

Randomized Controlled Clinical Trial of Fractional Doses of Inactivated Poliovirus Vaccine Administered Intradermally by Needle-Free Device in Cuba

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Background. As part of an evaluation of strategies to make inactivated poliovirus vaccine (IPV) affordable for developing countries, we conducted a clinical trial of fractional doses of IPV in Cuba.

Methods. We compared the immunogenicity and reactogenicity of fractional-dose IPV (0.1 mL, or 1/5 of a full dose) given intradermally using a needle-free jet injector device compared with full doses given intramuscularly. Subjects were randomized at birth to receive IPV at 6, 10, and 14 weeks.

Results. A total of 471 subjects were randomized to the 2 study groups, and 364 subjects fulfilled the study requirements. No significant differences at baseline were detected. Thirty days after completing the 3-dose schedule of IPV, 52.9%, 85.0%, and 69.0% of subjects in the fractional-dose IPV arm seroconverted for poliovirus types 1, 2, and 3, respectively, whereas 89.3%, 95.5%, and 98.9% of subjects in the full-dose IPV arm seroconverted for poliovirus types 1, 2, and 3, respectively (all comparisons, $P < .001$). The median titers of each poliovirus serotype were significantly lower in the intradermal arm than in the intramuscular arm ($P < .001$). Only minor local adverse effects and no moderate or serious adverse events were reported.

Conclusions. This large-scale evaluation demonstrates the feasibility of fractional doses of IPV given intradermally as an antigen-sparing strategy but also shows that IPV given to infants at 6, 10, and 14 weeks of age results in suboptimal immunogenicity (especially for the fractional-dose arm).

Trial Registration. Controlled-trials.com identifier: ISRCTN19673867.

In 1988, the World Health Assembly passed a resolution calling for the eradication of poliomyelitis by the year 2000 [1]. After implementation of the transmission interruption strategies, the number of countries that did not eradicate poliovirus types 1 and 3 circulation decreased to 4 in 2008 (from >125 polio-endemic countries in 1988), and the number of poliomyelitis cases decreased by >99% in the same period. In addition, 1 serotype had been eradicated, with the last case of in-

digenous wild poliovirus type 2 transmission reported in Aligarh, India, in October 1999 [2, 3]. However, as of the end of 2009, poliovirus types 1 and 3 remain endemic in Afghanistan, India, Nigeria, and Pakistan [4].

Because of the progress with implementation of the eradication strategies, the planning and preparations for the era after eradication of poliomyelitis began more than 10 years ago. The most important decision—to discontinue the routine use of oral poliovirus vaccine (OPV), because it contains live attenuated poliovirus—was suggested in 1997 [5] and was formally endorsed in 2004 by the Advisory Committee on Poliomyelitis Eradication [6] and in 2008 by the Scientific Advisory Group of Experts. The OPV cessation prerequisites have been published [7], the vaccination options have been identified [8], and the risks for paralytic disease following OPV cessation are being assessed in a series of studies conducted in developing countries [9].

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The need for an “affordable inactivated poliovirus vaccine (IPV)” appropriate for use in developing countries was added to the list of prerequisites in 2007 by the Advisory Committee on Poliomyelitis Eradication [10]. To achieve this prerequisite, a number of strategies are under evaluation, including (1) schedule reduction and antigen dose reduction (ie, fractional dose IPV), (2) adjuvant use (traditional and novel adjuvant), (3) optimization of production processes (ie, increased cell densities, new cell lines, and use of alternative inactivation agents), and (4) production of Sabin-IPV (ie, IPV produced from Sabin strains) in lower cost settings (ie, developing countries). For the near term, the most important of these strategies appears to be the development of Sabin-IPV. For the longer term, other approaches may become more important, especially the optimization of production processes and the possibility of non-infectious approaches to IPV production. The production of Sabin-IPV in developing countries appears to be feasible according to the proposed interim biocontainment requirements [11]. A Sabin-IPV development collaboration between the Netherlands Vaccine Institute, Japan Poliomyelitis Research Institute, and Bio Farma was established in 2005, and the pharmaceutical development for this product has been completed. Sabin-IPV is also being developed independently for licensure by the Japan Poliomyelitis Research Institute, by Panacea Biotec of India, and by the Kunming Vaccine Institute in China [12, 13].

