Safety and Immunogenicity of Inactivated Poliovirus Vaccine Made From Sabin Strains: A Phase II, Randomized, Positive-Controlled Trial

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(See the editorial commentary by Cochi and Linkins, on pages 169–71.)

Background. The production of Sabin inactivated poliovirus vaccine (IPV) can reduce biosafety requirements in the posteradication/post–oral poliovirus vaccine (OPV) era. We conducted a phase II, randomized, positive-controlled trial to assess the safety and immunogenicity of Sabin IPV.

Methods. The test groups (A, B, and C) received 3 doses of high, middle, and low D antigen (D Ag) of Sabin IPV at ages 2, 3, and 4 months, respectively. Infants in 2 control groups, group D and group E, received 3 doses of trivalent OPV and conventional IPV (cIPV), respectively, on the same schedule as that of groups A, B, and C. Serum samples were collected before and 30 days after the administration of the third dose.

Results. In total, 500 infants were randomly assigned to 5 groups, and 449 infants completed the vaccine series. No serious adverse events were associated with vaccinations. After 3 doses, the seroconversion rates in groups A, B, C, D, and E were 100%, 97.8%, 96.6%, 100%, and 90.1%, respectively, for type 1 poliovirus; 97.7%, 95.7%, 78.7%, 100%, and 90.1%, respectively, for type 2; and 98.8%, 98.9%, 93.3%, 100%, and 97.8%, respectively, for type 3.

Conclusions. Sabin IPV has good safety characteristics. The seroconversion rates for type 1 poliovirus (most appropriate concentration, 15 D Ag units [DU]), type 2 (32 DU), and type 3 (45 DU) Sabin IPV were similar to those of the OPV and cIPV control groups.

Clinical Trials Registration. NCT01056705.

In 1988, the 41st World Health Assembly (WHA) made a resolution aiming for the eradication of poliomyelitis by the year 2000 [1]. The principal method by which this was to be achieved was intensified vaccination using both oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV). During the final stages of poliomyelitis eradication, the public paid more attention to cases of vaccine-associated paralytic poliomyelitis and vaccine-derived poliovirus (VDPV) infection than to polio itself [2, 3]. There were 532 VDPV cases between 2000 and June 2011 [4]. Preexisting VDPV in immunodeficient individuals also presents a potential risk [5]. Use of IPV avoids the risk of both vaccine-associated paralytic poliomyelitis and VDPV infection. Therefore, the trend in the use of IPV becomes clear and necessary. The goal to eradicate poliomyelitis can only be reached if the use of OPV is stopped [6].

In May 2008, the 61st WHA formulated resolution WHA 61.1, which requested the Director-General of the World Health Organization (WHO) to undertake the research necessary to develop appropriate strategies and products, including safer processes for producing IPV and affordable strategies for its use [7]. In discussion with the WHO, the Bill & Melinda Gates Foundation commissioned Oliver Wyman to assess the state of IPV supply and the feasibility of producing an IPV-containing combination vaccine in the post–polio eradication era. The greatest forecasted demand for IPV to date has been 426 million doses annually [8].
Trivalent IPV is presently under development. We used Vero cells and Sabin strains to produce Sabin IPV by using microcarrier culture technology in a bioreactor and conducted a phase II, randomized, positive-controlled trial to assess the safety and immunogenicity of Sabin IPV.

