Evaluating Immunogenicity and Safety Effect on Combined Immune Effect of EV71 Inactivated Vaccine and HepB、MPSV-A、MR、JE-L：A Multi-center Randomized Controlled Trial

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Research unit:

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Background

To prevent and control the epidemic of HFMD and related diseases caused by EV71 infection, the development of EV71 vaccine has been developed in many countries or regions. According to the requirements of drug registration approval, we need to evaluate immunogenicity and safety effect on combined immune effect of EV71 inactivated vaccine and other vaccines (HepB、MPSV-A、MR、JE-L).

Method

Four experimental groups (HepB:3+EV71, MPSV-A:1+EV71, MR +EV71, JE-L+EV71) were included in this clinical trail. In addition to the meningococcal vaccine research group, the other three groups were followed up for the 4 times. The initial blood samples were collected, and the first dose vaccine was inoculated at the same time. EV71 second doses of vaccine were inoculated at 30 day, the blood was collected after 30 days of immunization with second doses. 6 months of safety follow-up was carried out in the whole clinical trial after vaccination. The meningococcal vaccine research group increased 1 follow-up after the second dose of MPSV-A vaccine. The index of immunogenicity and safety effect in four experimental groups need to be evaluated.

Study design and participants

The study was conducted in four provinces (Shandong, Shanxi, Shaanxi and Hunan) of China, which contains Haiyang city, Rushan city, Shimen County, Chen Cang District, Qishan County, Taigu County and Qi County. 6/8 months children were

recruited in this study, individuals were randomly assigned to experimental group and control group. Demographic information (age, sex, height and weight) was made and blood samples were collected for each individual in the same way.

Inclusion Criteria

Inclusion criteria for group Ⅰ（HepB:3+EV71）were as follows: (1)aged ⩾ 6 months; (2)sign the informed consent form; (3)the legal guardian participate in all the planned follow-up and be able to comply with all research procedures; (4)the subjects have completed the basic immunization of 2 needle recombinant hepatitis B vaccine, there is no inoculation history of EV71 vaccine, and there is no history of EV71 infection ; (5)the last vaccination intervals ⩾ 14 days ; (6)temperature ⩽ 37C° Inclusion criteria for group Ⅱ（MPSV-A:1+EV71）were as follows: (1)aged ⩾ 6 months; (2)sign the informed consent form; (3)the legal guardian participate in all the planned follow-up and be able to comply with all research procedures; (4)there is no inoculation history of EV71 vaccine, and there is no history of EV71 infection; (5)the last vaccination intervals ⩾ 14 days ; (6)temperature ⩽ 37C° Inclusion criteria for group Ⅲ（MR+EV71）were as follows: (1)aged ⩾ 8 months; (2)sign the informed consent form; (3)the legal guardian participate in all the planned follow-up and be able to comply with all research procedures; (4)there is no inoculation history of EV71 vaccine, and there is no history of EV71 infection; (5)the last vaccination intervals ⩾ 14 days and the last attenuated live vaccine intervals ⩾ 28 days ; (6)temperature ⩽ 37C° Inclusion criteria for group Ⅳ（JE-L+EV71）were as follows: (1)aged ⩾ 8 months; (2)sign

the informed consent form; (3)the legal guardian participate in all the planned follow-up and be able to comply with all research procedures; (4)there is no inoculation history of EV71 vaccine, and there is no history of EV71 infection; (5)the last vaccination intervals ⩾ 14 days and the last attenuated live vaccine intervals ⩾ 28 days ; (6)temperature ⩽ 37C°

Exclusion Criteria

Exclusion criteria for first needle: (1) the history or family history of anaphylaxis, convulsion, epilepsy, encephalopathy and psychosis; (2) the history of severe inoculation allergies; (3)patients with immunodeficiency and malignant tumors during the treatment period, receiving immunosuppressive therapy (oral steroid) or HIV due to low immunity, or family members have congenital immune disease; (4)Nonspecific immunoglobulin was injected within one month; (5)temperature > 37.1C° and infectious diseases; (6)the history of thrombocytopenia or other thrombocytopenia with a definite diagnosis; (7)respiratory disease, acute infection or chronic disease activity period; (8)severe cardiovascular disease (CVD, pulmonary edema, hypertension can not be controlled by drugs to the normal range), liver and kidney disease, and complications of diabetes; (9)infectious, suppurative and allergic dermatosis; (10)other conditions that may affect the evaluation of the trail Exclusion criteria for follow-up needle: (1)any serious adverse events that have a causal relationship with the inoculation of the upper dose of the vaccine; (2)the abnormality of 4 levels (local, systemic adverse reactions and vital signs) was judged to be related to vaccination; (3)other new

standards of "Exclusion criteria for first needle";(4)other conditions that may affect the evaluation of the trail

