Immunogenicity of Two Different Sequential Schedules of Inactivated Polio Vaccine Followed by Oral Polio Vaccine Versus Oral Polio Vaccine Alone in Healthy Infants in China

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Background. Two vaccination schedules where inactivated polio vaccine (IPV) was followed by oral polio vaccine (OPV) were compared to an OPV-only schedule.

Methods. Healthy Chinese infants received a 3-dose primary series of IPV-OPV-OPV (Group A), IPV-IPV-OPV (Group B), or OPV-OPV-OPV (Group C) at 2, 3, and 4 months of age. At pre-Dose 1, 1-month, and 14-months post-Dose 3, polio 1, 2, and 3 antibody titers were assessed by virus-neutralizing antibody assay with Sabin or wild-type strains. Adverse events were monitored.

Results. Anti-polio 1, 2, and 3 titers were ≥8 (1/dil) in >99% of participants, and Group A and Group B were noninferior to Group C at 1-month post-Dose 3 as assessed by Sabin strain-based assay (SSBA). In Group A 1-month post-Dose 3, there was no geometric mean antibody titers (GMT) differences for types 1 and 3; type 2 GMTs were ≈3-fold higher by wild-type strain-based assay (WTBA) versus SSBA. For Group B, GMTs were ≈1.7- and 3.6-fold higher for types 1 and 2 via WTBA, while type 3 GMTs were similar. For Group C, GMTs were ≈6.3- and 2-fold higher for types 1 and 3 with SSBA, and type 2 GMTs were similar. Antibodies persisted in >96.6% of participants. Adverse event incidence in each group was similar.

Conclusions. A primary series of 1 or 2 IPV doses followed by 2 or 1 OPV doses was immunogenic and noninferior to an OPV-only arm. SSBA was better at detecting antibodies elicited by OPV with antibody titers correlated to the number of OPV doses (NCT01475539).

Key words. China; immunogenicity; IPV; sequential regimen.

The World Health Assembly launched the Global Polio Eradication Initiative (GPEI) in 1988 [1]. Since then, the principal weapon has been oral polio vaccine (OPV) given through routine immunization activities to children <5 years of age complemented by national immunization days, by mop-up campaigns, or by supplementary immunization activities. Initially, the number of polio cases and countries with infection fell rapidly, as financing and political support increased in the mid-1990s [2]. Certification of wild poliovirus transmission-free status was achieved in the Americas in 1994, in the Western Pacific (including the People’s Republic of China where the last acute flaccid paralysis case associated with an indigenously circulating wild poliovirus was detected in 1994) in 2000 [3], and in European World Health Organization (WHO) regions (>3 billion people in 134 countries) in 2002 [4]. Persistent areas of wild poliovirus transmission in Northern Nigeria and the Pakistan–Afghanistan border region are foci of GPEI activities and represent virus exportation sources. During the 2011–2013 period, 7 previously polio-free countries were re-infected due to virus importations [5]. As poliomyelitis can only be prevented through...
immunization, GPEI is constantly assessing use of the existing vaccines (OPV and inactivated polio vaccine [IPV]) to prevent paralytic poliomyelitis and stop poliovirus circulation around the world.

In China, the last wild poliovirus outbreak occurred after an importation of wild poliovirus type 1 from Pakistan to Xinjiang province in late 2011 [6]. The Chinese national immunization schedule recommends a 3-dose OPV primary vaccination series given at 2, 3, and 4 months of age and an OPV booster dose at 4 years of age [7].

