB) (estimated by 90 thousand cases within 6 years). Because the distribution of outpatients and inpatients is not available, by using varying estimated proportions, the annual economic burden of mild EV71-associated HFMD would be about $161–323 million (≈1000–2000 million RMB). The estimated cost burden of EV71-associated HFDM would have been higher had we considered other costs, such as fatal cases, long-term sequelae, and cases managed outside of the healthcare system.

4. Vaccine candidates

The substantial and increasing morbidity and mortality of EV71-associated HFMD have motivated development of EV71 vaccines. Thus far, five organizations have completed pre-clinical development of inactivated EV71 whole-virus vaccines and are in different stages of clinical trials. Among these organizations, three are in mainland China [Beijing Vigoo Biological Co., Ltd. (Vigoo)

Table 1
Summary of EV71 vaccine candidates from mainland China.

Items		Beijing Vigoo	Sinovac	CAMS
Manufacturing processes	Cell lines	Vero cell	Vero cell	Human diploid cell KMB-17
	EV71 strain	EV71 C4 subgenotype (strain FY7VP5/AH/CHN/2008)	EV71 C4 subgenotype (strain H07)	EV71 C4 subgenotype (FY23strain)
	Production technique	Fermenter, inactivation(serum-containing media)	Cell factory, inactivation (serum-containing media)	Roller bottle, (serum-containing media)
Phase 3 efficacy trial	Trial design	A multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of the EV71 vaccine against EV71-associated disease, including HFMD/HA, CNS complications, and other non-HFMD diseases caused by EV71	A multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of the EV71 vaccine against EV71-associated disease, including HFMD/HA, CNS complications, and other non-HFMD diseases caused by EV71	A multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of the EV71 vaccine against EV71-associated HFMD/HA, CNS complications
	Period	From January 2012 to March 2013, including 12-month surveillance period	From January 2012 to March 2013, including 12-month surveillance period	From March 2012 to February 2013, including 9-month surveillance period
	Target population	Infants aged 6–35 months	Infants aged 6–35 months	Infants aged 6–71 months
	Sample size	10,245 (5120 in vaccine group and 5125 in placebo group)	10,077 (5044 in vaccine group and 5033 in placebo group)	12,000 (6000 in vaccine group and 6000 in placebo group)
	Dosage (μg of EV71)	320 U/0.5 ml (0.5 μg of EV71)	400 U/0.5 ml (1.0 μg of EV71)	100 U/0.5 ml
	Clinical trials. Gov. identifier	NCT0150824	NCT0150785	NCT0156958
	Regimen	Two dose with 28 days apart	Two dose with 28 days apart	Two dose with 28 days apart
	Other objectives	Safety Immunogenicity Antibody persistence Serological surrogate Batches consistency	Safety Immunogenicity Antibody persistence Serological surrogate	Safety Immunogenicity
	Vaccine efficacy (95% CI) against EV71 associated HFMD	90.9% (70.4–97.2)	94.8% (87.2–97.9)	97.4% (92.9–99.0)

[19,24–26], Sinovac Biotech Ltd. (Sinovac) [27–30], and Institute of Medical Biology, Chinese Academy of Medical Science (CAMS) [31,32] and have recently completed phase I to III trials for the vaccines they developed. The other two vaccines, developed by National Health Research Institutes (NHRI) of Taiwan (China) [33] and Inviragen Pte., Ltd. (Inviragen), of Singapore, have been studied in phase I clinical trials (Table 1).

For inactivated EV71 vaccines in mainland China, Vigoo, Sinovac and CAMS have established their respective C4 genotype vaccine strains, using the seed lot system and cell banks of Vero (Vigoo and Sinovac) or diploid cells (CAMS) in accordance with WHO guidelines and the Chinese Pharmacopoeia and related technical guidance from CFDA. Recently published phase III reports showed that the EV71 vaccines developed by three manufactures in mainland China all have good safety profiles in children less than 6 years old and provide protective immunity against EV71 infection-related HFMD, with vaccine efficacy of 90.9% for Vigoo [26], 94.6% for Sinovac [30], and 97.4% for CAMS [32]. Although EV71 vaccines offered no protection against HFMD caused by CV A16 or other enterovirus serotypes, other research suggested that EV71 vaccines induce broad cross-neutralizing activity against EV71 subgenotypes B4, B5, C2, and C5, which were prominent epidemic strains in other Western-pacific countries or areas [34]. These EV71 vaccine candidates have entered into the vaccine evaluation and licensing process of CFDA.

5. Considerations for developing recommendations for immunization

5.1. Target population

Because the 3 manufactures recruited children 6 months to 3 years old or 6 months to 5 years old in their phase III clinical trials for EV71 vaccine, the potential target age should be within these age ranges. Decision makers should also consider the level of EV71 maternal antibodies in newborn infants when evaluating the age distribution of disease. The immunization schedule should start at the youngest age the vaccine is effective, and before the EV71 disease incidence increases. According to available data, the lowest level of maternal antibody to EV71 during infancy is 7–12 months of age, and the peak disease incidence occurs at 12–23 months of age. Therefore, vaccination starting at 6 months age could protect children in a timely manner, before maternal antibodies disappear. Since the incidence rates of disease among children over 5 years old and among adults are very low, EV71 vaccine use over the age of 5 years will have limited benefit at either the individual level or the population level, with correspondingly little public health significance and cost-effectiveness.