METHODS

Study Design
The study population consisted of infants aged 60–90 days from 9 towns in Pingle City, GuanXi Province, China, who were recruited between 1 July 2009 and 1 May 2010. Infants were eligible for inclusion in the study if they were healthy; had been born at full term; did not currently have febrile illness; did not have a personal or family histories of allergies, epilepsy, or mental illness; did not have immunodeficiency; had not recently received a blood transfusion; had not recently received blood-derived products; had not recently received a blood transfusion; had not recently had a blood transfusion; had not recently undergone vaccination (in the previous 7 days); or did not have serious chronic illness. After the infants had been selected from a list of consecutive births and their eligibility had been confirmed, their parents or guardians were invited to participate, and written informed consent was obtained. In total, 500 healthy infants were randomly assigned to 1 of 5 groups. Groups A, B, and C received 3 doses of high, middle, and low D Ag content Sabin IPV at 2, 3, and 4 months of age, respectively. Infants in the control groups, group D and group E, received 3 doses of trivalent OPV and conventional IPV (cIPV), respectively, on the same schedule. To minimize the potential secondary exposure to circulating OPV viruses among participants in studies of IPV, we stopped intensified vaccination in the Sabin IPV trial area.

Participants were observed for safety purposes at hours 0.5, 6, 24, and 48 and days 3, 4, 5, 6, and 7 after vaccinations and were followed up for 3 weeks through home visits. Any adverse events were graded according to the guidelines issued by the Chinese State Food and Drug Administration [12].

The trial was designed according to the technical guidance principle for vaccine clinical trials [13] and was approved by the Chinese State Food and Drug Administration. The trial protocol and all relevant documents were approved by the ethical review committee of GuangXi Province. The trial was organized and guided by the Center for Clinical Vaccine Research, GuangXi Center for Disease Prevention and Control, and was audited by Beijing Simurui Science and Technology. All authors had full access to the data, and all vouch for the accuracy and completeness of both the data and the analyses. All authors drafted the manuscript and made the decision to submit it for publication.

Vaccine
The Sabin IPV used in this study was manufactured by the Institute of Medical Biology, Chinese Academy of Medical Sciences (Kunming, China), using good manufacturing practices. The following poliovirus master seeds were used: for type 1 poliovirus, Sabin SO +1; for type 2, Sabin SO +1; and for type 3, Pfizer RSO1. Vero cells of WHO seed P134 10-87 were obtained from the European Collection of Cell Cultures. The microcarrier culture method was used to cultivate Vero cells and polioviruses in bioreactors. The final scale of cell cultivation was 550-L bioreactors. Working virus seed was inoculated and then incubated at 33°C–34°C for 2–3 days. Virus suspension was then harvested, ultraconcentrated, and purified. A 1:4000 dilution of formalin was added to purified virus suspension, and the suspension was incubated at 37°C for 12 days. During the sixth day of inactivation, virus suspension was filtered and transferred into a new container to ensure complete inactivation. The indirect enzyme-linked immunosorbent assay method for detecting D Ag was established in our laboratory, using purified calf and rabbit antipoliovirus immunoglobulin G (IgG) as the capture and detector antibodies, respectively. The international IPV reference reagent WHO91/574 was used as a reference for calibration of Sabin IPV D Ag content. The 3 vaccine groups (A, B, and C) were 45, 64, and 67.5 D Ag units (DU); middle were 30, 32, and 45 DU; and low were 15, 16, and 22.5 DU/0.5 mL per dose for types 1, 2, and 3, respectively. The DNA and protein contents of all 3 lots of Sabin IPV were <100 pg and <10 µg per dose, respectively. The control trivalent OPV was manufactured by the Institute of Medical Biology and contained 6.0, 5.0, and 5.5 log10 50% cell culture infectious doses (CCID50) for types 1, 2, and 3, respectively. The control cIPV was manufactured by Sanofi Pasteur and contained 40 DU (for type 1 poliovirus), 8 DU (for type 2), and 32 DU (for type 3) per dose.

Statistical Analysis
We used SPSS version 16.0 software to compare groups, using Pearson χ² analysis or the Fisher exact test. We gave virus-neutralizing antibody titers that were below the limit of detection (ie, 1:8) an arbitrary value of 1:1. The virus-neutralizing antibody
titers were converted into log\(_{10}\) titers to calculate geometric mean titers (GMTs) and 95% confidence intervals. All reported \(P\) values are 2-sided. Analysis was done by intention to treat.

