Professor Fengcai Zhu: China leads the EV-71 vaccine research and development

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Human enterovirus 71 (EV71) is one of the main pathogens involved in infantile hand foot and mouth disease (HFMD). Prof. Fengcai Zhu from Jiangsu provincial center for disease prevention and control and his colleagues have completed the phase III evaluation of the EV71 vaccine for the first time globally, and found that EV71 vaccine provides high efficacy, satisfactory safety, and sustained immunogenicity. This finding was online published in the Lancet on May 29th (Efficacy, safety, and immunology of an inactivated alum-adjuvant enterovirus 71 vaccine in children in China: a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial).

Since first discovered in 1969, EV71 has being emerged as a serious worldwide health threat that causes HFMD and also potentially lead to fetal meningitis and encephalitis. More than 6 million cases of HFMD and 2,000 associated deaths have been reported globally in the past 10 years. To date there is no effective and safe vaccine for EV71 in the market yet.

The randomized, double-blind, placebo-controlled phase III trial led by Prof. Fengcai Zhu enrolled 10,245 healthy children aged 6-35 months from four centres (three in Jiangsu, one in Beijing) in China. They were randomly assigned to receive placebo [5,125] or inactivated EV71 vaccine [5,120] at day 0 and 28. Primary endpoints were EV71-associated HFMD and EV71-associated disease during the active surveillance period from day 56 to month 14. This study is registered with ClinicalTrials.gov, number NCT01508247.

Results of this clinical trial demonstrated that in the patients who received two-dose injection of vaccine and placebo, and were then followed in an active surveillance period, there were three cases of EV71-associated HFMD and eight cases of EV71-associated disease (HFMD, herpangina, neurological complications, and other non-specific illnesses caused by EV71) in the vaccine group [4,907]; comparing with 30 cases of EV71-associated HFMD and 41 cases of EV71-associated disease in the placebo group [4,939]. One year after the vaccination, the vaccine efficacy was 90.0% against EV71-associated HFMD and 80.4% against EV71-associated disease. Serious adverse events were reported by 62 of 5,117 (1.2%) participants in the vaccine group versus 75 of 5,123 in the placebo group (1.5%, P=0.27) throughout the research; and during the first 56 days, adverse events occurred in 3,644 (71.2%) versus 3,603 (70.3%; P=0.33).

Prof. Zhu said, "The 100% efficacy against EV71-associated hospitalization suggests its prevention of severe outcomes caused by EV71 infection, which is of major significance to public health." The vaccine was well tolerated and had a safety profile similar to inactivated poliovirus vaccines. Frequencies of adverse events were similar between the vaccine and placebo groups. No vaccine-related serious adverse events were reported. Moreover, an anti-EV71 titer of 1:32 can be regarded as the immunological surrogate endpoint for the protective antibody level needed for better EV71-associated disease prevention.

However, investigators emphasized that there was no evidence that the vaccine would cross-protect against another virus called coxsackievirus A 16 (CA16), which can also causes HFMD.

Various pathogens can cause HFMD, and EV71 vaccine has only been confirmed as effective against EV71-

associated disease. "In the 1-year surveillance period, only a small proportion of HFMD cases of were confirmed as EV71-associated. Therefore, despite of its high efficacy, even by universal immunization in children, the EV71 vaccine may have only a minor impact on reducing the overall number of cases of the disease," commenting on the results, Nigel Crawford and Steve Graham from the University of Melbourne and Murdoch Children's Research Institute in Australia said, "The next step is to assess the appropriateness of including an EV71 vaccine in China's national immunisation programme, including cost-benefit analysis. This trial led by Fengcai Zhu need to be shared internationally. This should include an assessment of potential cross-protection for other types of EV71 prevalent in other epidemic countries such as Singapore, Malaysia and Japan… The monitoring of epidemiological changes in EV71 is critical to the confirmation of vaccine efficacy in case of gene mutation." DXY.CN had an exclusive interview with Professor Fengcai Zhu, deputy director of the Jiangsu provincial center for disease prevention and control.

DXY.CN: Hand foot and mouth disease has attracted public attention ever since the HFMD outbreak in Fuyang in 2008, and according to your published papers, you and your team began to follow the epidemic status of HFMD in Jiangsu at almost the same time, how did you capture this issue in time?

