

## ORIGINAL ARTICLE

# Randomized, Placebo-Controlled Trial of Inactivated Poliovirus Vaccine in Cuba

The Cuba IPV Study Collaborative Group

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 ABSTRACT
 

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**BACKGROUND**

After poliomyelitis has been eradicated, access to live polioviruses will be highly restricted and the use of oral poliovirus vaccine (OPV) will probably be discontinued. Countries using OPV must decide whether to switch to inactivated poliovirus vaccine (IPV) or stop polio vaccination. Because data on the immunogenicity of IPV in tropical developing countries are limited, we conducted a randomized, controlled trial of IPV in Cuba.

**METHODS**

The study population consisted of healthy infants born in Havana. A total of 166 infants were randomly assigned to two groups. Group A received a combination of the diphtheria–pertussis–tetanus (DPT) vaccine, the *Haemophilus influenzae* type b (Hib) vaccine, and IPV (DPT-Hib-IPV) at 6, 10, and 14 weeks of age. Group B, the control group, received a combination of the DPT vaccine and the Hib vaccine at 6, 10, and 14 weeks of age. Another group (group C, 100 infants), which did not undergo randomization at the same time as groups A and B, received the DPT-Hib-IPV combination at 8 and 16 weeks of age. Serum samples were collected before vaccination and at least 4 weeks after the last dose. Stool samples were obtained before and 7 days after challenge with OPV.

**RESULTS**

The seroconversion rates in group A were 94%, 83%, and 100% for types 1, 2, and 3 poliovirus, respectively. There were no seroconversions in group B. The seroconversion rates in group C were 90%, 89%, and 90% for poliovirus types 1, 2, and 3, respectively. For groups A, B, and C, the virus isolation rates after challenge with OPV were 94%, 91%, and 97%, respectively, and the mean  $\log_{10}$  viral titers of any serotype were 3.46, 3.89, and 3.37, respectively. There was one major adverse event, an episode of hypotonia.

**CONCLUSIONS**

Vaccination with two or three doses of IPV resulted in a rate of seroconversion of at least 90%, except for seroconversion against type 2. The viral titer of OPV shed in the stool after OPV challenge was reduced in both groups receiving IPV. (ClinicalTrials.gov number, NCT00260312.)

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AT THE TIME THAT INTERRUPTION OF wild poliovirus transmission is achieved, the world will probably discontinue the use of oral poliovirus vaccine (OPV)<sup>1,2</sup> because of the potential for the vaccine virus to acquire the neurovirulence and transmission characteristics of wild poliovirus. Acquisition of these characteristics could then lead to endemic and epidemic transmission, as was documented during the past 6 years in Hispaniola, the Philippines, Madagascar, and China, and earlier in Egypt.<sup>3-6</sup>

Inactivated poliovirus vaccine (IPV) will be the only vaccine available for routine immunization if the use of OPV is discontinued.<sup>7,8</sup> Whereas industrialized countries may continue vaccinating against poliomyelitis with a combination vaccine that includes IPV, many developing countries may decide to stop polio vaccination and divert scarce resources to other health priorities. Important considerations include how and when to discontinue the use of OPV and whether to expand the use of IPV into developing countries.

Data on the immunogenicity of IPV in developing countries are limited, and the interpretation of the available data remains complicated by the potential secondary exposure of participants in studies of IPV to circulating OPV viruses or wild polioviruses.<sup>9-11</sup> This phenomenon may have led to an overestimate of the rates of IPV-induced humoral and mucosal immunity. To minimize this concern, IPV trials should be conducted in settings free of live polioviruses, where no OPV is used and there is no circulating wild poliovirus. Cuba has been free of polio since 1963, and OPV is administered only during annual national mass campaigns (typically during February and April), with documented absence of Sabin-vaccine viruses from each July to the following January.<sup>12-14</sup> Most developing countries routinely administer diphtheria and tetanus toxoids and pertussis vaccine (i.e., the DPT vaccine) to children at 6, 10, and 14 weeks of age; however, countries in the Western Hemisphere use a schedule of 8, 16, and 24 weeks of age. Because there is limited information on the extent to which maternal antibodies interfere with seroconversion when vaccine is administered early in life, it is critical that additional data be generated on IPV administered according to the accelerated schedule.<sup>15</sup> We performed a randomized, placebo-controlled trial in Cuba to evaluate the immunogenicity of IPV in combination with the DPT and *Haemophilus influ-*

*enzae* type b (Hib) vaccines (DPT-Hib-IPV) administered at 6, 10, and 14 weeks and at 8 and 16 weeks of age.