### Determination of Neutralizing Titers
Serum samples were collected from all infants before and 30 days after vaccination with 3 doses of each vaccine for detection of anti-poliovirus-neutralizing antibodies. The neutralization assay was performed by the National Institutes for Food and Drug Control, according to the method recommended by the WHO [14]. Each serum sample was tested in triplicate. The reciprocal of the highest serum dilution that inhibited 50% of the viral cytopathic effect was taken as the neutralization antibody titer against relative poliovirus. Seroconversion was defined as an increase in antibody titer by a factor of at least 4 from pre- to postvaccination values. If infants had an antibody titer of \(<1:8\) before vaccination, seroconversion was defined as an antibody titer of \(\geq 1:8\) after vaccination.

### RESULTS

#### Study Population
Of the 615 infants assessed for eligibility, 500 (81.3%) were selected to participate in the phase II clinical trial (Figure 1). Of these 500, 15 in group A, 8 in group B, 11 in group C, 8 in group D, and 9 in group E withdrew during the period of the study. The main reasons for withdrawal involved parents’ move to another city for work and parents’ withdrawal of consent for blood sampling. The basic characteristics of participants are shown in Table 1. There was no significant difference between any of the groups in terms of the ratio of males to females (\(P = .09\)) or age (\(P = .83\)).

#### Adverse Events After Vaccination
Adverse events are shown in Table 2. There was no significant difference in the prevalence or severity of local reactions, including pain, redness, and swelling, among the groups (\(P > .05\)). All local reactions were mild, except those for 1 infant in Sabin IPV group A, who experienced localized redness (diameter, 40 mm) after the first vaccination. All systemic reactions, including irritability, diarrhea, nausea/vomiting, drowsiness, and tiredness, were mild or moderate in severity, and there was no significant difference among groups in either their prevalence or severity (\(P > .05\) for all comparisons). The most frequent systemic reaction was fever. The prevalence of fever was significantly higher in Sabin IPV group A (41.0%) than in groups C (23.0%), D (22.0%), or E (20.0%; \(P < .05\) for all comparisons). The prevalence of fever in Sabin IPV groups B and C did not differ significantly from the prevalence in the control OPV and IPV groups (\(P > .05\) for all comparisons). A serious adverse event occurred in 2 infants. Subject 009 (a male in group C) developed enteritis after receiving the first dose of Sabin IPV. He was hospitalized, and his participation in the study continued after his recovery. Subject 125 (a male in group A) also developed enteritis after receiving the first dose of Sabin IPV. He was also hospitalized, and his participation in the study was discontinued by his parents. It is thought that neither serious adverse event was caused by the vaccination.

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**Figure 1.** Flow of infants through the study. See Methods for a description of the vaccines received by each study group.

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Immunogenicity After 3 Doses of Vaccine

The seropositivity rates (antibody titer, $\geq 1:8$) in all antibody-negative infants before vaccination were 100% after 3 doses (data not shown). GMTs and seroconversion rates are shown in Table 3. After 3 doses, seroconversion rates in groups A, B, C, D, and E were 100%, 97.8%, 96.6%, 100%, and 90.1%, respectively, for type 1 poliovirus; 97.7%, 95.7%, 78.7%, 100%, and 90.1%, respectively, for type 2; and 98.8%, 98.9%, 93.3%, 100%, and 97.8%, respectively, for type 3. These differences were not significant ($P > .05$ for all comparisons), with the exception of type 2 in Sabin IPV group C, whose 78.7% seroconversion rate was significantly lower than that in the other groups ($P < .05$). The GMT in Sabin IPV group B for type 1 was 2981, which was higher than that of IPV (386; $P < .05$) and similar to that of OPV (3315; $P > .05$); for type 2 it was 155, which was lower than that of OPV (410; $P < .05$) but similar to that of IPV (192; $P > .05$); for type 3 it was 492, which was similar to that of both OPV and IPV (545 and 705, respectively; $P > .05$ for both comparisons).