OPV is easy to administer, inexpensive, and uniquely induces strong intestinal mucosal immunity [8, 9]. Although OPV is safe, rare adverse events (AEs) do occur and cause vaccine-associated paralytic poliomyelitis (VAPP) [10]. The overall incidence of VAPP has been estimated at 4 cases/1,000,000 birth cohorts/y, with large variations depending on hygiene and socioeconomic considerations, vaccine type, and recipient age. In China, VAPP incidence has been described ranging from 0.27 to 2.82/million in 2007 [11]. Also, OPV viruses proliferating within their hosts can revert and reacquire neurovirulence and transmissibility characteristics similar to wild polioviruses (known as vaccine-derived poliovirus [VDPV]). When adequate ecological conditions are present, VDPV has caused outbreaks of paralytic disease (cVDPV) [12]. Furthermore, chronic shedding of VDPV has been reported in vaccine recipients with immunodeficiencies (iVDPV). The risks and burden posed by VAPP, cVDPV, and iVDPV have led many countries to migrate from exclusive OPV use to the IPV-only use or to the use of different mixed/sequential IPV/OPV regimens (ie, IPV-then-OPV, OPV-then-IPV, or mixed IPV and OPV regimens where the vaccines are administered at the same time on 1 or more occasions during the infant series). Many trials have been performed to assess IPV/OPV regimens to date (reviewed in [13]), particularly IPV-then-OPV sequential schedules. Results from several clinical studies indicate if Dose 1 is IPV, postprimary series antibody levels increased compared to OPV-only schedules; this sequential schedule also induced some mucosal intestinal and/or nasopharyngeal immunity [14–33] (Sanoï Pasteur. Study HE9812; unpublished; data on file. Sanoï Pasteur. Study IPV33-EXT; unpublished; data on file). Participants immunized with IPV are less likely to excrete poliovirus in feces after exposure compared to first-time OPV recipients; however, they are not less likely compared to multi-OPV recipients. Therefore, their excretion of poliovirus can be for shorter periods and with fewer viruses in their feces [20, 23, 28], potentially decreasing their role in poliovirus transmission in areas where the fecal-oral spread is predominant. In addition, these schedules are able to drastically reduce the VAPP burden when deployed on a large scale due to the immune burden afforded by the IPV dosing prior to OPV receipt [34, 35].

In this context, and within the scope of WHO recommendations [36], China is considering transitioning to IPV but, contrary to the OPV-then-IPV schedule currently recommended by WHO, is envisaging an IPV-then-OPV sequential regimen to primarily address VAPP risks.

This Phase IV trial was therefore designed to assess the systemic immunogenicity and safety (and not the intestinal mucosal immunity) of 2 different IPV-then-OPV sequential regimens in Chinese infants with the overall aim to generate local data allowing local authorities to define the best strategy for polio immunization.

METHODS

Study Design and Participants

This was a Phase IV, randomized, open-label study conducted in 1 center in China (ClinicalTrials.gov NCT01475539). The local independent ethics committee of the Guangxi province Center for Disease Prevention and Control approved the study protocol prior to the start of the study, and a single amendment was added (serological analysis by a second laboratory [see below]). The study was conducted in accordance with local regulations, Good Clinical Practice, the International Conference on Harmonization guidelines, and the Edinburgh revision of the Declaration of Helsinki. Before enrollment, at least 1 parent or legally acceptable representative, if literate, signed a written informed consent form (ICF); if unable to read and sign the ICF, it was signed and dated by an impartial witness as testimony that the information contained in the ICF had been accurately explained to and understood by the participant’s parent/representative.

Healthy infants aged 2–3 months, born at full term (>37 weeks) and weighing ≥2.5 kg, were eligible for enrollment. The main exclusion criteria were participation in a separate clinical study, receipt of a nonstudy vaccine before or during the study (excluding DTaP, Hib, BCG, and hepatitis B, which were to be administered ≥7 days prior or after any of study vaccinations), receipt of any poliomyelitis vaccine or poliomyelitis infection or any blood or blood-derived products before the study, congenital or acquired immunodeficiency (in either the participant or in his/her close contacts), known hypersensitivity to any vaccine component, and any bleeding disorder contraindicating intramuscular injection.

Participants were randomized to receive a 3-dose primary series of either IPV-OPV-OPV (Group A), IPV-IPV-OPV (Group B), or OPV-OPV-OPV (Group C) at 2, 3, and 4 months of age. The Sponsor’s statistics department created a 1:1:1 randomization list. Vaccines were administered
either intramuscularly into the anterolateral area of the thigh (IPV) or orally (OPV).

**Vaccines**

IPV was Imovax polio® (batch number G0480-1) manufactured by Sanofi Pasteur SA, France, and supplied as a sterile suspension in a prefilled single-dose syringe (0.5 mL) containing inactivated poliovirus types 1 (Mahoney strain; 40 D-Ag units), 2 (MEF-1 strain; 8 D-Ag units), and 3 (Saukett stain; 32 D-Ag units), 2-phenoxethanol (2–3 μL), formaldehyde (2–20 μg), and water for injection (≤0.5 mL). OPV (batch number 201101415) was a live poliovirus vaccine, manufactured by the Medical Biology Institute of the Chinese Academy of Medical Sciences and contained attenuated poliovirus strains (types 1, 2, and 3) grown separately in monkey kidney cell cultures. After cultivation and harvesting, the resultant trivalent vaccine is formulated as a solid white dragee candy presentation.