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## METHODS

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### STUDY DESIGN

The study population consisted of infants born in the four principal maternity hospitals in Havana from July 10 through November 10, 2001. Infants were eligible for inclusion if they were healthy, were born at full term (after at least 37 weeks of gestation), weighed at least 2.5 kg at birth, and had 1- and 5-minute Apgar scores of at least 7. Infants not meeting these criteria and those requiring hospitalization during the study were excluded.

After the infants had been selected from a list of consecutive births and their eligibility had been determined, their parents or guardians were invited to participate and written informed consent was obtained. The infants were then randomly assigned to one of two groups by the Cuban Ministry of Public Health Epidemiology Division with the use of Epidat 2.1 software. Group A received a combination pentavalent vaccine (DPT-Hib-IPV). Group B, the control group, received a tetravalent vaccine containing the DPT and Hib vaccines (DPT-Hib). Both groups received the vaccine at 6, 10, and 14 weeks of age.

A third group (group C) was included to assess a schedule of two doses of DPT-Hib-IPV given at 8 and 16 weeks of age. Unfortunately, the interval that was free of Sabin-vaccine virus in Cuba was too short to allow the assessment of a group receiving a full three-dose schedule (at 8, 16, and 24 weeks of age); nevertheless, we believed that inclusion of the group receiving a two-dose schedule could yield programmatically useful data. The infants in group C did not undergo randomization with the infants in the other two groups because they had to start receiving vaccine earlier than the infants in groups A and B in order to receive the challenge OPV dose on time (i.e., during the national OPV campaign on March 12 and 13, 2002).

Minor adverse events, such as injection-site discomfort, were monitored for 7 days after vaccination. Other adverse events were recorded with the use of a protocol established by the national surveillance system for vaccine-associated adverse events in Cuba.

The study was approved by the institutional review boards of the Pedro Kourí Institute in Havana and the Centers for Disease Control and Prevention in Atlanta. The Cuban Ministry of Public Health was responsible for operational aspects of the study, and the Pedro Kourí Institute conducted laboratory analyses. The institutions of the Cuba IPV Study Collaborative Group and their representatives take responsibility for the overall content and integrity of this article.

#### STATISTICAL ANALYSIS

Our target sample size (100 per group) allowed for attrition and was based on the lowest predicted seroconversion rate for the group receiving IPV at 6, 10, and 14 weeks (60%) according to data from Thailand.<sup>10</sup> To achieve a probability of 0.85 that the estimate from this study was in error by 10% or less, we needed to enroll at least 50 infants in each group receiving IPV. This calculation was based on the normal approximation to the binomial distribution. The proportions of subjects shedding virus after challenge in the control and intervention groups were compared with the use of a two-tailed Fisher's exact test. Assuming a predicted rate of excretion after challenge in the IPV and control groups of 60% and 85%, respectively, we calculated a minimum sample size of 55 infants for each group, so that we would have a power of 90% to detect a significant difference at the 0.05 level.

#### VACCINES

PENTAct-HIB is a combination vaccine produced by Sanofi Pasteur containing *H. influenzae* type b vaccine, DPT vaccine, and IPV. It is an injectable suspension formed by reconstituting lyophilized polyribosylribitol phosphate–tetanus-toxoid conjugated vaccine (PRP-T) (Act-HIB, Sanofi Pasteur) with a syringe filled with a DPT–IPV liquid combination (Tetracoq). TETRAct-HIB is a combination vaccine produced by Sanofi Pasteur containing *H. influenzae* type b vaccine and DPT. It is an injectable suspension formed by reconstituting lyophilized PRP-T (Act-HIB) with a syringe or ampule (0.5 ml) of DPT (DTCoq). The vaccines were masked for groups A and B (but not C). The study vaccines were donated by the manufacturer, which did not participate in study implementation, data analyses, or the preparation of the manuscript. The OPV in the national campaign was a live attenuated vaccine containing at least  $10^6$ ,  $10^5$ , and

$10^{5-8}$  median tissue-culture infective doses (TCID<sub>50</sub>) to poliovirus types 1, 2, and 3, respectively.