**DISCUSSION**

During this final stage of poliomyelitis eradication, the trend toward the use of IPV has become ever more clear, and the demand for IPV has increased concomitantly. However, biosafety requirements have also become more stringent. Use of a Sabin IPV can come with reduced biosafety requirements, and the vaccine could be produced in developing countries. Furthermore, development of Sabin IPV is encouraged by the WHO. Resolution WHA 61.1 on poliomyelitis mandated the development of safer processes for the production of IPV and affordable strategies for its use.

During development of the Sabin IPV, given the biosafety considerations, we paid great attention to the use of an attenuated virus. Before inactivation, 9 batches (including 3 each of

| Table 1. Basic Characteristics of the Infants Enrolled in the Study, According to Study Group |
|---------------------------------------------|----------------|----------------|----------------|----------------|----------------|
| Characteristic                             | Group A (n = 99$^a$) | Group B (n = 100) | Group C (n = 100) | Group D (n = 100) | Group E (n = 100) |
| Male sex, no. (%)                          | 64 (64.7)         | 59 (59.0)        | 47 (47.0)         | 53 (63.0)        | 50 (50.0)        |
| Age, days, median (95% CI)                 | 77 (73–77)        | 74 (72–76)       | 75 (73–77)        | 76 (73–77)       | 74 (72–76)       |

Seropositivity, by poliovirus type

<table>
<thead>
<tr>
<th>Type 1, subjects, % (95% CI)</th>
<th>Group A (n = 99$^a$)</th>
<th>Group B (n = 100)</th>
<th>Group C (n = 100)</th>
<th>Group D (n = 100)</th>
<th>Group E (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2, subjects, % (95% CI)</td>
<td>55 (45–65)</td>
<td>53 (43–63)</td>
<td>45 (35–55)</td>
<td>43 (33–55)</td>
<td>53 (43–63)</td>
</tr>
<tr>
<td>Type 3, subjects, % (95% CI)</td>
<td>26 (17–35)</td>
<td>31 (22–40)</td>
<td>36 (27–45)</td>
<td>32 (23–41)</td>
<td>41 (31–51)</td>
</tr>
</tbody>
</table>

See Methods for a description of the vaccines received by each study group.

**Table 2. Adverse Events in Infants After 3 Doses of Vaccine, According to Study Group**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Group A (n = 99$^a$)</th>
<th>Group B (n = 100)</th>
<th>Group C (n = 100)</th>
<th>Group D (n = 100)</th>
<th>Group E (n = 100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local$^b$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>.28</td>
</tr>
<tr>
<td>Redness</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>.15</td>
</tr>
<tr>
<td>Swelling</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>.41</td>
</tr>
<tr>
<td>Systemic$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever$^d$</td>
<td>41</td>
<td>32</td>
<td>23</td>
<td>22</td>
<td>20</td>
<td>.003</td>
</tr>
<tr>
<td>Irritability</td>
<td>19</td>
<td>13</td>
<td>13</td>
<td>11</td>
<td>20</td>
<td>.28</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>17</td>
<td>15</td>
<td>17</td>
<td>17</td>
<td>.60</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td>12</td>
<td>.73</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>10</td>
<td>12</td>
<td>13</td>
<td>8</td>
<td>10</td>
<td>.81</td>
</tr>
<tr>
<td>Tiredness</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>.94</td>
</tr>
</tbody>
</table>

See Methods for a description of the vaccines received by each study group.

$^a$ Data are for 99 infants; 1 infant was withdrawn before the first dose because parents withdrew informed consent.

$^b$ All were mild except for those for 1 infant in Sabin IPV group A, who had redness (diameter, 40 mm) after the first dose.

$^c$ Defined as an axillary temperature of $\geq 37.1^\circ C$.

