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Immunogenicity and persistence from different 3-dose schedules of live and inactivated polio vaccines in Chinese infants

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ABSTRACT

Background: OPV is the only poliovirus vaccine used in the China EPI system, although IPV is available in the private market. We compared immunigencity and persistence among different schedules of IPV and OPV.

Methods: 536 Chinese infants were enrolled into 4 groups receiving different schedules administered at 2, 3, and 4 months of age: IPV–OPV–OPV, IPV–IPV–OPV, IPV–IPV–IPV, and OPV–OPV–OPV. The I–I–I group received an 18-month IPV booster dose. Blood samples were collected before the first dose, after the third dose, and at 18 months for all groups, and also after the booster dose for the I–I–I group. Polio neutralizing antibody titers were assessed, and seroprotection rates were calculated after primary immunization and at 18 months of age.

Results: Before the first dose, GMTs of the 4 groups ranged from 2.96 to 6.89, and seroprotection rates ranged from 17.6% to 54.3%. After 3 doses, the GMT of the I–O–O and I–I–O groups ranged from 901.09 to 1,110.12, and the GMT of the I–I–I group range was 212.02 to 537.52, significantly lower than for the 2 sequential schedules ($P < 0.001$). Seroprotection rates were 98.1% to 100%, with no significant differences among groups. At 18 months of age, the GMTs declined to a range of 527.00 to 683.44 in the I–O–O and I–I–O groups, and declined to 150.04 to 239.89 in the I–I–I group, significantly lower than for the other 3 groups ($P < 0.001$).

Conclusions: The sequential schedules achieved high GMTs and seroprotection. The IPV-only schedule achieved high seroprotection but with lower GMTs. Sequential schedules are suitable for China. With the 2 sequential schedules, GMTs remained high at 18 months of age and were not inferior to the OPV-only schedule. Thus, with a sequential schedule, the booster dose could be given at 4 years of age, the same age as the current OPV booster dose.

In 1988, when the World Health Assembly called for the eradication of polio by 2000, there were more than 350,000 children paralyzed annually by polio. Since then, more than 10 billion doses of oral polio vaccine (OPV) have been administered to more than 2.5 billion children worldwide. At the end of 2012, there were only 223 polio cases in 5 countries, the lowest number ever recorded, and these cases occurred in the fewest districts of the fewest countries ever. The Polio Eradication and Endgame Strategic Plan 2013–2018 calls for OPV cessation, following certification of wild poliovirus eradication, to eliminate emergence and spread of vaccine-derived polioviruses (VDPV) [1]. VDPVs can emerge by phenotypic reversion of vaccine strains and spread in underimmunized populations, resulting in circulating VDPVs (cVDPVs). In 2012, more countries suffered polio outbreaks due to cVDPVs than due to wild poliovirus. To prevent emergence of VDPVs, the 2013–2018 plan requires introduction of at least one dose of inactivated polio vaccine (IPV) into routine immunization programs by October 2015 in countries using an all-OPV routine schedule.

Currently, 144 countries, including China, use OPV in their EPI program [1]. Through the use of OPV in routine immunization and supplementary immunization campaigns, China and the Western Pacific Region of WHO eliminated polio and were certified polio-free in 2000 [2–4]. In 2004, China reported its first cVDPV, which resulted in 3 cases [5]. Between 1996 and 2002, the China national

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polio laboratory reported 4 VDPV type 2 strains in acute flaccid paralysis (AFP) cases [6]. Between 2007 and 2012, VDPV cases were continuously reported in Shandong, Guangxi, and Shanxi provinces through the AFP surveillance system [7–10].

Vaccine-associated paralytic poliomyelitis (VAPP) is another rare consequence of the use of live polio vaccine. VAPP is due to reversion of attenuation in primary vaccinees and their close contacts [11]. The incidence of VAPP is approximately 2 to 4 cases per million birth cohort using an all-OPV schedule, with the greatest risk from the first dose given to a non-immune individual. Given the large number of OPV doses administered annually in China, the expected VAPP rate has been estimated to be 76–161 cases per year [12].

Prior to 2009, OPV was the only polio vaccine available in China. In the China EPI schedule, OPV is administered at 2, 3, and 4 months of age, with a booster dose given at 4 years of age. In 2009, IPV produced by sanofi pasteur was introduced into the private market in China, giving parents an additional vaccine choice. Also in 2009, the Chinese Center for Disease Control and Prevention (CDC) issued guidance for IPV use, recommending that IPV should be used in persons with contraindications to OPV and should be administered at 2, 3, 4, and 18 months of age.

To provide data to inform decision making for the introduction of IPV into China's EPI system, we compared immunogenicity and seroprotection among different three-dose IPV and OPV combination schedules and IPV- or OPV-only schedules.