Vaccine inoculation and follow-up

Test I (HepB:3+EV71):

Experimental group - 6 month old HepB third dose and EV71 first dose were inoculated at the same time, 7 month old EV71 second dose was inoculated, blood samples from the participants were collected at 8 month old;

Control group 1- 6 month old HepB third dose was inoculated separately, blood samples from the participants were collected after two months;

Control group 2 - 6 month old EV71 first doses was inoculated, 7 month old EV71 second dose was inoculated, blood samples from the participants were collected at 8 month old.

Test II (MPSV-A:1+EV71):

Experimental group - 6 month old MPSV-A first dose and EV71 first dose were inoculated at the same time, 7 month old EV71 second dose was inoculated, 9 month old MPSV-A second dose was inoculated, blood samples from the participants were collected at 10 month old;

Control group 1- 6 month old MPSV-A first dose was inoculated separately, 9 month old MPSV-A second dose was inoculated separately, blood samples from the participants were collected at 10 month old;

Control group 2 - 6 month old EV71 first doses was inoculated, 7 month old EV71 second dose was inoculated, blood samples from the participants were collected

at 10 month old.

Test III (MR+EV71):

Experimental group - 8 month old MR first dose and EV71 first dose were inoculated at the same time, 9 month old EV71 second dose was inoculated, blood samples from the participants were collected at 10 month old.

Control group 1- 8 month old MR first dose was inoculated separately, blood samples from the participants were collected at 10 month old;

Control group 2 - 8 month old EV71 first doses was inoculated, 9 month old EV71 second dose was inoculated, blood samples from the participants were collected at 10 month old.

TestIV(JE-L+EV71):

Experimental group - 8 month old JE-L first dose and EV71 first dose were inoculated at the same time, 9 month old EV71 second dose was inoculated, blood samples from the participants were collected at 10 month old.

Control group 1- 8month old JE-L first dose was inoculated separately, blood samples from the participants were collected at 10 month old;

Control group 2 - 8 month old EV71 first doses was inoculated, 9 month old EV71 second dose was inoculated, blood samples from the participants were collected at 10 month old.

EV71 vaccine 0.5ml per dose, Wuhan Biological Products Co., Ltd., Wuhan, Hubei Province, China; 10μg HepB 0.5ml per dose, Wuhan Biological Products Co., Ltd., Wuhan, Hubei Province, China; 30ug MPSV-A 0.5ml per dose, Wuhan Biological

Products Co., Ltd., Wuhan, Hubei Province, China; MR 0.5ml per dose, Beijiing Biological Products Co., Ltd., Beijing, China; JE-L 0.5ml per dose, Chengdu Biological Products Co., Ltd., Chengdu,Sichuan Province, China

Immunogenicity end point

Detection of serum antibody EV71 vaccine by culture neutralization test, the definition of positive for neutralizing antibody titers of <1:8 before inoculation, inoculation after neutralizing antibody titers than 1:8; or before inoculation neutralizing antibody titer is above 1:8, the titer of neutralizing antibody after vaccination appeared more than 4 times the growth. Hepatitis B vaccine seroconversion was defined as Anti-HBs<10mIU/ml before inoculation, Anti-HBs after inoculation was more than 10mIU/ml. Leprosy vaccine using measles rubella immunoglobulin ELISA detection test, measles >200U/ml positive for rubella >20U/ml positive or positive before inoculation; after inoculation, antibody positive growth is more than 4 times. Japanese encephalitis vaccine serum samples by using PRNT test before immunization antibody titer after inoculation was less than 1:5, at 1:10, or after vaccination antibody titer than before inoculation is no less than 4 times of growth is positive. Meningococcal vaccine samples A meningococcal bactericidal antibody level in serum by micro bactericidal antibody test, the antibody titer after inoculation than before inoculation is no less than 4 times of growth is positive.

Safety assessment

Safety assessment Participants were provided with diary cards to record the

occurrence and severity of solicited local reactions at the injection site (pain, induration, erythema, edema, pruritus) during 7 days after vaccination, solicited systemic reactions (fever, headache, fatigued, cough, myalgia, asthenia, vertigo, diarrhea), and any unsolicited adverse during 29 days after vaccination.