**Serology**

A 2-mL blood sample was taken prior to Dose 1, and at 1 month and 14 months after Dose 3 (at approximately 5 and 18 months of age, respectively) to measure anti-polio 1, 2, and 3 antibody concentrations. The immunological assays were performed by the National Institute for Food and Drug Control laboratory in China, using a Sabin strain–based neutralization assay (SSBA), and by the Sponsor’s central laboratory, Global Clinical Immunology (GCI) in the United States, using a wild-type strain–based (Mahoney, MEF-1, Saukett) neutralization assay (WTBA). The SSBA data were used for the primary study objective of the assessment of noninferiority, and WTBA data were used as an observational objective to investigate potential differences resulting from the strains used in the 2 assays.

**Reactogenicity and Safety**

Participants were monitored for 30 minutes postvaccination for immediate AEs. Parents/legal representatives used diary cards to record the duration and intensity of any solicited (ie, predefined) injection site (tenderness, erythema, swelling) and systemic (fever, vomiting, abnormal crying, drowsiness, appetite loss, irritability) event for 7 days after each vaccination. For the solicited injection site reactions and fever intensity assessment, both the China State Food and Drug Administration (SFDA) and the Sponsor’s scales were used. Although differences between the scales are minor, the China SFDA scale was used for data analysis. Axillary rather than rectal temperature was recorded for cultural and compliance reasons. All solicited events were considered as related to the vaccination, and termed as solicited reactions.

The nature, duration, and intensity of unsolicited AEs and any action taken were recorded by the parents/legal representative for 28 days after each vaccination. Any unsolicited injection site reaction (in Groups A and B) was by convention considered vaccination related, and so termed an adverse reaction; the causality for the remaining unsolicited AEs were assessed by the Investigator. Serious AEs (SAEs) were collected throughout the study, and their causality was assessed by the Investigator.

**Statistical Analyses**

The primary study objective was to demonstrate noninferiority of immune responses in Group A (IPV-OPV-OPV) and Group B (IPV-IPV-OPV) compared to the reference Group C (OPV-OPV-OPV) in terms of seroprotection (titer ≥8 [1/dil]) at 1 month post-Dose 3. Noninferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) of the difference in seroprotection between groups (using Group C as the reference in each case) was greater than −10% (α = 2.5%). Noninferiority of Groups A and B to Group C was established if noninferiority was shown for each of the 3 poliovirus serotypes for each group comparison. Secondary objectives were to further describe without statistical comparisons the immune response in each group at 1 month and 14 months post-Dose 3; reactogenicity was also described.

For all immunological analyses, the per-protocol analysis set was used, and for all safety analyses the safety analysis set was used. The 95% CIs of all point estimates were calculated by exact binomial distribution (Clopper-Pearson method). In addition to seroprotection and geometric mean titers, the seroconversion (≥4-fold increase in titer) from pre-Dose 1 to 1 month post-Dose 3 was calculated, taking account of the predicted decline in maternal antibody present in the pre-Dose 1 sample and assuming a half-life of 28 days. Reverse cumulative distribution curves and concordance plots for the assays were also constructed. The sample size was calculated by the Farrington and Manning formula, and to obtain an overall power for the study of 80% the individual power for each hypothesis tested was ≥90%. The expected response in the reference group (Group C: OPV-OPV-OPV) was based on the results obtained during a previous trial performed in China [37]. With the assumption of a 10% dropout rate from the per-protocol analysis set at 1 month post-Dose 3, 152 participants per group (ie, 456 total) were required for each hypothesis to achieve a power of 90%. The statistical analyses were performed with SAS software Version 9.1 or greater (SAS Institute, Cary, NC).

**Results**

**Participants Studied**

Participants were enrolled (N = 456) and received ≥1 vaccination (152 participants/study group) between November
2011 and June 2012. Of these, 152 participants in each of Groups A and B, and 150 participants in Group C completed the primary phase of the study, and 148, 150, and 149 completed the antibody persistence series in Groups A, B, and C, respectively. The participant flow is presented in Figure 1, and demography was similar in each group.