#### SAMPLE COLLECTION

Serologic specimens were taken from infants immediately before administration of the first vaccine dose and approximately 4 weeks after the last dose of study vaccine (preceding the national OPV campaign on March 12 and 13, 2002). Serologic specimens were stored at  $-20^{\circ}\text{C}$  at the Pedro Kourí Institute and tested collectively to determine antibody titers for poliovirus types 1, 2, and 3. To evaluate the effect of IPV on intestinal excretion of poliovirus after challenge, a stool specimen was obtained from each study infant 2 or 3 days before administration of the OPV challenge and 7 days afterward. The initial stool specimen was collected to verify our assumption that no child was excreting poliovirus before receiving the challenge dose.

#### DETERMINATION OF NEUTRALIZING ANTIBODIES

Neutralizing antibodies were determined by the method recommended by the World Health Organization (WHO).<sup>16</sup> Microneutralization was performed on microtiter plates with the use of serial dilutions, by a factor of two, of serum beginning at 1:8. At each dilution, 25  $\mu\text{l}$  of serum was mixed with 25  $\mu\text{l}$  of Eagle's medium containing 100 TCID<sub>50</sub> (range, 32 to 320) of Sabin poliovirus type 1, 2, or 3. The virus–serum mixture was incubated for 4 hours at  $37^{\circ}\text{C}$  in an atmosphere of 5% carbon dioxide. One hundred microliters of HEP-2 (Cincinnati subline) cell suspension (200,000 cells per milliliter) was added and incubated as before for 5 days. Each serum sample was tested in triplicate. Each test batch was accompanied by a cell control, a “serum toxicity” control (for the possible cytopathic effect of the serum alone), and virus dose and titration controls with the use of an in-house reference serum validated against the international standard.

Seroconversion was defined as an increase by a factor of four in antibody titer from prevaccination to postvaccination values, with correction for maternal antibody decay at an estimated half-life of 30 days. If the predicted end-point titer for maternal antibody decay was 7 or less (the cutoff value for detection), a second serum titer of 14 or more would indicate seroconversion. The association between prevaccination and postvaccination antibody titers was assessed by a two-tailed Spearman rank-order correlation coefficient test.

**ISOLATION AND IDENTIFICATION OF POLIOVIRUS IN STOOL**

Isolation of the virus was performed by WHO-recommended methods, with the following modifications.<sup>16</sup> A 20% suspension was made of each stool sample in phosphate-buffered saline with antibiotics. The samples were clarified by centrifugation at 10,000 rpm. The supernatant was stored at  $-20^{\circ}\text{C}$  until 0.2 ml of supernatant was inoculated onto rhabdomyosarcoma and L20B cell lines. The tubes were incubated at  $37^{\circ}\text{C}$  and examined 24 hours later. Those showing cytopathic effect were frozen and thawed for passage to new cell tubes. A sample was observed for up to 12 days before it was determined to be negative. In those tubes in which a cytopathic effect appeared in the L20B cells, identification was made by neutralization with poliovirus hyperimmune serum samples. Samples showing cytopathic effect only in rhabdomyosarcoma cells were passed to L20B cells. If the cytopathic effect persisted, identification proceeded as described above. Isolates positive for poliovirus were titrated by a micromethod in four replicates with  $\log_{10}$  dilutions from 1 to 6, with the use of L20B cells concentrated at 100,000 per milliliter.

**RESULTS****ENROLLMENT**

Two hundred sixty-six of 1062 screened infants (25.0%) were enrolled in the trial (Fig. 1). By the end of the study, 88 infants had not received one or more vaccinations: 30 in group A, 30 in group B, and 28 in group C. The reasons for withdrawal are summarized in Figure 1. The decision to withdraw consent for further vaccinations was mainly due to one major adverse event, a transient episode of hypotonia in an infant after the first dose, which was attributed to the pertussis-antigen component. In addition, there were five episodes of persistent crying. The percentages of males in groups A, B, and C were 52%, 63%, and 54%, respectively, at the end of the study, as compared with 53%, 68%, and 43% at initial enrollment. The 178 infants completing all study vaccinations resided in neighborhoods widely spread throughout and representative of Havana.

