ORIGINAL ARTICLE

Priming after a Fractional Dose of Inactivated Poliovirus Vaccine

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ABSTRACT

BACKGROUND

To reduce the costs of maintaining a poliovirus immunization base in low-income areas, we assessed the extent of priming immune responses after the administration of inactivated poliovirus vaccine (IPV).

METHODS

We compared the immunogenicity and reactogenicity of a fractional dose of IPV (one fifth of a full dose) administered intradermally with a full dose administered intramuscularly in Cuban infants at the ages of 4 and 8 months. Blood was collected from infants at the ages of 4 months, 8 months, 8 months 7 days, and 8 months 30 days to assess single-dose seroconversion, single-dose priming of immune responses, and two-dose seroconversion. Specimens were tested with a neutralization assay.

RESULTS

A total of 320 infants underwent randomization, and 310 infants (96.9%) fulfilled the study requirements. In the group receiving the first fractional dose of IPV, seroconversion to poliovirus types 1, 2, and 3 occurred in 16.6%, 47.1%, and 14.7% of participants, respectively, as compared with 46.6%, 62.8%, and 32.0% in the group receiving the first full dose of IPV ($P<0.008$ for all comparisons). A priming immune response to poliovirus types 1, 2, and 3 occurred in 90.8%, 94.0%, and 89.6% of participants, respectively, in the group receiving the fractional dose as compared with 97.6%, 98.3%, and 98.1% in the group receiving the full dose ($P=0.01$ for the comparison with type 3). After the administration of the second dose of IPV in the group receiving fractional doses, cumulative two-dose seroconversion to poliovirus types 1, 2, and 3 occurred in 93.6%, 98.1%, and 93.0% of participants, respectively, as compared with 100.0%, 100.0%, and 99.4% in the group receiving the full dose ($P<0.006$ for the comparisons of types 1 and 3). The group receiving intradermal injections had the greatest number of adverse events, most of which were minor in intensity and none of which had serious consequences.

CONCLUSIONS

This evaluation shows that vaccinating infants with a single fractional dose of IPV can induce priming and seroconversion in more than 90% of immunized infants. (Funded by the World Health Organization and the Pan American Health Organization; Australian New Zealand Clinical Trials Registry number, ACTRN12610001046099.)

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In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally by the year 2000.[1] Although substantial progress toward the eradication goal has been achieved, by the end of 2010,[2] poliovirus types 1 and 3 continued to circulate in four countries in which poliomyelitis is endemic, and periodic importations led to epidemic spread in more than 20 countries in 2009 and 2010.[3-5] Concurrently, progress in India suggested that interruption of transmission might be feasible in 2011,[6] and indeed, no cases of infection with wild-type poliovirus have been reported in India since January 13, 2011.[7]

In tandem with these eradication efforts, the planning for the posteradication era began more than a decade ago. The most important goal — to cease use of the oral poliovirus vaccine (OPV) after the eradication of wild-type poliovirus — was suggested in 1997[8] and formally endorsed by technical oversight committees in 2004[9] and 2008.[10] The prerequisites for OPV cessation have been reported,[11] the vaccination options have been identified,[12] and the risks of paralytic disease from poliomyelitis after cessation of the OPV have been broadly defined.[13]

In 2008, the World Health Assembly asked the World Health Organization (WHO) to "develop appropriate strategies and products for managing risks, including safer processes for IPV [inactivated poliovirus vaccine] production and affordable strategies for its use."[14] A number of strategies intended to make IPV affordable in developing countries are being evaluated, including schedule reduction (administration of fewer doses), dose reduction (the use of fractional-dose IPV), antigen reduction (with the use of traditional and novel adjuvants), optimization of production processes (increases in cell density, use of new cell lines, and use of alternative inactivation agents), and production of Sabin–IPV in developing countries.[15-17] The schedule-reduction approach, in which two doses of IPV are administered, has been evaluated in multiple studies,[18] which suggest that two doses of IPV could induce seroconversion to all three poliovirus serotypes in more than 90% of those vaccinated, provided that an appropriate schedule is followed (i.e., the first dose is not administered before 2 months of age, and the interval between the doses is 2 months or more).