1. Materials and methods

1.1. Study design

The study was approved by Medical Ethics Committee of Beijing CDC. Twenty Beijing city immunization clinics participated in this study; they were divided into 4 groups of 5 clinics each. Each group of clinics was assigned to use 1 of 4 poliovirus vaccination schedules for patients participating in the study: IPV–OPV–OPV (I–O–O), IPV–IPV–OPV (I–I–O), IPV–IPV–IPV (I–I–I), and OPV–OPV–OPV (O–O–O). Group O–O–O was considered the control group, as this schedule is the current national EPI schedule. In each clinic, parents or guardians of infants meeting study inclusion criteria were invited to have their infant participate in this study. Infants of parents or guardians who agreed to participate became the study subjects. We chose this design to minimize immunization schedule administration errors, since participating clinics used the same schedule for all of their participating infants.

The study objectives were to (1) compare immunogenicity of the different schedules following the 3-dose primary series using the 2-, 3-, and 4-month polio vaccination ages of the China EPI system, (2) compare the persistence of polio antibody at 18 months of age, and (3) understand the immunogenicity of an 18-month booster dose for the IPV–IPV–IPV schedule.

1.2. Study population

To be eligible for inclusion in the study, infants must have been between 60 and 89 days old on enrollment, have resided in Beijing for the previous 2 months, been born full term (≥36 weeks) with birth weight ≥2.5 kg, and have parents with the ability to follow the study protocol. Parents or guardians provided written informed consent prior to enrolment. During routine immunization visits at 2 months of age, parents or legal guardians were informed of the study and invited to participate. Parents or guardians who agreed to participate signed written, informed consent. Non-enrolled infants at participating clinics were given OPV on the standard China EPI schedule.

1.3. Study vaccines

The trivalent IPV used in this study was produced by sanofi pasteur (France), 0.5 ml per dose, (type 1, 40 DU (D-antigen unit); type 2, 8 DU; type 3, 32 DU), and was administered by intramuscular injection in the thigh. The OPV used was produced by Tian Tan (Beijing, China), 1gram per dose, (type 1, $10^{5.8}$ $TCID_{50}$ (50% tissue culture infectious dose); type 2, $10^{4.8}$ $TCID_{50}$; type 3, $10^{5.3}$ $TCID_{50}$, given by the oral route. IPV was donated by sanofi pasteur; OPV was purchased by the government, as it is an EPI vaccine.

1.4. Study procedures

The three study doses were given at 2, 3, and 4 months of age. The I–I–I group was also given a booster dose at 18 months.

Blood collection was at 2 months of age (before the first dose), 5 months of age (after the third dose), 18 months of age, and 19 months age (after the booster dose, and only for the I–I–I group).

A total of 553 infants was enrolled: 159, 121, 125, and 148 infants in the I–O–O, I–I–O, I–I–I, and O–O–O groups, respectively. Blood samples were obtained on all 553 infants before they received their first poliovirus vaccine dose. By one month after the third scheduled dose at 5 months of age, 108 infants had been withdrawn from the study by their parents or guardians, leaving 122, 103, 114, and 160 infants in groups I–O–O, I–I–O, I–I–I, and O–O–O, respectively, who finished the second blood sampling. By 18 months of age, 48 infants withdrew, and 88, 72, 96, and 76 infants remained in groups I–O–O, I–I–O, I–I–I and O–O–O, respectively, and provided blood specimens. By 1 month after the booster dose of IPV in group I–I–I, 12 infants withdrew, and blood samples were obtain from the remaining 84 infants.

1.5. Laboratory testing

All blood samples were at least 2 ml in volume. Blood specimens were stored overnight, and serum was separated and frozen at −20 °C. All serum samples were tested for neutralizing antibodies for poliovirus types 1, 2, and 3 by Beijing CDC polio lab (a WHO-accredited polio lab) by using means of a modified micro neutralization assay. WHO standard procedures for determining immunity to poliovirus using the microneutralization test were followed [13]. Antibodies were tested against Sabin strains, and serum from WHO was used as a standard. Hep-2 cells were obtained from the National Institute for Food and Drug Control. Serum was inactivated at 56 °C for 30 min. The starting dilution was 1:4, ending at 1:1,024. Neutralizing antibody titers ≥1:8 were taken as positive, protective levels. The unobserved titers (less than 1:4 or more than 1:1,024) were assigned values of 1:2 and 1:2048 for analytic purposes. Geometric mean titers (GMT) and protective rates were calculated.

1.6. Statistical analyses

GMT and protective rate were used to descript the titer distributions of the study groups. ANOVA was used to compare GMTs among groups. The χ^2 test or Fisher's exact probability test was used to compare protective rates among groups. Multiple comparisons were done using least-significant. We used SPSS17.0 statistical software. A *P*-value less than 0.05 was used as a significant difference.

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