Of the 300 IPV doses administered, 34 (11%) were given to infants more than 7 days before or after the date they were due to be given the dose. Eliminating the data from these children did not

affect the results, and therefore they were included in the analyses. The median ages at which each dose was given are summarized in Table 1.

**SEROCONVERSION**

Group A (which received DPT-Hib-IPV at 6, 10, and 14 weeks of age) had seroconversion rates of 49 of 52 recipients (94%), 43 of 52 (83%), and 52 of 52 (100%) for poliovirus types 1, 2, and 3, respectively (Table 2). As anticipated, there were no seroconversions in group B (which received DPT-Hib at 6, 10, and 14 weeks), a result consistent with the absence of circulating polioviruses in the population. Group C (which received DPT-Hib-IPV at 8 and 16 weeks) had seroconversion rates of 65 of 72 recipients (90%), 64 of 72 (89%), and 65 of 72 (90%) for poliovirus types 1, 2, and 3, respectively.

**INTERFERENCE OF MATERNAL ANTIBODY**

The potential interference of preexisting maternal antibody was assessed by plotting pre- and postvaccination  $\log_2$  titers for poliovirus types 1 and 2 in intervention groups A and C (data not shown). Poliovirus type 2 was the only type for which pre- and postvaccination antibodies had a significant inverse correlation (for group A, Spearman's correlation coefficient,  $-0.49$ ;  $P < 0.001$ ; for group C, Spearman's correlation coefficient,  $-0.54$ ;  $P < 0.001$ ); this result implies interference with maternal antibody.

**ISOLATION OF POLIOVIRUS IN STOOLS**

Table 3 summarizes the results from stool specimens taken 7 days after the national OPV campaign. No polioviruses were isolated in initial stool specimens, before the campaign, from infants in any of the groups. In the second stool specimen, after OPV administration, the rates of isolation of any type of poliovirus were 49 of 52 infants (94%), 49 of 54 (91%), and 70 of 72 (97%) in groups A, B, and C, respectively. The excretion rates did not differ according to group when each IPV intervention group (A and C) was compared separately with group B. Among those shedding poliovirus, the mean  $\log_{10}$  titers in groups A, B, and C were 3.46, 3.89, and 3.37, respectively. Both IPV groups had lower mean viral titers than the control group ( $P = 0.06$  for group A and  $P = 0.005$  for group C), with the reduction in group C reaching statistical significance based on a two-tailed Mann-Whitney test.

## DISCUSSION

These data assess the immunogenicity of IPV in a tropical developing country where study participants were not exposed secondarily to circulating wild-type or OPV viruses. Despite the absence of secondary exposure, our study documented high levels of seroconversion for poliovirus types 1 and 3 after the administration of three doses of IPV at the ages of 6, 10, and 14 weeks, with a somewhat lower rate of seroconversion for type 2. Two IPV doses, administered at the ages of 8 and 16 weeks, resulted in moderately lower overall seroconversion rates. Similar proportions of infants in each study group excreted virus after OPV challenge; however, both groups receiving IPV had lower viral titers than the control group.

IPV immunogenicity is directly related to the prevalence and titer of maternally derived antibody.<sup>8-10,18,19</sup> Indirectly, IPV-induced immunogenicity levels can be inferred by the administration schedule (i.e., number of doses, age at first dose, and interval between doses).<sup>9</sup> Therefore, the WHO-recommended immunization schedule for developing countries, with doses administered at the ages of 6, 10, and 14 weeks, provides a substantial challenge to IPV performance. Nevertheless, in Cuba, administration of three doses resulted in rates of seroconversion to poliovirus types 1 and 3 of at least 90%. Maternally derived antibody interfered with type 2 seroconversion, resulting in somewhat lower rates of seroconversion to type 2. Type 2 seroconversion could be boosted by an additional dose given at 9 months of age (with measles vaccine), although the costs and benefits of this added dose would need to be considered.