Given that the immunogenicity of IPV is greatly affected by maternally derived antibodies,[19,20] we conducted a two-dose trial of fractional as compared with full-dose IPV administered in infants at the ages of 4 and 8 months.[21,22] Given the interest in further reducing the costs of IPV use, we also evaluated immune responses after one dose. We chose Cuba as the trial site because oral poliovirus vaccine (OPV) is used only twice a year in national campaigns (usually February and April) in Cuba, thereby minimizing the exposure of the study population to the Sabin virus.[23]

METHODS

STUDY DESIGN

We conducted a randomized, controlled clinical trial in which laboratory investigators were unaware of group assignments. Investigators at study sites were aware of group assignments, since different methods were used to administer each vaccine type (intradermal injection for the fractional dose and intramuscular injection for the full dose). The field work was conducted between July 6, 2009, and January 28, 2009, at 13 vaccination sites in 4 districts of Camagüey Province, Cuba. We had three specific objectives: first, to compare humoral antibody responses (seroconversion and antibody titer) after administration of two fractional doses of IPV or two full doses of IPV, the first at 4 months of age and the second at 8 months of age; second, to evaluate the dose-specific immune responses, including one-dose priming immune responses; and third, to determine what adverse events would follow the fractional-dose vaccination as compared with the full-dose vaccination. (For full details of the study design, see the protocol, available with the full text of this article at NEJM.org.)

STUDY POPULATION

Recruitment took place during the routine immunization visit at 2 months of age, at which time the parent or legal guardian was informed about the study and invited to participate. Participation was contingent on provision of informed consent by the parent or guardian, an Apgar score of 9 or more at 5 minutes (according to a review of records), a birth weight of 2.5 kg or more (according to records), a medical examination suggesting that the infant was healthy and breast-fed, and a weight for height above the 10th percentile on a growth chart at the age of 4 months. If an infant's weight for height fell below the 10th per-

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centile on the growth curve during the study period, the infant was withdrawn from the study.

STUDY OVERSIGHT

The study was approved by the Cuban National Regulatory Agency and Ministry of Health; the institutional review board of the Pedro Kouri Institute, in Havana, Cuba; the ethical review committees of the Camagüey Provincial Health Office, in Cuba; and the WHO, in Geneva. The study was carried out in compliance with Good Clinical Practice guidelines. All the authors vouch for the completeness and accuracy of the data and analyses presented and for the fidelity of the study report to the protocol. All study vaccines were donated by Netherlands Vaccine Institute (NVI). NVI had no role in the study design or implementation, data analysis, or manuscript preparation or the decision to submit the manuscript for publication.

STUDY PROCEDURES

Infants born during either March or April 2009 in the participating health center catchment areas were eligible for participation. These infants were randomly assigned to receive either a fractional dose of IPV (0.1 ml, or one fifth of the full dose) or a full dose at the ages of 4 and 8 months. Randomization was performed by having parents draw sealed envelopes containing the group assignment just before administration of the first vaccine dose and after a pediatrician's evaluation to determine whether the infant met the inclusion criteria.

The vaccines (produced by NVI) were formulated to contain at least 32-D, 8-D, or 40-D antigen units of poliovirus serotypes 1, 2, and 3, respectively, and were shipped in appropriate cold-chain conditions from the manufacturer to Havana. They were administered intradermally with a needle-free device (Biojector 2000, Bioject Medical Technologies) or intramuscularly with an "auto-disable" syringe and needle. The needle-free device was approved by the U.S. Food and Drug Administration for intramuscular and subcutaneous administration and on a case-by-case base for investigational intradermal administration with the use of a spacer. The device has been used previously to administer fractional-dose IPV[22,23] and was approved by the Cuban Medical Device Agency for use in this study.

After each vaccination, the infants were monitored for 60 minutes for immediate adverse events and were also evaluated by qualified medical staff during home visits at 24 and 48 hours. Adverse events were classified as minor, moderate, or severe in intensity and as serious or not serious in consequence. No other vaccines were administered concurrently with or for an interval of 2 weeks before or after each IPV vaccination.

Blood specimens were collected at 4 months (baseline), at 8 months, at 8 months 7 days, and at 8 months 30 days. An automated, single-use, heel-stick device (Tenderfoot, International Technidyne) was used to collect the specimens. After coagulation, the serum was separated, frozen, and stored at the study site at –20°C until transport to the Pedro Kouri Institute. The specimens were tested in triplicate with a modified neutralization assay for antibodies to poliovirus types 1, 2, and 3.[24,25] The starting dilution was a reciprocal titer of 8. Seropositivity (a detectable antibody level) was defined as a reciprocal titer of 8 or more.[26] Seroconversion was defined as an increase in the antibody titer that was four times as high as the baseline titer. Participants who did not meet this criterion for seroconversion were also evaluated for seroconversion on the basis of an increase in the antibody titer that was at least four times as high as the expected value of the decline in maternally derived antibodies. The half-life of antibody decay was assumed to be 30 days.[20] For infants whose blood was seronegative, a change to seropositive status in a successive specimen (i.e., a reciprocal titer of 8 or more) was considered to indicate seroconversion. The definition of a priming immune response was the absence of seroconversion after the first dose of IPV and an antibody titer at 8 months 7 days that was four times as high as the titer at 8 months, or a nondetectable reciprocal titer at 8 months and a detectable reciprocal titer at 8 months 7 days.[27]

STATISTICAL ANALYSIS

We calculated that a minimum of 138 participants in each of the two study groups would be needed to detect a difference of 20% or more, at an alpha level of 0.05 and a beta level of 0.10 (two-tailed test). For those calculations, we assumed seroconversion end points of 40% and 60% for the fractional-dose and full-dose groups, respectively. To account for attrition, we increased the sample size to 160 per group.