IPV dose reduction through intradermal delivery to both stretch available supplies and reduce cost, with a potential for rapid implementation, appears a feasible approach. Intradermal administration has been evaluated for many antigens and vaccines. Many of these evaluations have been published and have provided excellent results for rabies (intradermal rabies vaccination has been recommended by the World Health Organization for prophylaxis after exposure [14]), seasonal influenza vaccine [15, 16], hepatitis B vaccine [17, 18], and inactivated poliovirus vaccines. The intradermal administration of IPV was first evaluated in the 1950s. However, additional work was discontinued at that time because the oil-in-water adjuvant was not suitable for intradermal administration owing to local adverse events [19, 20]. In the 1980s, small studies with fractional dose IPV in India suggested that a schedule of 1/5 of a full dose of IPV given intradermally could result in seroconversion rates similar to those of a schedule with full-dose IPV given intramuscularly [21–23].

The potential advantages and challenges of intradermal delivery for vaccination have recently been reviewed [24]. There is a theoretical advantage of using the dermis as the site of vaccination, including the high density of dendritic cells in the skin compared with the muscle [25] and the possibility of inducing mucosal immunity when presenting an antigen to the

skin [26] because of cross-communication between the skin and mucosal surfaces. The intradermal route has also shown an advantage over the intramuscular route for the administration of rabies vaccine when rabies immunoglobulin is coadministered, in which case the coadministration does not affect the neutralization antibody titers [27]. Because the immunogenicity of IPV is greatly affected by maternally derived antibody [28, 29], it was thought that, similar to rabies vaccination in the presence of rabies immunoglobulin serum antibodies, intradermal immunization could minimize the inhibitory effect of the passively acquired antibody and thus lead to higher seroconversion rates.

The difficulties of administering any vaccine intradermally with needle and syringe are well recognized. Therefore, we took advantage of the availability of “investigational use” needle-free jet injection devices appropriate for intradermal delivery. In this study we used a device made by Bioject. IPV has been administered intramuscularly by jet injectors and demonstrated efficacy [30, 31].

The immunogenicity of IPV is affected by levels of maternally derived antibody [28, 29]. Given that the half-life of maternally derived antibody decay is ~1 month [32], a delay in administration of IPV usually results in much higher seroconversion rates [33, 34]. However, many countries use a schedule of 6, 10, and 14 weeks of age for administration of routine vaccines [35], often referred to as the Expanded Program on Immunization schedule, making this schedule less optimal for IPV use. However, this schedule needed to be reconsidered for intradermal fractional dose IPV, not only because many countries are using it, but also because it constitutes the most difficult test for IPV, since maternally derived antibody levels are still high in infants of this age.

To permit an unbiased evaluation of fractional-dose IPV, a clinical study design was selected that enrolled newborns and infants that were vaccinated at 6, 10, and 14 weeks of age with either fractional-dose IPV or full-dose IPV, before these infants had an opportunity to be exposed to poliovirus secondarily through trivalent oral poliovirus vaccine [tOPV] use. Cuba provided an ideal trial site because it administers tOPV only twice a year in national campaigns (usually February and April), and several studies have demonstrated that 6–8 weeks after the last campaign, no poliovirus can be found in sewage or in stool samples from children [36]. The study was designed to provide a conclusive head-to-head comparison of the immunogenicity of fractional-dose IPV and full-dose IPV.

METHODS

This was a randomized, controlled clinical trial. Only the laboratory investigators could be blinded to the study arm allocation of subjects because of the different modes of vaccine adminis-

tration (intradermal or intramuscular). The field work of the study was conducted between 1 August 2006 and 31 March 2007 in 3 maternity hospitals and 15 vaccination sites in 5 districts of Camagüey Province, Cuba.

The study had 3 specific objectives: (1) to compare humoral antibody responses (seroconversion and antibody titer) after a 3-dose schedule of either fractional-dose IPV or full-dose IPV; (2) to evaluate the dose-specific immune responses; and (3) to determine adverse events following fractional- and full-dose IPV administration.

Voluntary, informed consent for participation of newborns was obtained from parents in accordance with ethical principles, including the Declaration of Helsinki. The study was approved by the National Regulatory Agency and the Ministry of Health, Cuba; the Institutional Review Boards of Pedro Kouri Institute; and ethical review committees from Pedro Kouri Institute, Cuba, Camagüey Provincial Health Office, Cuba and the World Health Organization, Geneva, Switzerland, and was performed in compliance with good clinical practice guidelines. All authors vouch for the completeness and accuracy of the data and analysis presented.

In terms of sample size, a minimum sample size of 138 participants in each of the 2 study groups was needed to determine noninferiority of $\geq |20\%|$ of the study vaccination (fractional-dose IPV) compared with full-dose IPV ($\alpha = 0.05, \beta = 0.10$ [2-tailed test]). Because of invariable attrition of study subjects, we substantially inflated the sample size.