**Immunogenicity**

Table 1 presents the results of the analysis of noninferiority for immunogenicity between Groups A and C and Groups B and C at 1 month post-Dose 3 (SSBA data). Seroprotective antibody levels (titer ≥8 [1/dil]) were demonstrated in >99% of participants for anti-polio 1, 2, and 3 in each
group, and noninferiority was demonstrated for anti-polio 1, 2, and 3 for each comparison.

Table 2 presents the seroprotection rates, and geometric mean antibody titers (GMT) for anti-polio 1, 2, 3 in each group, at pre-Dose 1, 1 month post-Dose 3, and 14 months post-Dose 3, using both SSBA and WTBA, as well as the seroconversion (≥4-fold increase) from pre-Dose 1 to 1 month post-Dose 3 (taking maternal antibodies into account). Figure 2 presents the reverse cumulative distribution curves (RCD) for anti-polio antibody titers observed for the 3 groups pre-Dose 1 and 1 month post-Dose 3. Figure 3 presents concordance plots for each anti-polio antibody at 1 month post-Dose 3 between the SSBA and WTBA data.

The seroprotection rates from the WTBA (Table 2) are generally similar to those obtained from the SSBA, with >99% of participants in each group and for each anti-polio antibody achieving a titer ≥8 (1/dil) at 1 month post-Dose 3. For GMT values, the pre-Dose 1 data were higher by SSBA in each group and for each poliovirus type, with no overlap of 95% CIs in any case.

In Group A (IPV-OPV-OPV) at 1 month post-Dose 3, there was no difference in GMT for types 1 and 3, and for type 2 the GMT was ≈3-fold higher for the WTBA data compared to the SSBA data, with nonoverlapping 95% CIs; for Group B (IPV-IPV-OPV), the titers were ≈1.7- and 3.6-fold higher for types 1 and 2 from the WTBA assay (with no overlap of 95% CIs), while for type 3 the GMT were similar for both assay methods; and for Group C (OPV-OPV-OPV), the titers were approximately 6.3- and 2-fold higher for types 1 and 3 using the SSBA data (with nonoverlapping 95% CIs), and similar for type 2 for both assays.

Seroconversion rates were high regardless of group, with no differences according to the assay (Table 2).

Fourteen months post-Dose 3, GMT declined in all groups (regardless of assay) and the overall persistence was better in Group B. Nevertheless, almost all participants still achieved poliovirus antibody titers ≥8 (1/dil).

The RCD curves (Figure 2) and assay concordance data (Figure 3) illustrate that the SSBA biased titers in favor of OPV recipients, with a more pronounced effect in cases of OPV-only administrations (Group C).

### Safety and Tolerability

There were no immediate AEs (≤30 minutes after any vaccination). Solicited IPV injection site reactions (Groups A and B only) and systemic reactions (all groups), all grades and for those rated by the Investigator as Grade 3, occurred with similar frequencies within the groups. The solicited IPV injection site reactions, all grades and for those rated by the Investigator as Grade 3, occurred with similar frequencies within the Group B participants between dose 1 and dose 2. Some small differences were noted, such as injection site swelling, which occurred more frequently in Group A (3.9%) than Group B (0.7%), but were not considered to be of clinical significance.

Overall, in participants experiencing solicited adverse reactions in the 7 days after any dose of any vaccine, the incidence of Grade 3 reactions was low (0%–5.9%) for individual solicited reactions.

The incidence of unsolicited AEs within 28 days after any vaccination was similar in each group: Group A = 65.1%, Group B = 65.8%, and Group C = 61.2%.

The incidence of SAEs ≤28 days after any vaccination was 2.0% (Group A), 4.6% (Group B), and 5.3% (Group C); all were systemic (mainly respiratory disorders) events and none was considered to be vaccination related.