Statistical analyses were performed with the

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use of statistical packages from the R Foundation for Statistical Computing[28] and the SAS Institute (version 6.4).[29] Comparisons of the proportions of infants with seroconversion in the study groups were conducted with the use of chi-square tests (with the Yates-corrected test, or with Fisher's exact test if the number of data in a cell was 5 or less). The differences in the distribution of antibody titers were tested with the Kolmogorov–Smirnov nonparametric method.[30] The 95% confidence intervals for median values were derived by means of simulation.[31] A single post hoc subgroup analysis was conducted.

RESULTS

STUDY POPULATION

A total of 320 participants underwent randomization, and 310 participants (96.9%) completed the study (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Among the 10 participants who did not complete the study, 3 were in the fractional-dose group and 7 were in the full-dose group. The reasons for withdrawal or exclusion were as follows: 3 participants moved out of the study area, 1 had a respiratory illness, and 6 had evidence of exposure to OPV through contact with close relatives who had been vaccinated during the February and March 2009 campaigns.

After randomization, the baseline attributes, type-specific seroprevalence, and poliovirus antibody titers of the two study groups were similar except with regard to the seroprevalence comparison for poliovirus type 2 (P=0.002). Poliovirus seroprevalence in the fractional-dose and full-dose groups was 29.3% and 33.3% for type 1, 34.4 and 46.4% for type 2, and 8.3% and 9.2% for type 3, respectively (Table 1).

Table 1. Baseline Characteristics of the Study Participants.*

Variable	Fractional Dose of IPV (N=157)	Full Dose of IPV (N=153)
Male sex — no. (%)	82 (52.2)	87 (56.9)
Median birth weight (95% CI) — kg	3.40 (3.35 to 3.50)	3.42 (3.40 to 3.54)
Poliovirus type 1		
Seroprevalence — no. (%)	46 (29.3)	51 (33.3)
Median reciprocal titer (95% CI)†	<8 (<8 to <8)	<8 (<8 to <8)
Poliovirus type 2		
Seroprevalence — no. (%)	54 (34.4)	71 (46.4)
Median reciprocal titer (95% CI)†	<8 (<8 to <8)	<8 (<8 to <8)
Poliovirus type 3		
Seroprevalence — no. (%)	13 (8.3)	14 (9.2)
Median reciprocal titer (95% CI)†	<8 (<8 to <8)	<8 (<8 to 8)

* None of the between-group differences were significant except for the comparison of poliovirus type 2 seroprevalence (P=0.002 by a Yates-corrected chi-square test). Seroprevalence was defined as an antibody titer of at least 1:8. IPV denotes inactivated poliovirus vaccine.

† The median titer and corresponding 95% confidence interval (CI) are below or above observed dilution ranges (i.e., reciprocal titer, 8 to 1224).

CHANGES IN IMMUNITY

After a single dose of IPV, seroconversion to poliovirus types 1, 2, and 3 occurred in 16.6%, 47.1%, and 14.7% of infants in the fractional-dose group and in 46.6%, 62.8%, and 32.0% of infants in the full-dose group, respectively (P<0.008 for all comparisons). The definition of a priming immune response to poliovirus types 1, 2, and 3 was met in 90.8%, 94.0%, and 89.6% of infants in the fractional-dose group and 97.6%, 98.3%, and 98.1% of those in the full-dose group, respectively; only the between-group comparison for poliovirus type 3 was significant (P=0.01). The cumulative rates of seroconversion to poliovirus types 1, 2, and 3 after two doses of IPV were 93.6%, 98.1%, and 93.0% in the fractional-dose group and 100%, 100%, and 99.4% in the full-dose group, respectively (P<0.006 for the between-group comparisons of types 1 and 3); the between-group differences in the rates of cumulative seroconversion after two doses for the various vaccines were as follows: 6.4 percentage points for type 1 (95% confidence interval [CI], 2.0 to 11.7), 1.9 percentage points for type 2 (95% CI, –1.5 to 5.9), and 6.4 percentage points for type 3 (95% CI, 1.6 to 11.9) (Table 2).