Prof. Zhu: Jiangsu provincial center for disease prevention and control is one of the leading institutes that carry out clinical research on vaccines in China. The investigations on EV71 have started as early as 2003, and the virus isolation of EV71 was completed. However, this topic hasn't become well-known and widely discussed until 2008. Although HFMD is a disease common in children throughout the world, the cases that cause complication or even death mainly occur in Southeast Asia.

DXY.CN: Several viruses can cause HFMD, including EV71, CoxA 16 and so on, why do you choose EV71 as the main subject of your research?

Prof. Zhu: EV71 is the predominant strain in the cases of severe conditions and death, and is also the main pathogen that causes severe cases.

DXY.CN: According to the papers published by your team, the incidence of HFMD in southern Jiangsu is higher than that in northern part. However, the three clinical research sites in Jiangsu were Donghai, Pizhou and Baoying, two of which locate in northern Jiangsu and the other locates in the middle of Jiangsu. Why did you choose the three sites?

Prof. Zhu: We choose the site based on our prediction on the incidence of this year in the site. For example, EV71-associated HFMD doesn't frequently occur every year, usually the outbreaks appear every two or three years. After every infection peak, the incidence would be reduced by the immune barrier formed afterwards. Then as there are more and more susceptible newborn, the new infection peak appears again. In accordance with the requirements of clinical trial design, on the basis of epidemic scale, we need to predict when and where to launch disease surveillance, which currently cannot be accurately predicted. In order to collect clinical data, multicentre surveillance was adopted to guarantee the relatively high incidence in some of the observation sites. For this study, we monitored a peak in Baoying, but there were just no peaks in the other sites. Back to the historical statistics, the differences of incidences between southern and northern Jiangsu in other epidemiological studies may be not objective. The relatively high economic level and clinic visiting rate could potentially account for the conclusion of higher HFMD incidence in southern Jiangsu, which may deviate, to some extent, from the actual situation.

DXY.CN: Your research needed multiple blood sample and repeated long-term follow-up, but the compliance of recruited cases was rather satisfactory, which is more difficult with infants. Do you have any experience on the management of clinic trail to share with us?

Prof. Zhu: For these long-term studies, compliance needs to be carefully taken into consideration. In our study, several measures were taken during recruitment; local resident without plan to migrate in one year was prior included. Then adequate informed consent was provided, and the participants were informed of times of follow-up, and time-points of vaccination and blood collection. During the informed consent process, guardians without guarantee to visit sustainably would be excluded to further lower the proportion of lost to follow-up.

We have performed four regular follow-ups during the research process that were supported by local centers for disease prevention and control, and township health centers, which assured the ratio of follow-up to the greatest

extent. Moreover, we provided the convenience for clinic visiting and higher proportion of reimbursement of hospital visiting as much as we could, for instance, participants could take the "green pathway" in the hospital during the surveillance period, or could be given a higher proportion or total reimbursement of medical costs on HFMD. As for blood collection, we have also gained the support from local medical institutions, blood collection were performed by experienced nurses to minimize the pain of the participants to ensure the rest blood collections.

DXY.CN: Currently the duration of observation period for immunological protection is 14 months, how do you think about extending the protection period of this vaccine?

Prof. Zhu: In accordance with relevant state regulation, there should be an observation period of at least 12 months, and injection period lasts 2 months, adding up to 14 months. But it doesn't mean the vaccine would protect against EV71 for only 12 months. More than 90% cases were found to have neutralizing antibodies at a protective level at the end of surveillance period. Therefore, it can be considered that the protection of vaccine would last more than 12 months. Careful observation and follow-up will certainly be carried out in participants to obtain efficacy data on vaccine protection. However, onset ages of HFMD and its severe condition are mainly under 1 year, and the HFMD incidence in children above three years is low, so the efficiency of further surveillance would be low, and thus we would stop monitoring at age 3.

DXY.CN: 1,704 cases of HFMD were included in this study, of which only 2.1% were confirmed as confirmed as EV71-associated. Although HFMD was not one of the preset clinical end-points, is there any further research or data demonstrating the vaccine protection against non-determined EV71-assocaited HFMD?

Prof. Zhu: Firstly, combination of active surveillance and passive detection were adopted in our surveillance system, which is more sensitive than in general situation. Suspected HFMD cases detected by either monitoring method were identified as HFMD patients in this trail. Hence most detected cases were mild, and we also monitored some cases that didn't go for clinic visiting and get diagnosed. If we choose diagnosed HFMD patients in the hospitals as cardinal, the share of EV71-associated cases would be higher.