During prenatal visits, pregnant mothers and prospective fathers were contacted, informed about the study, and asked if they were willing to participate. Newborns were eligible for participation and subjects were eligible to continue if (1) informed consent was obtained, (2) the infant's apgar score was ≥ 9 at 5 min, (3) the infant's birth weight was >2.5 kg, (4) the infant was healthy at 6 weeks on the basis of a medical examination and was being breastfed, and (5) the infant's weight-to-height ratio was above 10th percentile on the growth chart. Infants were excluded if (1) suffering from an acute or chronic disease, (2) temperature $>37.0^{\circ}\text{C}$ at vaccination visit or in the last 24 h before visit, (3) given a diagnosis of seizure illness, (4) on immunosuppressive therapy or immunostimulant therapy (during the previous month), and (5) given a diagnosis of or suspected to have severe allergic or immunodeficiency dis-

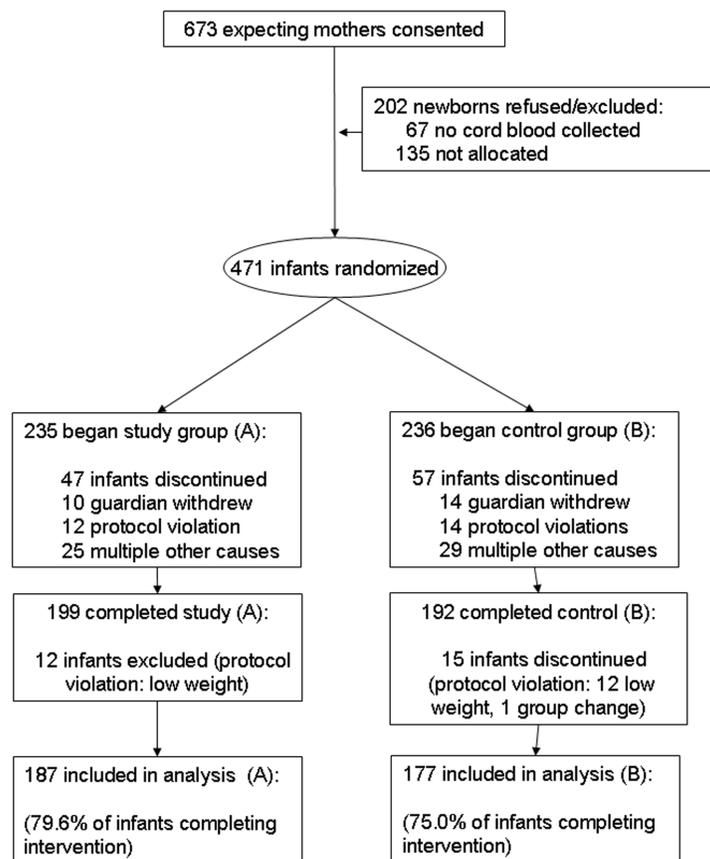


Figure 1. Description of eligible, enrolled, and participating subjects in the trial of inactivated poliovirus vaccine (IPV) in Cuba. Subjects were randomized to 1 of 2 study arms: arm A, who received fractional-dose IPV administered intradermally (*left*), or arm B, who received full-dose IPV administered intramuscularly (*right*).

Table 1. Baseline Attributes of Study Subjects, by Study Arm, Fractional Inactivated Poliovirus Vaccine (IPV) Clinical Trial, Cuba, 2006–2007

Attribute	Study arm	
	Arm A (n = 187)	Arm B (n = 177)
Male, no. (%) of subjects	96 (51.3)	93 (52.5)
Birth weight, kg, median (95% CI)	3.4 (3.3–3.5)	3.4 (3.3–3.4)
Poliovirus type 1 seropositivity		
Seroprevalence at birth, ^a % of subjects	88.8	83.1
Median titer (95% CI)	27 (22–37)	37 (22–45)
Poliovirus type 2 seropositivity		
Seroprevalence at birth, ^a % of subjects	85.6	91.0
Median titer (95% CI)	22 (22–32)	37 (27–45)
Poliovirus type 3 seropositivity		
Seroprevalence at birth, ^a % of subjects	40.1	44.1
Median titer (95% CI)	<8 (<8 to <8)	<8 (<8–8)

NOTE. Subjects in arm A received fractional IPV administered intradermally, and subjects in arm B received full-dose IPV administered intramuscularly. None of the differences were significant at the .05 level. CI, confidence interval.

^a Antibody titer \geq 1:8.

order. In addition, if a subject fell from above 10th percentile to below 10th percentile weight-to-height ratio on the growth curve during the study period, then the subject was also excluded.