The median reciprocal antibody titers against poliovirus type 1 in the two groups were similar at 4 months (<8) and remained lower than 8 or increased marginally (to 11) at 8 months. However, at 8 months 7 days, the titers in both groups showed a robust increase (to 713 in the fractional-dose group and to 1448 or higher in the full-dose group, P<0.001); the titers remained relatively stable at 8 months 30 days (450 in the fractional-dose group and 1448 or higher in the full-dose group, P<0.001). Similarly, the median reciprocal antibody titers against poliovirus type 2 were similar at 4 months (<8), increased at 8 months to 9 in the fractional-dose group

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Table 2. Rates of Seroconversion and Priming Immune Response after One or Two Doses of Inactivated Poliovirus Vaccine for Poliovirus Types 1, 2, and 3.*

Immune Response	Fractional IPV Dose (N=157)	Full IPV Dose (N=153)	P Value	Between-Group Difference (95% CI)
	no./total no. (%)			*percentage points*
Poliovirus type 1				
Seroconversion after first dose	26/157 (16.6)	71/153 (46.4)	<0.001	29.8 (19.2 to 39.6)
Priming response	119/131 (90.8)	80/82 (97.6)	0.1	6.8 (–1.3 to 13.7)
Seroconversion between visits 3 and 4	2/12 (16.7)	2/2 (100)	0.13	83.3 (–3.2 to 97.1)
Seroconversion after second dose	121/131 (92.4)	82/82 (100)	0.01	7.6 (0.9 to 14.0)
Cumulative seroconversion	147/157 (93.6)	153/153 (100)	0.002	6.4 (2.0 to 11.7)
Poliovirus type 2				
Seroconversion after first dose	74/157 (47.1)	96/153 (62.7)	0.008	15.7 (4.1 to 26.6)
Priming response	78/83 (94.0)	56/57 (98.2)	0.42	4.3 (–5.4 to 12.5)
Seroconversion between visits 3 and 4	2/5 (40.0)	1/1 (100)	>0.99	60.0 (NP)
Seroconversion after second dose	80/83 (96.4)	57/57 (100)	0.41	3.6 (–4.7 to 10.9)
Cumulative seroconversion	154/157 (98.1)	153/153 (100)	0.26	1.9 (–1.5 to 5.9)
Poliovirus type 3				
Seroconversion after first dose	23/157 (14.6)	49/153 (32.0)	<0.001	17.3 (7.5 to 26.9)
Priming response	120/134 (89.6)	102/104 (98.1)	0.01	8.5 (1.5 to 15.5)
Seroconversion between visits 3 and 4	3/14 (21.4)	1/2 (50.0)	0.90	28.6 (NP)
Seroconversion after second dose	123/134 (91.8)	103/104 (99.0)	0.018	7.2 (0.9 to 13.7)
Cumulative seroconversion	146/157 (93.0)	152/153 (99.3)	0.006	6.4 (1.6 to 11.9)

* Seroconversion was defined as an increase in the antibody titer that was four times as high as the expected decline in maternally derived antibodies. Cumulative seroconversion reflects the sum of the seroconversions occurring after the first and the second dose. P values were calculated with the use of chi-square tests (with the Yates-corrected test, or with Fisher's exact test if the number of participants in a cell was 5 or fewer). NP denotes not presented (i.e., the numbers of participants in the cells were too small to calculate meaningful 95% confidence intervals).

and 28 in the full-dose group, rose at 8 months 7 days to 1448 or higher in both groups (P<0.001), and at 8 months 30 days remained at 898 in the fractional-dose group and 1448 or higher in the full-dose group (P<0.001). Finally, the median reciprocal antibody titers to poliovirus type 3 at 4 months and 8 months were lower than 8 in both groups, increased at 8 months 7 days to 357 in the fractional-dose group and to 1448 or more in the full-dose group (P<0.001), and then decreased at 8 months 30 days to 71 in the fractional-dose group and 898 in the full-dose group (P<0.001) (Table 3).

Figure 1 shows median reciprocal antibody titers according to study group and seroconversion status after the first dose of IPV at 4 months. As expected, the median titers differed significantly between the groups at 8 months; they did not differ significantly at 8 months 7 days or at 8 months 30 days (with the exception of the titer for poliovirus type 2 in the fractional-dose group and for poliovirus type 3 in the full-dose group).

ADVERSE EVENTS

Most adverse events were classified as minor in intensity and not serious in consequence (Table 4). Minor reactions at the injection site were frequent, especially induration, pain, and redness. There were 114 adverse events in the fractional-dose group, as compared with 11 in the full-dose group. Among the 114 adverse events in the fractional-dose group, 84 (73.7%) were redness at the injection site, 25 (21.9%) induration at the injection site, 3 (2.6%) a temperature of 38.5°C or higher, and 2 other events. All injection-site reactions but one involved an area smaller than 5 mm in diameter. As expected, the prevalence of these events in the fractional-dose group, which received in-

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tradermal injections, was significantly higher than that in the full-dose group, which received intramuscular injections (Table 4).