Although these results are encouraging, they must be viewed in the context of Cuba, where there are generally good standards of public health and hygiene. Mothers born after 1962 in Cuba have only vaccine-induced immunity against polio.<sup>14</sup> Whether these results can be generalized to settings with more recent circulation of wild polioviruses remains uncertain. A WHO evaluation demonstrated interference of maternally derived antibody with types 1 and 2 seroconversion in Thailand, a country with more recent circulation of wild poliovirus.<sup>10</sup>

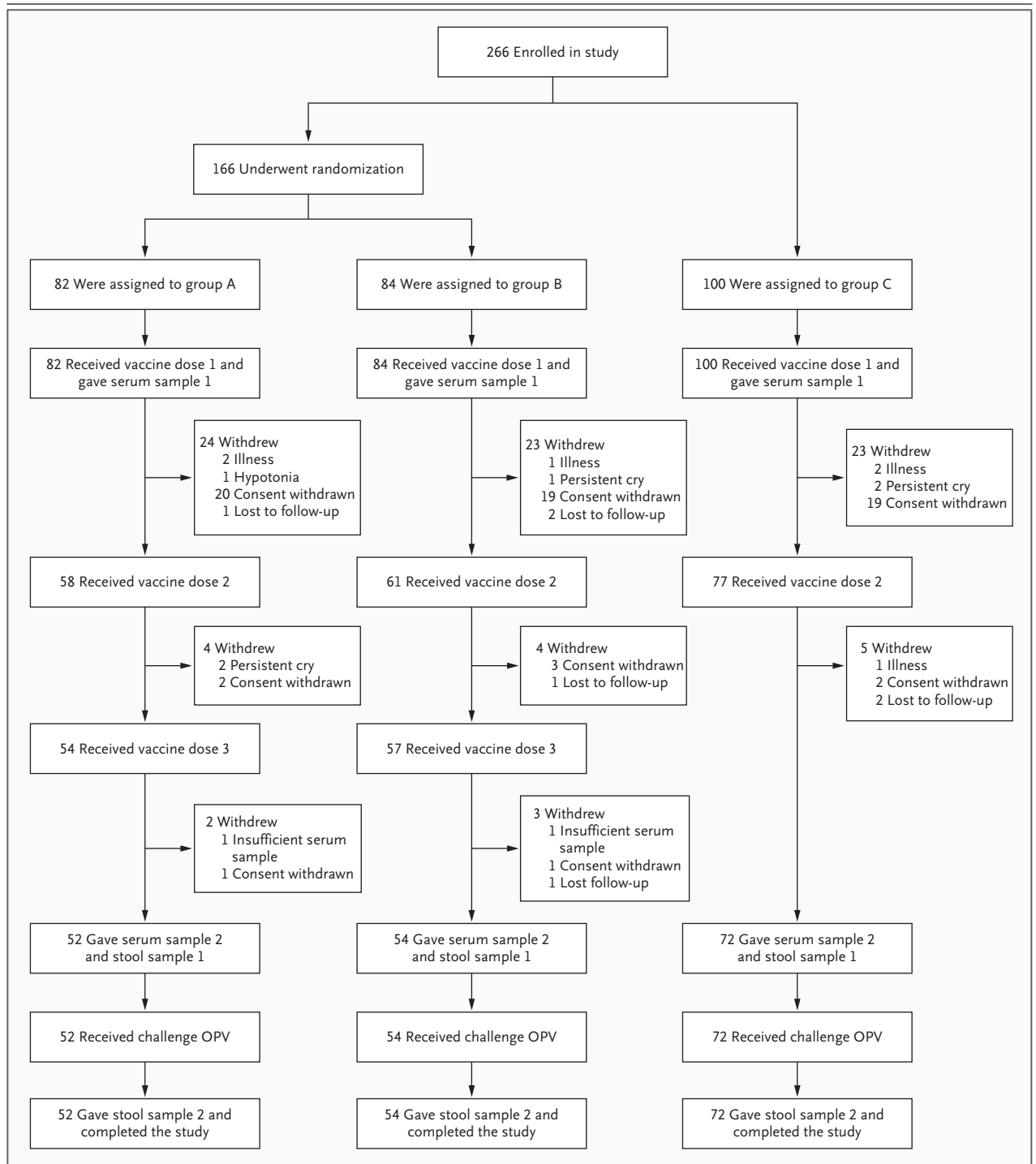
Two doses of IPV administered at 8 and 16 weeks of age produced only moderately lower rates of seroconversion than three doses given at 6, 10, and 14 weeks of age, a result suggesting that