Subjects were randomized to receive either a fractional (0.1 mL, or 1/5) dose of IPV or full doses of IPV at 6, 10, and 14 weeks of age produced by the Statens Serum Institute, Copenhagen, Denmark, formulated to contain at least 32, 8, and 40-D antigen of poliovirus serotypes 1, 2, and 3, respectively. The vaccines were shipped under appropriate cold-chain conditions from the manufacturer to Havana. Independent testing of the

IPV demonstrated that the vaccine met all potency and release requirements.

IPV was administered either intradermally with a needle-free device (Biojector 2000; Bioject) or intramuscularly with a pre-filled syringe and needle. The needle-free device was approved by the 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 for intradermal delivery of DNA-based vaccine candidates in clinical trials [37, 38], of live viral vectors [39], and of inactivated influenza vac-

Table 2. Seroconversion Rates and Poliovirus Antibody Titers Following a 3-Dose Schedule of Inactivated Poliovirus Vaccine (IPV) Administered at 6, 10, and 14 Weeks of Age by Study Arm, Fractional IPV Clinical Trial, Cuba, 2006–2007

Poliovirus type	Study arm		P
	Arm A (n = 187)	Arm B (n = 177)	
Type 1			
Seroconversion rate, % of subjects	52.9	89.3	<.001
Median titer (95% CI) ^a	19 (19–22)	85 (54–99)	<.001
Type 2			
Seroconversion, % of subjects	85.0	95.5	.001
Median titer (95% CI) ^a	45 (45–54)	214 (178–295)	<.001
Type 3			
Seroconversion rate, % of patients	69.0	98.9	<.001
Median titer (95% CI) ^a	32 (24–45)	295 (214–355)	<.001

NOTE. Seroconversion was defined as a 4-fold increase in titer over expected decline in maternally derived antibody (see Methods). Subjects in arm A received fractional-dose IPV administered intradermally. Subjects in arm B received full-dose IPV administered intramuscularly. CI, confidence interval.

^a Median titer of seroconverted subjects only.