DISCUSSION

This study provides data on a priming immune response after the administration of an initial fractional dose of IPV and on seroconversion after the administration of a first dose, second dose, or cumulative two-dose schedule of IPV (4 and 8 months after birth) that may be appropriate after wild-type poliovirus has been eradicated. First, the study showed that after a first dose of IPV, seroconversion and priming resulted in an immune response in at least 90% of infants. Second, it showed that the administration of IPV in infants at 4 months and 8 months of age resulted in seroconversion in more than 90% of infants, with correspondingly high antibody titers, regardless of whether fractional or full doses were used. Third, the study showed that although the median antibody titer in both study groups was high, it was significantly lower in the fractional-dose group at both 7 days and 30 days after a second IPV vaccination. No serious safety problems were identified.

The primary goal of the study was to assess the priming immune response after a single dose of IPV. Our results suggest that 86.9% or more of infants who did not undergo seroconversion after a first dose of IPV did have a priming immune response. The magnitude of the increase in median antibody titers in the 7-day period after administration of a second dose of IPV is noteworthy, as is the decline in titers between the assessments performed at 8 months 7 days and 8 months 30 days. We are not suggesting that a priming immune response is protective against clinical disease, but we believe that this may prove to be the case when more data are available.

Data from one efficacy trial[32] suggest that the efficacy of a single dose of IPV is low, but the trial had limitations. The confidence intervals for the efficacy estimates were wide.[32] On the other hand, data from countries in which a single dose of IPV was followed by a dose of OPV, such as Hungary, and analyses from other countries in which a sequential schedule was used, suggest that a single dose of IPV has been efficacious against vaccine-associated paralytic poliomyelitis induced by Sabin polioviruses.[33,34]

Table 3. Median Reciprocal Antibody Titers.*

Visit	Fractional Dose of IVP (N=157)	Full Dose of IVP (N=153)	P Value†
	titer (95% CI)		
Poliovirus type 1			
4 mo	<8 (<8 to <8)	<8 (<8 to <8)	NS
8 mo	<8 (<8 to <8)	11 (9 to 14)	NS
8 mo 7 days	713 (566 to 898)‡	≥1448 (≥1448 to ≥1448)§	<0.001
8 mo 30 days	450 (357 to 566)‡	≥1448 (≥1448 to ≥1448)§	<0.001
Poliovirus type 2			
4 mo	<8 (<8 to <8)	<8 (<8 to 9)	NS
8 mo	9 (<8 to 11)	28 (18 to 36)	NS
8 mo 7 days	≥1448 (≥1448 to ≥1448)¶	≥1448 (≥1448 to ≥1448)‖	<0.001
8 mo 30 days	898 (713 to ≥1448)¶	≥1448 (≥1448 to ≥1448)‖	<0.001
Poliovirus type 3			
4 mo	<8 (<8 to <8)	<8 (<8 to <8)	NS
8 mo	<8 (<8 to <8)	<8 (<8 to <8)	NS
8 mo 7 days	357 (225 to 566)**	≥1448 (≥1448 to ≥1448)††	<0.001
8 mo 30 days	71 (36 to 113)**	898 (566 to ≥1448)††	<0.001

* Median titers and corresponding 95% confidence intervals are below or above observed dilution ranges (i.e., reciprocal titer, 8 to 1224).
† P values were calculated in accordance with Kolmogorov–Smirnov nonparametric testing of antibody titer distribution. NS denotes not significant.
‡ P=0.001 for the within-group comparison.
§ P=0.02 for the within-group comparison.
¶ P=0.004 for the within-group comparison.
‖ P=0.30 for the within-group comparison.
** P<0.001 for the within-group comparison.
†† P=0.001 for the within-group comparison.

These data are particularly relevant to the current policy discussions regarding an eventual global switch from trivalent OPV to bivalent OPV for both routine and supplementary immunization. We found that for poliovirus type 2, a single fractional dose produced seroconversion in almost half the infants (47.1%) and a priming response in almost all of those who did not undergo seroconversion (94.0%). Furthermore, two-dose schedules have been shown to yield seroconversion rates of more than 80% in studies in Cuba and other countries, particularly when the doses are administered at 2 and 4 months of age.[18,21,22] Our results extend these findings and suggest that for the post-eradication era, two doses of IPV given at the ages of 4 and 8 months (which in our study resulted in almost 100% seroconversion and high antibody titers in the full-dose group, with moderately lower seroconversion rates and significantly lower antibody ti-