### Discussion

This trial investigated immunogenicity and safety profiles of 2 different IPV-followed-by-OPV sequential schedules versus an OPV-only schedule in healthy infants in China. Such trials have been performed with several IPV-containing vaccines in 8 countries (Brazil, China, France, Guatemala, Mexico, Taiwan, United Kingdom, and United States) since 1986 and have explored regimens consisting of 1 or 2 consecutive doses of IPV-containing vaccines followed by 1 or 2 OPV administered as “2+1,” “3+1,” or “3+0” primary immunization regimens [14–33] (Sanofi Pasteur. Study HE9812; unpublished; data on file. Sanofi Pasteur. Study IPV33-EXT; unpublished; data on file). These trials have been either nonrandomized open-label studies or
<table>
<thead>
<tr>
<th>Group A</th>
<th>IPV-OPV-OPV</th>
<th>Group B</th>
<th>IPV-OPV-IPV</th>
<th>Group C</th>
<th>OPV-OPV-OPV</th>
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<tbody>
<tr>
<td></td>
<td>Pre-Dose 1</td>
<td>1 Month Post-Dose 3</td>
<td>14 Months Post-Dose 3</td>
<td>Pre-dose 1</td>
<td>1 Month Post-Dose 3</td>
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<tr>
<td>Seroprotection (≥8 [1/dil]) (%)</td>
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<td>Anti-polio 1</td>
<td></td>
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<tr>
<td>SSBA</td>
<td>44.7 (36.6;53.0)</td>
<td>100 (97.6;100)</td>
<td>100 (97.5;100)</td>
<td>43.9 (35.8;52.3)</td>
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</tr>
<tr>
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<td>18.4 (12.5;25.6)</td>
<td>100 (97.6;100)</td>
<td>100 (97.5;100)</td>
<td>17.0 (11.3;24.1)</td>
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<tr>
<td>SSBA</td>
<td>42.0 (34.0;50.3)</td>
<td>100 (97.6;100)</td>
<td>100 (97.5;100)</td>
<td>32.4 (25.0;40.6)</td>
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<td>38.3 (30.4;46.6)</td>
<td>100 (97.6;100)</td>
<td>100 (97.5;100)</td>
<td>20.0 (13.8;27.4)</td>
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<tr>
<td>SSBA</td>
<td>28.0 (21.0;35.9)</td>
<td>99.3 (96.3;100)</td>
<td>98.0 (94.2;99.6)</td>
<td>21.6 (15.3;29.1)</td>
<td>100 (97.5;100)</td>
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<tr>
<td>WTBA</td>
<td>20.9 (14.7;28.4)</td>
<td>100 (97.6;100)</td>
<td>98.0 (94.2;99.6)</td>
<td>15.9 (10.3;22.8)</td>
<td>99.3 (96.3;100)</td>
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<td>Geometric mean titer (1/dil)</td>
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<tr>
<td>SSBA</td>
<td>8.45 (7.11;10.0)</td>
<td>2101 (1715;2573)</td>
<td>581 (467;723)</td>
<td>9.08 (7.62;10.8)</td>
<td>1542 (1251;1900)</td>
</tr>
<tr>
<td>WTBA</td>
<td>3.37 (2.92;3.88)</td>
<td>1829 (1467;2280)</td>
<td>330 (267;407)</td>
<td>3.42 (2.95;3.97)</td>
<td>2572 (2043;3239)</td>
</tr>
<tr>
<td>Anti-polio 2</td>
<td></td>
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<tr>
<td>SSBA</td>
<td>7.87 (6.75;9.18)</td>
<td>743 (653;844)</td>
<td>299 (235;354)</td>
<td>6.92 (6.00;7.98)</td>
<td>2285 (1945;2683)</td>
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<tr>
<td>WTBA</td>
<td>5.17 (4.37;6.11)</td>
<td>2190 (1914;2506)</td>
<td>669 (562;795)</td>
<td>4.11 (3.48;4.85)</td>
<td>8229 (7152;9469)</td>
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<tr>
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<td>6.17 (5.39;7.07)</td>
<td>1473 (1235;1755)</td>
<td>242 (196;298)</td>
<td>5.60 (4.96;6.27)</td>
<td>1854 (1442;2384)</td>
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<td>3.58 (3.13;4.09)</td>
<td>1409 (1171;1694)</td>
<td>154 (126;189)</td>
<td>3.22 (2.87;3.60)</td>
<td>2053 (1580;2666)</td>
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<td>Seroconversiona (%)</td>
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<tr>
<td>SSBA</td>
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<td>NA</td>
<td>99.3% (96.4;100)</td>
<td>100% (97.5;100)</td>
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<tr>
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<tr>
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<tr>
<td>WTBA</td>
<td>98.7% (95.3;99.8)</td>
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<td>96.7% (92.5;98.9)</td>
<td>98.0% (94.2;99.6)</td>
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</table>