$^d$ P = .17, .005, .003, and .001 for comparisons of group A with groups B, C, D, and E, respectively. $P = .15, .11$, and .05 for comparisons of group B with groups C, D, and E, respectively. $P = .78$ and .61 for comparisons of group C with groups D and E. $P = .78$ for the comparison of group D with group E.
types 1, 2, and 3 poliovirus) of purified virus suspension were produced in a 550-L capacity bioreactor. All batches passed the simian neurovirulence test, performed according to the method recommended by the WHO [15], which indicates that the production process we established is stable and maintains attenuation.

The safety data from this phase II clinical trial suggest that the Sabin IPV was well tolerated; no serious adverse events were observed, and all local and systemic reactions were mild or moderate and transient. The 2 serious adverse events that did occur had no known relationship to the vaccine.

The prevalence of fever was significantly higher in group A than in the other groups. This could have been related to the high D Ag content, which was about 4 times that in vaccine given to group C. The high D Ag content may have induced stronger immune responses and adverse events and so produced higher neutralizing antibody levels and a higher prevalence of fever in the subjects who received this dose.

The seropositivity rates (antibody titer, ≥1:8) in all infants who were antibody negative before vaccination were 100% after 3 doses, suggesting that Sabin IPV groups A, B, and C and the OPV and IPV control groups elicited good immune responses.

The GMTs of the 3 poliovirus types obtained from Sabin IPV groups A and B were not inferior to those obtained from the OPV or IPV control groups (except for the comparison of type 2 between group B and OPV). Given these data, the most appropriate D Ag contents per dose for use in a phase III clinical trial are likely 15 DU (for type 1 poliovirus), 32 DU (for type 2), and 45 DU (for type 3).

The GMTs within Sabin IPV groups A, B, and C decreased with D Ag content per dose. However, after 3 doses, the GMTs of Sabin IPV groups A, B, and C ranged from 1789 to 6335 for type 1 poliovirus, from 101 to 338 for type 2, and from 307 to 884 for type 3. This indicates that the GMT was highest for type 1 poliovirus, intermediate for type 3, and lowest for type 2, which in turn suggests that the immunogenicity of type 1 poliovirus is high, the immunogenicity of type 3 is intermediate, and the immunogenicity of type 2 is low. The reason for the lower GMTs induced by type 2 is not clear, particularly because the same virus strains were used to make both Sabin IPV and OPV. The type 2 poliovirus D Ag content was greater in Sabin IPV than that of type 1, yet the immunogenicity was much lower than for type 1. This result is contrary to that for OPV, in which the type 2 poliovirus titer was an order of magnitude lower per dose.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n = 85a)</th>
<th>Group B (n = 92a)</th>
<th>Group C (n = 89a)</th>
<th>Group D (n = 92a)</th>
<th>Group E (n = 91a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 poliovirus GMT (95% CI)</td>
<td>Before vaccination 3.0 (2.1–4.3) 6.9 (4.6–10.3) 5.4 (3.6–7.9) 4.4 (3.0–6.4) 5.9 (4.0–8.7)</td>
<td>After vaccination 6335 (5392–7442) 2981 (2446–3634) 1789 (1453–2203) 3315 (2703–4064) 386 (297–502)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion Subjects, no.</td>
<td>85b</td>
<td>90b</td>
<td>86b</td>
<td>92b</td>
<td>91b</td>
</tr>
<tr>
<td>Rate, % (95% CI)</td>
<td>100 (95.8–100.0) 97.8 (92.4–99.7) 96.6 (90.5–99.3) 100 (96.1–100.0) 90.1 (82.1–95.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 poliovirus GMT (95% CI)</td>
<td>Before vaccination 1.9 (1.5–2.5) 2.5 (1.8–3.4) 2.8 (2.0–3.9) 2.3 (1.8–3.0) 3.4 (2.4–4.6)</td>
<td>After vaccination 338 (272–421) 155 (127–188) 101 (79–128) 410 (348–483) 192 (147–252)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion Subjects, no.</td>
<td>83b</td>
<td>88b</td>
<td>70b</td>
<td>92b</td>
<td>82b</td>
</tr>
<tr>
<td>Rate, % (95% CI)</td>
<td>97.7 (91.8–99.7) 95.7 (89.2–98.8) 78.7 (68.7–86.6) 100 (96.1–100.0) 90.1 (82.1–95.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 3 poliovirus GMT (95% CI)</td>
<td>Before vaccination 1.6 (1.2–2.0) 1.5 (1.2–1.9) 2.1 (1.5–2.9) 1.8 (1.4–2.2) 1.8 (1.4–2.4)</td>
<td>After vaccination 884 (732–1068) 492 (408–593) 307 (245–385) 545 (443–669) 705 (557–894)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion Subjects, no.</td>
<td>84b</td>
<td>91b</td>
<td>83b</td>
<td>92b</td>
<td>89b</td>
</tr>
<tr>
<td>Rate, % (95% CI)</td>
<td>98.8 (93.6–100.0) 98.9 (94.1–100.0) 93.3 (85.9–97.5) 100 (96.1–100.0) 97.8 (92.3–99.7)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