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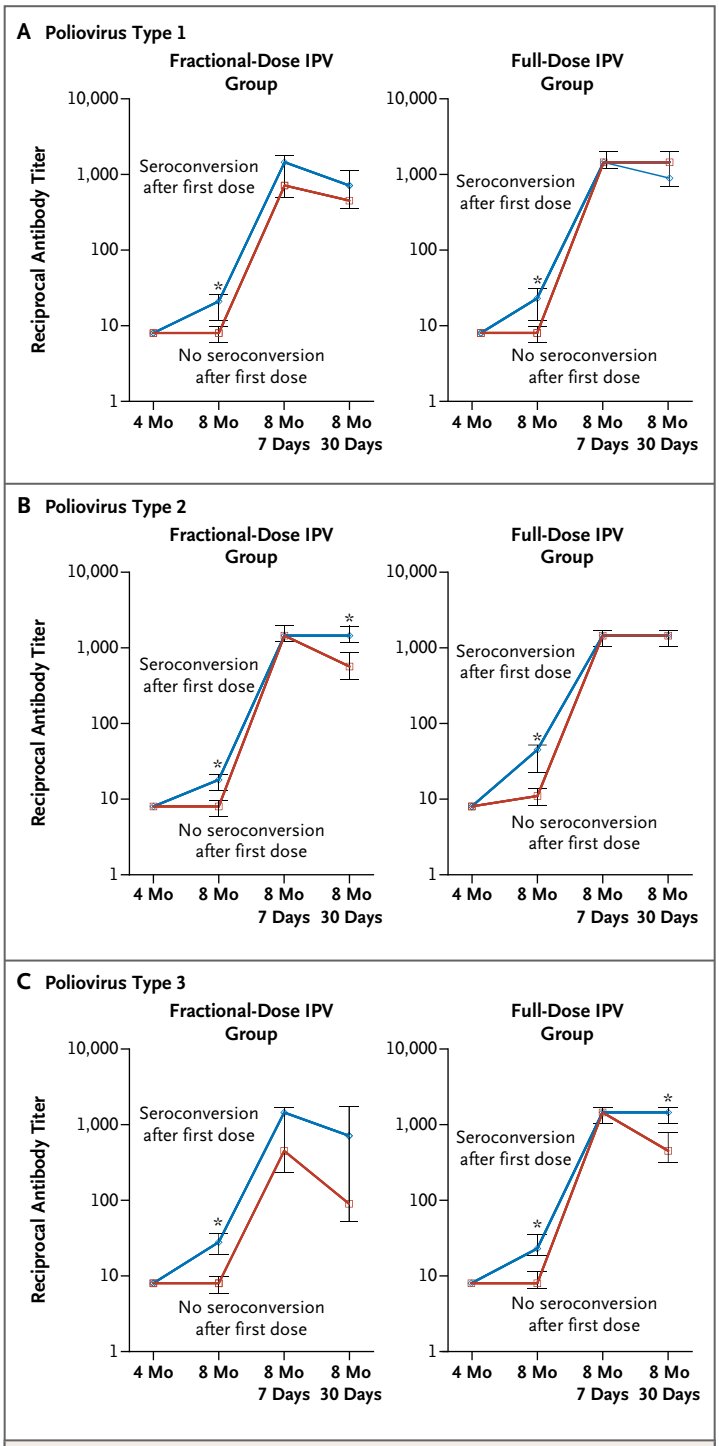

Figure 1. Median Antibody Titers at Each Study Visit According to Study Group and Conversion Status after First Dose.

Median antibody titers are shown for type 1 poliovirus in Panel A, for type 2 poliovirus in Panel B, and for type 3 poliovirus in Panel C. I bars denote 95% confidence intervals, and asterisks a significant difference at P<0.05.

ters in the fractional-dose group) could provide a lower-cost alternative to the three-dose and four-dose schedules used currently.

This trial also expands the number of policy options that could make IPV affordable for use in developing countries. First, two fractional doses of IPV administered on an appropriate schedule (e.g., an older age at administration and a longer interval between doses) appear to induce seroconversion in a high proportion of vaccinees (>90%) and would immediately reduce the cost of vaccination on such a schedule from the current $6.00 per vaccinee (based on UNICEF's IPV procurement price of approximately $3.00 per dose) to $1.20. Second, a one-dose IPV priming schedule could further reduce the cost to 60 cents. Since the other strategies for making IPV affordable are expected to further reduce its price, the WHO expects the tiered pricing of IPV for developing countries to be decreased to the break-even price with OPV, at less than 50 cents per immunizing dose.[35-37]

The study has some limitations. Although every effort was made to prevent secondary exposure to the vaccine virus, we identified and withdrew six infants because of demonstrated or probable exposure to OPV administered during the February and May 2009 immunization campaigns in Cuba. One remaining issue may be uncertainty regarding the long-term persistence of antibody titers in developing countries. Data from industrialized countries suggest that antibody titers decline rapidly after immunization and then remain relatively stable for many years.[38]