**Figure 1 (facing page). Enrollment of Study Participants and Completion of the Vaccine Trial.**

Group A received a combination of diphtheria–pertussis–tetanus vaccine, *Haemophilus influenzae* type b vaccine, and inactivated poliovirus vaccine (DPT-Hib-IPV) at 6, 10, and 14 weeks of age. Group B, the control group, received a combination of DPT vaccine and Hib vaccine at 6, 10, and 14 weeks. Group C received the DPT-Hib-IPV combination at 8 and 16 weeks. The study was conducted between September 2001 and March 2002. OPV denotes oral poliovirus vaccine. Infants withdrawn from the study were referred back to the routine Cuban vaccination program. Any illnesses were typical (non–life-threatening) pediatric illnesses that were present at the time of the next scheduled dose and resulted in postponement of vaccination. Hypotonia is a transient, shocklike state occurring within 24 hours after vaccination, from which our patient completely recovered. It was attributed to the pertussis component of the vaccine. The rate of occurrence in our study was 1 in 573 doses (0.17%). A rate of 0.06% is cited in the literature.<sup>17</sup> Persistent crying was defined as acute, uncontrollable crying lasting at least 3 hours and occurring within 48 hours after vaccination. It was attributed to the pertussis component of the vaccine. The rate of occurrence in our study was 5 in 573 doses (0.87%). A rate of 3.50% is cited in the literature.<sup>17</sup>

administering doses at 2, 4, and 6 months of age would result in higher rates of seroconversion to IPV in Cuba. Since the 2-, 4-, and 6-month schedule is used extensively in the Western Hemisphere, such countries could expect high IPV immunogenicity if they added IPV to the currently used combination vaccines. Tropical developing countries considering adding IPV to a 6-, 10-, and 14-week schedule, however, should consider adding an additional IPV dose at 9 months (with measles vaccine) or in the second year of life (with DPT), to ensure high seroconversion rates.<sup>20</sup> If OPV vaccination is phased out, then high seroconversion after IPV will be essential, since there will be no catch-up indirect immunization by secondary spread from OPV.

Data on IPV performance from developing countries are limited.<sup>1,3,21-24</sup> These data demonstrate that the seroconversion or seroprevalence levels achieved by IPV may be inflated by secondary exposure to OPV, which is used in routine programs or mass campaigns in most tropical developing countries. More important, the reported decreases in viral excretion after challenge vaccine doses (with trivalent or monovalent OPV) in these studies appear to be due almost exclusively to mucosal immunity gained from secondary



OPV exposure. For example, in an evaluation conducted in Oman, 13% of subjects in a four-dose OPV group, 10% of those in a three-dose IPV group, and 11% of those in a combined four-dose OPV and three-dose IPV group excreted poliovirus type 1 one week after challenge with monovalent

OPV type 1.<sup>10</sup> If one does not account for the secondary OPV “contamination effect,” the Oman excretion data would suggest that IPV conferred substantial mucosal resistance that was similar to that in the two groups receiving OPV. This finding is in direct conflict with our data from

**Table 1. Ages at Which Infants Received Doses of Vaccine.\***

Dose	Group A	Group B	Group C
	<i>median days of age (range)</i>		
1	43 (27–54)	43 (29–51)	58 (30–68)
2	72 (64–76)	71 (65–85)	114 (92–116)
3	100 (91–108)	99 (95–114)	—

\* Group A received a combination of diphtheria–pertussis–tetanus vaccine, *Haemophilus influenzae* type b vaccine, and inactivated poliovirus vaccine (DPT-Hib-IPV) at 6, 10, and 14 weeks of age. Group B, the control group, received a combination of DPT vaccine and Hib vaccine at 6, 10, and 14 weeks. Group C received the DPT-Hib-IPV combination at 8 and 16 weeks. The dash denotes not applicable.