In summary, the EV71 vaccine should be considered for children from 6 month to 59 months or age, as early as possible, completing the schedule before 12 months of age. For children over 5 years of age, we would not recommend using EV71 vaccine unless the epidemiology changes such that older children begin acquire disease at substantially higher rates.

5.2. Immunization schedule

Based on the results from EV71 vaccine clinical trials, the immunogenicity of a single dose of vaccine does not provide protective immunity; however 2 doses, separated by at least one month, are protective.

There is no evidence to support use of a booster dose for EV71 vaccine at this time. We should closely monitor the persistence of EV71 antibody levels, long-term protection with the vaccine, and vaccine effectiveness following the vaccine's introduction. Several years of vaccinating young children with only a primary series will

result in lower exposure to EV71 virus. In this situation, waning immunity following vaccination could lead to the need for a booster dose.

The China immunization schedule is crowded during the first 2 years of life. If EV71 vaccine is to be started at 6 months of age, its administration will overlap with administration of hepatitis B vaccine at 6 months; measles containing vaccine (MCV) and Japanese encephalitis vaccine (JE) at 8 months; group A meningococcal polysaccharide vaccine from 6 to 18 months; hepatitis A vaccine at 18 months; and MMR, diphtheria–tetanus–acellular-pertussis, and JE vaccines at 18–24 months.

In order to improve vaccine uptake and reduce missed opportunities to vaccinate, we usually encourage co-administration of two or more age-recommended vaccines at a single clinic visit.

As an inactivated vaccine, EV71 vaccine should not have problems with immunogenicity or safety when administered concurrently with other vaccines. However, there are no data on concurrent vaccination with EV71 vaccine. Before such data are available, we could consider the first dose of EV71 to be given at 7 months of age followed by a second dose at 9 months. Neither age is currently used for vaccination in the China immunization schedule. Meanwhile, co-administration of EV71 with other vaccines should be studied. When the appropriate data are available, we could consider two doses of EV71 vaccine given concurrently with other vaccines starting at 6 months of age.

5.3. Forecasting the economic value of EV71 vaccines

Understanding a vaccine's potential economic value prior to licensure can identify appropriate target populations, establish vaccine price points, and ultimately improve acceptance for a vaccine. As per WHO convention, a cost-effectiveness threshold based on China's gross domestic product (GDP) per capita can be used to determine economic value. Vaccination is considered highly cost-effective when the incremental cost-effectiveness ratio (ICER) is less than the GDP per capita, cost-effective when the ICER is between one and three times the GDP per capita, and not cost-effective when the ICER exceeds three times the GDP per capita.

A study conducted in 2010 suggested that routine vaccination of EV71 vaccine in China (estimated EV71 infection incidence of 0.04%) may be cost-effective when the vaccine costs $25 or less and vaccine efficacy is ≥70%, or vaccine cost is $10 and efficacy ≥50% [35]. Since additional evidence of vaccine safety, efficacy, and other information (e.g., dose requirements) are now available from the phase I to III clinical trials, we can better understand the cost-effectiveness of EV71 vaccine. In the phase III trials of the three EV71 vaccine candidates, the EV71 infection incidence in the placebo group ranged from 6.7 to 25.2 cases per 1000 person-year among young children less than 6 years of age, and the efficacy of the vaccines against HFMD caused by EV71 was 90.9–97.4% in the intention-to-treat population. Using this information in the model above, even at the lowest EV71 risk in China (0.6%), immunization is highly cost-effective when vaccination costs are ≤$75 with 90% vaccine efficacy.

5.4. Vaccine usage

There are two options of using a new vaccine like EV71 vaccine in China—in the private market or in the national immunization program. In recent years, new vaccines have been introduced first into the private market of both developed and developing countries, and this subsequently paved the way for introduction into the public sector. However, if EV71 vaccine is used in the private market only, it will be difficult to achieve high coverage, especially if the vaccine is expensive and must be paid for out-of-pocket by parents. Thus, children who receive the vaccine could be protected, but the population may not have sufficient herd immunity, which is around 82%, to interrupt transmission in communities due to low coverage.

There are several factors which could impact EV71 vaccine introduction into a government's national immunization program. These include burden of EV71-associated HFMD, perception of disease importance, ability of the country to finance vaccine purchase with or without donor support, evidence of safety and effectiveness for the new vaccine from large population usage, capacity of the immunization system, and political and other considerations. If we have enough information from phase VI clinical trials and post marketing surveillance and decide to introduce the vaccine into the national immunization program, we also need to consider whether a catch-up program is necessary. Such a decision could be based on surveillance data, policy history, vaccine uptake, and serological survey studies. A catch up campaign could build herd immunity quickly and then be followed by routine immunization with high coverage for new birth cohorts. Such a strategy might eliminate EV71 transmission, if this is a goal of control for EV71 related HFMD. A modeling study will be helpful to additional clarity on which immunization strategy is most acceptable for China.