There were more minor adverse events associated with the use of fractional-dose IPV than with full-dose IPV owing to the fact that the fractional doses were administered intradermally. Previous surveys of parents have shown that the increase in minor local adverse events after intradermal administration of IPV did not affect their preference with respect to the route of administration.[21,22]

Our study shows that the administration of a single fractional dose of IPV for priming is a feasible, lower-cost alternative to schedules in which multiple full doses are used. It is also a feasible alternative to hexavalent combination IPV vaccines when available for use in developing countries. A fractional dose could be administered together with the diphtheria–tetanus toxoids and pertussis vaccine (DTP) in infants between 4 and

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Table 4. Adverse Events.*

Event	Fractional Dose of IVP (N=157)		Full Dose of IVP (N=153)	
	Dose 1	Dose 2	Dose 1	Dose 2
	number (percent)			
Temperature ≥38.0°C	1 (0.6)	2 (1.3)	2 (1.3)	0
Infiltration†	0	1 (0.6)	0	0
Redness	47 (30.0)‡	37 (23.6)§	3 (2.0)‡	2 (1.3)§
Induration	11 (7.0)¶	14 (8.9)‖	2 (1.3)¶	1 (0.7)‖
Other	1 (0.6)**	0	1 (0.7)††	0

* Among the five infants with elevated temperatures, the temperatures were between 38.0 and 38.9°C, and the elevated temperature was classified as moderate in intensity; all other adverse events were classified as minor, except in the case of one infant in the fractional dose group who after the first dose had an induration measuring 0.6 mm in diameter, which was classified as moderate in intensity.
† Infiltration was defined as a combination of local signs and symptoms (redness, induration, pain).
‡ P<0.001 for the between-group difference in redness after dose 1.
§ P<0.001 for the between-group difference in redness after dose 2.
¶ P=0.03 for the between-group difference in induration after dose 1.
‖ P=0.002 for the between-group difference in induration after dose 2.
** This patient had restlessness.
†† This patient had weakness.

6 months of age, or together with measles vaccine in infants between 9 and 12 months of age. If full protection against poliomyelitis is needed (e.g., if an outbreak is anticipated), a second fractional dose or a full dose could be administered rapidly in mass campaigns. This second dose would be expected to rapidly boost antibody titers to high levels (especially in those whose immune system has been primed). In addition, since vaccine efficacy is probably dependent on antibody production, this boost would protect individual children from the paralytic consequences of poliomyelitis at an affordable cost.

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REFERENCES

1. World Health Assembly. Global eradication of poliomyelitis by the year 2000. Geneva: World Health Organization, 1988 (resolution WHA 11.28).
2. Apparent global interruption of wild poliovirus type 2 transmission. MMWR Morb Mortal Wkly Rep 2001;50:222-4. [Erratum, MMWR Morb Mortal Wkly Rep 2001;50:249.]
3. Outbreaks following wild poliovirus importations — Europe, Africa, and Asia, January 2009–September 2010. MMWR Morb Mortal Wkly Rep 2010;59:1393-9.
4. Outbreak of poliomyelitis in Tajikistan in 2010: risk for importation and impact on polio surveillance in Europe? Euro Surveill 2010;15(17):pii=19558.
5. Grard G, Dexler JF, Lekana-Douki S, et al. Type 1 wild poliovirus and putative enterovirus 109 in an outbreak of acute flaccid paralysis in Congo, October-November 2010. Euro Surveill 2010;15(47): pii=19723.
6. Progress towards eradicating poliomyelitis in India, January 2009-October 2010. Wkly Epidemiol Rec 2010;85: 497-503.
7. Progress towards global eradication of wild poliovirus transmission, January 2011-March 2012. Wkly Epidemiol Rec 2012;87:195-200.
8. Dove AW, Racaniello VR. The polio eradication effort: should vaccine eradication be next? Science 1997;277:779-80.
9. Conclusions and recommendations of the Ad Hoc Advisory Committee on Poliomyelitis Eradication, Geneva, 21-22 September 2004. Wkly Epidemiol Rec 2004; 79:401-7.
10. Meeting of the Immunization Strategic Advisory Group of Experts, November 2008 — conclusions and recommendations. Wkly Epidemiol Rec 2009;84:1-16.
11. Polio Eradication Initiative. Cessation of routine oral polio vaccine (OPV) use after global polio eradication: framework for national policy makers in OPV-using countries. Geneva: World Health Organization, 2005 (WHO/POLIO/05.02).
12. Technical Consultative Group to the World Health Organization on the Global Eradication of Poliomyelitis. "End-game" issues for the global polio eradication initiative. Clin Infect Dis 2002;34:72-7.