The nature of vaccine is specific immunity. According to our research result, EV71 vaccine only protects against EV71-associated HFMD. We has not found the evidence that it could cross-protect against CoxA 16 which means this EV-71 vaccine cannot prevent CoxA 16-associated HFMD, while the potential of cross-protection against other viruses needs further evaluation. However, it should be emphasized that EV71 leads to more severe conditions and deaths than other relevant viruses. Therefore, the prevention of EV71-associated HFMD is crucial to public health.

DXY.CN: There were 5 control cases in each patient confirmed as EV71-associated disease to determinate its level of antibody, then the optimal cutoff point was selected on the basis of Youden index; however, there were only 51 cases of EV71-associated disease, is this sample size big enough?

Prof. Zhu: In this trial, we evaluate the possibility of HFMD occurrence after vaccination by capturing the EV71-associated HFMD /EV71-associated disease as primary endpoint, which is also the most direct way to access the vaccine efficacy. However, the cost of this trial is huge. Finding the cut-off value of antibody titer as surrogate immunologic endpoint to verify the efficacy of the EV71 vaccine could provide another alternative way; it would be much quicker and convenient if we can predict the efficacy of EV71 vaccine by the surrogate immunologic endpoint, that is, by measuring the neutralizing antibody titers one month after vaccination, which is of great value in the future development of vaccine. This cut-off is the so-called surrogate immunologic endpoint that was determinate by ROC curve. There were 5 control cases for each sample, so around 300 cases were selected for the 51 samples, the number of which was not too small. However, whether the result is repeatable is very important. Actually, there is another study that can prove the repeatability of the current research but has not published at the moment. More institutions and cases are needed to further verify this finding.

DXY.CN: When will EV71 vaccine be available in the Chinese market? Do you have any plans for the further researches on EV71 vaccine?

Prof. Zhu: Our materials will be submitted to China SFDA, but at present the concrete schedule is unascertained. A large amount of work is needed, including the evaluation of the efficacy of EV71 vaccine in newborns and infants (2, 3, 4 months); further investigation on the interaction between vaccines received by children at 6-35 months of age and

EV71 vaccine or on the immunogenicity, efficacy of EV71; cost-benefit analysis for EV71 vaccine (whether including an EV71 vaccine in China's national immunization programme); phrase IV trail on post-marketing surveillance for rare adverse events after vaccination; and the like.

DXY.CN: Your research paper reports the result of phrase II trail on EV71 for the first time in the world. You have already published three articles in the world's top medical journals, NEJM and The Lancet, do you have any experience on topic selection and research design to share with the physicians and researchers in China?

Prof. Zhu: There may be some differences between our research fields. However, whichever way we look at it, the topic selection is of the first importance. Solving the major clinical or public health problems is the primary issue; then study design should follow the international standards. What's more, literature review is indispensable. Based on these considerations and throughout discussion and summary, we have published two papers on EV71-associated vaccines in the Lancet (including this paper), of which we are very proud.

DXY.CN: Since the outbreak of the first streptococcus suis infection of China in Nantong in 1998, infectious diarrhea of Xuzhou in 1999, enterovirus meningitis of Yancheng in 2001, severe acute respiratory syndrome in 2003, family clustering of avian influenza in 2007, hydrophobis in 2009, anthrax of Ganyu in 2012 and the ever-rising cases of rabies and avian influenza, you have always been worked at the frontier of prevention and control for epidemic diseases; as the increasing information requirements for public health emergency of communicable disease, more and more media interviews come up to you, what's your opinions on the role of physicians in cases of epidemic disease?

Prof. Zhu: Firstly, I think there is still some gap between the actual level of our understanding and ability versus public's anticipation. Once these epidemic diseases occur, both the public and we would hope to know the actual situation as soon as possible. What we can do is to report what we have actually found, better in detailed content and some known preventive knowledge to the public.

Secondly, what we should pay attention to is that public always wants to know more information about the patients; however, we need to do our best to protect their privacy. Unfortunately, invasion of patients' privacy is not unusual.

Thirdly, similar to drug development, the development of vaccine needs time. For example, we have spent three years in the development of EV71 vaccine, but sometimes the public anticipation is urgent, for they don't comprehensively understand the research procedure. In future, publicity and education on relevant issues should be prompted, the more the public knows, the more rationale their anticipation will be.

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Footnote

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