In addition to private use, routine immunization, and catch up immunization policies, we might also consider other immunization activities. First, we might consider partial introduction into the immunization program if introduction into the entire country is not possible or not necessary. Such a policy will need criteria for selecting areas based on the epidemiology and laboratory surveillance of EV71 disease. Second, we might need to consider whether EV71 vaccine can be used during an outbreak. The effectiveness of outbreak response immunization would need to be carefully evaluated.

5.5. Public acceptance and willingness-to-pay for an EV71 vaccine

Public acceptance should be considered in light of a novel vaccine without any experience by the public. Evidence shows concerns over the safety of vaccines, big business involvement, and the introduction of a vaccine into the EPI system. Public concerns can affect parental decisions to vaccinate. Parents should know that the current developed EV71 vaccines have been viewed as a promising solution for controlling severe or fatal HFMD, which is overwhelmingly caused by EV71, but might offer no protection against HFMD/HA caused by CV A16 or other enterovirus serotypes. The studies on vaccine acceptance for EV71 vaccine need to be done to explore public acceptance and willingness-to-pay (WTP) for EV71, as well as the price range of WTP if the vaccine will be used in private market.

6. Considerations for post marketing monitoring

The usage of a vaccine might change the disease epidemiology, and related risks should be considered before vaccine introduction. Once the vaccine is introduced, post-marketing monitoring for safety, impact, and epidemiological changes is essential.

6.1. Post marketing evaluation

The results of clinic trials show that vaccine efficacy and safety are good for all three potential vaccines; however, the three vaccines were made using different virus strains and dosages, and the clinical trials were conducted in different sites. Since sample sizes are limited during prelicensure clinical trials, rare adverse reactions may go undetected. Therefore, as a new vaccine with no global experience, the safety profile that emerges when EV71 vaccine is used in a large population must be monitored carefully. A consolidated phase IV clinical trial that includes all three vaccines

might be helpful to assess efficacy and optimize dosage. In addition, co-administration with other vaccines, emergency immunization response effectiveness, and persistency of protection should be part of EV71 post marketing evaluation.

6.2. Potential change of the epidemiological characteristics of HFMD

Widespread use of EV71 vaccine will impact natural transmission of wild EV71 virus and might change its epidemiological characteristics. Use of the vaccine could cause short-term effects and long-term effects. Short-term effects include that the vaccine can provide protection to the individual after vaccination, and, if the coverage is high, the incidence of the disease could decrease rapidly following vaccine introduction. The long-term effect of vaccination will be a slower process—we may need to monitor epidemiological changes for several years or even decades. One of the long-term risks is that when vaccine is used in private market and the coverage is neither very high nor very low, the incidence of the disease could decrease compared with pre-vaccine era, but many individuals would remain unprotected. This will lead to a situation in which unvaccinated children have a small chance to be infected by wild EV71 infection, and they could remain susceptible to older ages, even to adulthood. When susceptibility shifts from young children to older children and adults, the epidemiologic characteristics could also change, as the peak age group may occur in older children and adults. If this risk is identified through the surveillance system, we might consider introducing EV71 vaccine into the routine immunization program after a wide catch up campaign to reduce the size of the susceptible population.

The use of EV 71 vaccine could build herd immunity in the population and could produce selective pressures on EV71 and related viruses circulating in the environment. The pathogen spectrum of HFMD may change to CV A16 or other viruses that could cause serious disease. In order to monitor this possibility, we need to strengthen the laboratory-based surveillance system.

6.3. Future vaccine research and development

A logical next step of vaccine development for HFMD is multivalent vaccines and combination vaccines. Multivalent vaccines could be developed with EV71 and CV A16 virus antigens to provide more comprehensive protection for HFMD. However, decisions should be based on analysis of CV A16 pathogenesis, disease burden, the severity of the disease, cost analysis, and other considerations before deciding whether it is necessary to invest in CV A16 vaccine development.

For combination vaccines, we can learn lessons from IPV-containing combination vaccine development. Combination vaccines against a variety of diseases will greatly improve accessibility of the routine immunization program. The potential antigens that could be considered in combination with EV71 vaccine include IPV, DTP, HBV, Hib, and possibly others. However, most of them are administered to children before 6 months of age, and so addition study of the EV71 vaccine of infants younger than 6 month will be needed.

7. Conclusions

EV71 vaccine will be available soon. Immunization strategy should be based on disease epidemiology, vaccine characters, economic analysis, potential for changes in disease epidemiology, and program demand. Once EV71 is introduced, monitoring for safety, vaccine effectiveness, and impact are essential in order to update vaccination strategy with emerging evidence.

Conflict of interest statement

Authors declare there are no conflicts of interest.

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