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13. Bruce Aylward R, Sutter RW, Cochi SL, Thompson KM, Jafari H, Heymann D. Risk management in a polio-free world. Risk Anal 2006;26:1441-8.
14. World Health Assembly. Poliomyelitis: mechanism for management of potential risks to eradication. Geneva: World Health Organization, 2008 (resolution WHA 61.1).
15. Kreeftenberg H, van der Velden T, Kersten G, van der Heuvel N, de Bruijn M. Technology transfer of Sabin-IPV to new developing country markets. Biologicals 2006;34:155-8.
16. Simizu B, Abe S, Yamamoto H, et al. Development of inactivated poliovirus vaccine derived from Sabin strains. Biologicals 2006;34:151-4.
17. Liao G, Li R, Li C, et al. Safety and immunogenicity of inactivated poliovirus vaccine made from Sabin strains (Sabin IPV): a phase-II randomized positive-controlled trial. J Infect Dis 2012;205:237-43.
18. Sutter RW, Cáceres VM, Mas Lago P. The role of routine polio immunization in the post-certification era. Bull World Health Organ 2004;82:31-9.
19. WHO Collaborative Study Group on Oral and Inactivated Polio Vaccines. Combined immunization of infants with oral and inactivated poliovirus vaccines: results of a randomized trial in the Gambia, Oman, and Thailand. J Infect Dis 1997; 175:Suppl 1:S215-S227.
20. Cohen-Abbo A, Culley BS, Reed GW, et al. Seroresponse to trivalent oral poliovirus vaccine as a function of dosage interval. Pediatr Infect Dis J 1995;14:100-6.
21. Resik S, Tejeda A, Mas Lago P, et al. Randomized controlled clinical trial of fractional doses of inactivated poliovirus vaccine administered intradermally by needle-free device in Cuba. J Infect Dis 2010;201:1344-52.
22. Mohammed AJ, AlAwaidy S, Bawikar S, et al. Fractional doses of inactivated poliovirus vaccine in Oman. N Engl J Med 2010;362:2351-9.
23. Más Lago P, Gary HE Jr, Pérez LS, et al. Poliovirus detection in wastewater and stools following an immunization campaign in Havana, Cuba. Int J Epidemiol 2003;32:772-7.
24. World Health Organization Collaborative Study Group on Oral Poliovirus Vaccine. Factors affecting the immunogenicity of oral poliovirus vaccine: a prospective evaluation in Brazil and the Gambia. J Infect Dis 1995;171:1097-106.
25. Expanded Programme on Immunization. Report of a WHO informal consultation on polio neutralization antibody assays, Nashville, 5-6 December 1991. Geneva: World Health Organization, 1991 (WHO/EPI/RD/91.3 Rev 1).
26. Sutter RW, Kew OM, Cochi SL Aylward BA. Poliovirus vaccine — live. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 6th ed. Philadelphia: W.B. Saunders, 2012: 598-645.
27. Sutter RW, Suleiman AJM, Malankar P, et al. Trial of a supplemental dose of four poliovirus vaccines. N Engl J Med 2000;343:767-73.
28. R Development Core Team. R: a language and environment for computing. Vienna: R Foundation for Statistical Computing, 2006 (http://www.R-project.org).
29. SAS/STAT user's guide, version 6.4. 4th ed. Cary, NC: SAS Institute, 1989.
30. Conover WJ. Practical nonparametric statistics. New York: John Wiley & Sons, 1971.
31. Efron B, Tibshirani R. An introduction to the Bootstrap. London: Chapman & Hall/CRC, 1993.
32. Robertson SE, Traverso HP, Drucker JA, et al. Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine. Lancet 1988;1:897-9.
33. Kapusinszky B, Molnár Z, Szomor KN, Berencsi G. Molecular characterization of poliovirus isolates from children who contracted vaccine-associated paralytic poliomyelitis (VAPP) following administration of monovalent type 3 oral poliovirus vaccine in the 1960s in Hungary. FEMS Immunol Med Microbiol 2010;58:211-7.
34. Alexander LN, Seward JF, Santibanez TA, et al. Vaccine policy changes and epidemiology of poliomyelitis in the United States. JAMA 2004;292:1696-701.
35. Sangrujee N, Cáceres VM, Cochi SL. Cost analysis of post-polio certification immunization policies. Bull World Health Organ 2004;82:9-15.
36. Griffiths UK, Botham L, Schoub BD. The cost-effectiveness of alternative polio immunization policies in South Africa. Vaccine 2006;24:5670-8.
37. Sutter RW, Mohammed AJ. Poliovirus vaccine and vaccine-derived poliovirus. N Engl J Med 2010;363:1870-1.
38. Böttiger M. A study of the sero-immunity that has protected the Swedish population against poliomyelitis for 25 years. Scand J Infect Dis 1987;19:595-601.
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