See Methods for a description of the vaccines received by each study group.

Abbreviations: CI, confidence interval, GMT, geometric mean titer.
a Subjects whose blood samples were collected.
b Subjects whose blood samples had been determined and the neutralizing antibody titers were obtained.
(10^3 CCID_{50}) than that for type 1 (10^6 CCID_{50}); however, type 2 immunogenicity was at about the same level as that of type 1.

Why was the immunogenicity of type 2 poliovirus so different in OPV (live virus) and IPV (inactivated virus)? The observed discrepancy may be related to the structure of the antigenic sites of the viral capsid protein and to the harmful effect of formalin treatment. Better results were obtained using β-propiolactone as an inactivation reagent [16]. There has been 1 report of antigenic characterization of formalin-inactivated Sabin IPV [17]. Neutralizing antibodies play a major role in human immunity to poliomyelitis. The results of this phase II clinical trial show that the GMTs of antibodies to 3 types of poliovirus reached a high level (101–6335) after 3 vaccinations. From this, we expect that the use of D Ag contents of 15 DU (for type 1 poliovirus), 32 DU (for type 2), and 45 DU (for type 3) per dose will elicit an effective humoral immune response. The forthcoming phase III clinical trial will further confirm the suitability of such D Ag contents. Of course, any successful Sabin IPV must meet existing clinical trial will further confirm the suitability of such D Ag contents. Of course, any successful Sabin IPV must meet existing safety, stability, immunogenicity, and fiscal requirements.

Several institutes are developing Sabin IPV, including the National Vaccine Institute in the Netherlands [18–20], the Japan Poliomyelitis Research Institute in Japan [21, 22], the Institute of Medical Biology at the Chinese Academy Medical of Sciences in China [23], the Beijing Biological Products Research Institute in China, and Panacea Biotech in India. At present, our Sabin IPV production is carried out in 550-L bioreactors. However, production can be expanded to meet any future demand. Several important points should be considered during the development of such a vaccine: establishing production process and quality control methods; confirming safety, stability, and immunogenicity; and achieving an appropriate production scale and a suitable per-unit cost. A low-cost vaccine can be used widely in low- and middle-income countries. Immune response to IPV can be increased through the inclusion of an adjuvant [24]. We have studied the efficacy of aluminum hydroxide adjuvant in a rat model, and the data suggested a 2-fold increase in immunogenicity in adjuvant-supplemented formulations (unpublished data). More studies of the affordability of Sabin IPV are needed. Affordability may be improved by (1) reducing the total volume per dose (by adopting intradermal delivery), (2) using an adjuvant, (3) using a novel inactivation reagent, (4) using combination vaccines, and (5) reducing the number of doses [17]. Successful development of Sabin IPV is critical for the final eradication of poliomyelitis, especially in the post–polio eradication/post-OPV era.

Notes

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