Data are % or geometric mean titer (95% confidence interval).
Abbreviations: NA, not applicable; SSBA, Sabin strain–based neutralization assay; WTBA, wild-type strain–based neutralization assay.

aFrom pre- to 1 month post-dose 3 and defined as an increase in the antibody titer that was 4 times or more higher than the expected decline in the maternally derived antibodies measured in pre-dose 1 samples.
randomized controlled trials between sequential schedules and IPV-only and/or OPV-only schedules. In addition, some trials have investigated the prevalence, intensity, duration, and genetics of poliovirus excretion after an OPV vaccination/challenge. In the current trial, a standalone IPV has been used whereas in some trials combination vaccines containing IPV have been used (whole-cell Pertussis-IPV backboned combinations or acellular Pertussis-IPV backboned combinations). Furthermore, the assays used to evaluate the concentration of neutralizing antibodies have varied among studies using seroneutralization assays based on Sabin strains or wild-type Salk strains.

The results obtained from this trial demonstrate the non-inferiority of the 2 different IPV-then-OPV sequential schedules to the OPV-only regimen as measured by the percentage of participants reaching protective levels post-Dose 3. These results are consistent with the studies done previously with similar design and similar objectives. The best

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**Figure 2.** Reverse cumulative distribution curves for anti-polio 1, anti-polio 2, and anti-polio 3 at pre-Dose 1 (unbolded lines) and 1-month post-Dose 3 (bolded lines) for Sabin strain–based neutralization assay (SSBA) (left) and wild-type strain-based neutralization assay (WTBA) (right) results (Per Protocol population).
performance in terms of antibody levels (GMT) was the IPV-IPV-OPV primary series, recognizing that no formal statistical comparisons have been made (the trial has not been powered for such comparisons). This observation has already been made in similarly designed studies [14] (Sanofi Pasteur. Study IPV33-EXT; unpublished; data on file).

The public health advantages of such an IPV-then-OPV sequential schedule has been highlighted on several occasions, and such a regimen has been used in the United States from 1997 to the end of 1999 [38] and also for a while in Israel [39] and Denmark [40] with successful results. The role that can be played by such an IPV-then-OPV sequential regimen is also highlighted by WHO in its revised position paper on poliomyelitis vaccinations [36], but recognizing that WHO does not support the introduction of IPV-then-OPV sequential schedule in countries where there is high risk of poliovirus importations, preferring the OPV-then-IPV sequential regimen where IPV is having the potential to boost intestinal immunity induced by prior OPV.

Seroprevalence against poliovirus before vaccination was high at study enrollment (2 months) and similar to what was observed in previous trials done in China [32, 37], illustrating the still-high prevalence of poliovirus antibodies in Chinese pregnant women. This has not impaired the immunogenicity performance of the 2 IPV-then-OPV sequential regimens. No tOPV or mOPV1 Supplementary Immunization Activities occurred in the Guangxi region within the time frame that the study was conducted, and

Figure 3. Concordance plots for data obtained 1-month post-Dose 3 between Sabin strain–based neutralization assay (National Institutes for Food and Drug Control [NIFDC] titers) and wild-type strain–based neutralization assay (Global Clinical Immunology [GCI] titers).
the household demographic and socioeconomic characteristics of study participants’ families were not favorable for poliovirus transmission.

A further observation emerging from this study is that the use of the SSBA biases the assessment of antibody levels in favor of OPV-elicted antibodies while the use of WTBA biases to favor antibodies elicited by IPV. The virological basis for such an observation has been explored [41, 42], and this is not unexpected. The role of this variable in assay standardization has been explored [43, 44] but underappreciated, and should be given additional weight when interpreting clinical trials exploring the performances of sequential or mixed regimen combining the use of IPV (including Sabin IPV) and OPV, particularly when considering that vaccination is aiming at inducing protection against the clinical consequences of being infected by poliovirus harboring paralytic phenotypes. Nevertheless, the full clinical relevance of such differences is yet to be documented.

In conclusion, this trial confirmed the noninferiority of 2 different IPV-then-OPV sequential regimens versus an OPV-only regimen in Chinese infants.

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