Cuba and earlier data from industrialized countries.<sup>25-27</sup>

In our study, the prevalence of excretion after receiving trivalent OPV was high (more than 90% for any poliovirus) and was similar among all three groups, including the control group, but viral titers were lower in both IPV groups, suggesting an effect of IPV vaccination on replication of polioviruses. These data from stool titers are consistent with a body of literature suggesting that previous vaccination with IPV can reduce the prevalence, duration, and titers of poliovirus in the stool.<sup>25-27</sup>

**Table 2. Prevacination and Postvaccination Antibody Titers and Seroconversion Rates According to Study Group and Poliovirus Type.\***

Poliovirus Type	Group A (N=52)	Group B (N=54)	Group C (N=72)
<b>Type 1</b>			
Median titer — value (95% CI)			
Before vaccination	33 (11–45)	27 (13–45)	22 (13–27)
After vaccination	304 (180–428)	Not detectable	304 (177–428)
Seroconversion			
No. of infants	49	0	65
Rate — % (95% CI) †	94 (84–99)	0 (0–5)	90 (81–96)
<b>Type 2</b>			
Median titer — value (95% CI)			
Before vaccination	22 (9–38)	21 (9–27)	11 (8–66)
After vaccination	304 (98–536)	Not detectable	197 (84–428)
Seroconversion			
No. of infants	43	0	64
Rate — % (95% CI) †	83 (70–92)	0 (0–5)	89 (79–95)
<b>Type 3</b>			
Median titer — value (95% CI)			
Before vaccination	Not detectable	Not detectable	Not detectable
After vaccination	858 (500–1216)	Not detectable	723 (332–916)
Seroconversion			
No. of infants	52	0	65
Rate — % (95% CI) †	100 (94–100)	0 (0–5)	90 (81–96)

\* Group A received a combination of diphtheria–pertussis–tetanus vaccine, *Haemophilus influenzae* type b vaccine, and inactivated poliovirus vaccine (DPT-Hib-IPV) at 6, 10, and 14 weeks of age. Group B, the control group, received a combination of DPT vaccine and Hib vaccine at 6, 10, and 14 weeks. Group C received the DPT-Hib-IPV combination at 8 and 16 weeks. Antibody titers were the reciprocals of antiserum dilution that neutralized 50% of wells.

† Exact confidence intervals are based on the binomial distribution.

**Table 3. Isolation of Poliovirus in Stool Samples 1 Week after Oral Poliovirus Vaccine Challenge According to Study Group and Poliovirus Type.\***

Group†	No. of Infants	Type 1		Type 2		Type 3		Any Type of Poliovirus		Mean Log <sub>10</sub> Titer in Fecal Sample (95% CI)‡
		No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	
A	52	10	19 (10–33)	45	87 (74–94)	5	10 (3–21)	49	94 (84–99)	3.46 (3.17–3.75)
B	54	9	17 (8–29)	48	89 (77–96)	3	6 (1–15)	49	91 (80–97)	3.89 (3.64–4.14)
C	72	13	18 (10–29)	67	93 (85–98)	10	14 (7–24)	70	97 (90–100)	3.37 (3.14–3.60)

\* All stool samples taken from study participants just before the challenge dose were negative for poliovirus. Exact confidence intervals (CIs) are based on the binomial distribution.

† Group A received a combination of diphtheria–pertussis–tetanus vaccine, *Haemophilus influenzae* type b vaccine, and inactivated poliovirus vaccine (DPT-Hib-IPV) at 6, 10, and 14 weeks of age. Group B, the control group, received a combination of DPT vaccine and Hib vaccine at 6, 10, and 14 weeks. Group C received the DPT-Hib-IPV combination at 8 and 16 weeks.

‡ Mean values are given for excretors of poliovirus.

Our study has limitations, and the results should be interpreted with caution. Maternally derived antibodies in Cuba were vaccine induced and have not been boosted by circulating wild polioviruses. To assess mucosal immunity, we examined a single stool sample for shedding of OPV administered during the national immunization campaign. Finally, our study was affected by substantial attrition due primarily to one major adverse event.

As more countries, including middle-income countries, switch to the use of IPV, there will be increasing opportunities to study the natural history of Sabin viruses in an IPV environment. The WHO is implementing demonstration projects that introduce IPV into large areas within tropical developing countries. It will also be important to evaluate the effect of increasing demand for IPV

on its affordability in developing countries. These demonstration projects and other studies will provide additional, critical information to the WHO and its member countries as they determine the role of IPV in routine immunization programs to safely protect children from all three poliovirus types and to respond to reemergent polioviruses.

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No potential conflict of interest relevant to this article was reported.

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