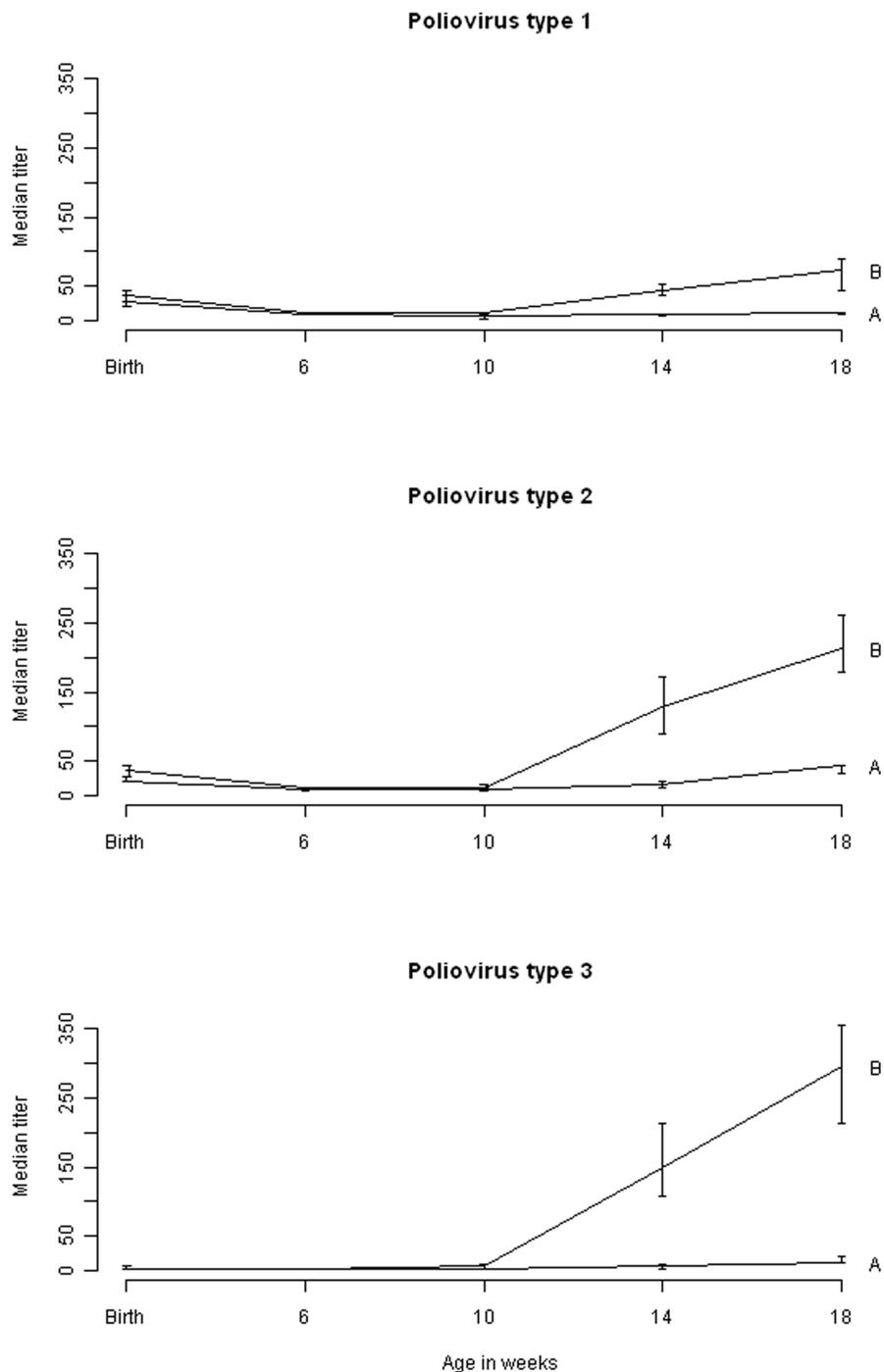


Figure 2. Median polio antibody titer and 95% confidence interval, by study arm and study visit (at birth and at 6, 10, 14, and 18 weeks of age), Cuba, 2006–2007.

cines [40]. The device was approved by the Cuban Medical Device Agency for use in this study.

After vaccination, subjects were observed for 60 min to monitor immediate adverse events. In addition, subjects were evaluated for adverse events by qualified medical staff at 24, 48, and 72 h and at 7 days after each vaccination by conducting

home visits. No other vaccines were administered concurrently, and there was an interval of 2 weeks after each IPV vaccination before other routine childhood immunizations were provided by the health services.

Blood specimens were collected at birth (cord blood), and at 6, 10, 14, and 18 weeks of age. To collect the blood specimens

Table 3. Seroconversion by Vaccine Dose and Study Arm, Fractional Inactivated Poliovirus Vaccine (IPV) Clinical Trial, Cuba, 2006–2007

Poliovirus type, dose	Proportion (%) of subjects with seroconversion, by study arm		P
	Arm A (n = 187)	Arm B (n = 177)	
Type 1			
Dose 1	9/187 (4.8)	34/177 (19.2)	<.001
Dose 2	42/178 (23.6)	78/143 (54.6)	<.001
Dose 3	38/136 (27.9)	29/65 (44.6)	.03
Other ^a	10/98 (10.2)	17/36 (47.2)	<.001
None	88/187 (47.1)	19/177 (10.7)	<.001
Type 2			
Dose 1	35/187 (18.7)	63/177 (35.6)	<.001
Dose 2	68/152 (44.7)	71/114 (62.3)	.007
Dose 3	53/84 (63.1)	31/43 (72.1)	>.05
Other ^a	3/31 (9.7)	4/12 (33.3)	>.05
None	28/187 (15.0)	8/177 (4.5)	.002
Type 3			
Dose 1	14/187 (7.5)	75/177 (42.4)	<.001
Dose 2	67/173 (38.7)	90/102 (88.2)	<.001
Dose 3	47/106 (44.3)	9/12 (75.0)	>.05
Other ^a	1/59 (1.7)	1/3 (33.3)	>.05
None	58/187 (31.0)	2/177 (1.1)	<.001

NOTE. Subjects in arm A received fractional-dose IPV administered intradermally. Subjects in arm B received full-dose IPV administered intramuscularly.

^a Seroconversion between doses 1–2, 2–3, or 1–3.

from the subject, an automated single-use heel stick device (Tenderfoot; International Technidyne) was used. After coagulation, the serum was separated, frozen, and stored at the study site at -20°C until shipment to Pedro Kouri Institute, Havana.

The specimens were tested in triplicate using a modified neutralization assay for antibody to poliovirus types 1, 2, and 3, respectively [41]. The starting dilution was a reciprocal titer of 8. Seropositivity was defined as a reciprocal titer ≥ 8 [41]. Seroconversion was defined as a 4-fold increase over expected decline in the maternally derived antibody titer of a successive specimen. In addition, if subject did not seroconvert according to this definition, subjects were evaluated for seroconversion following the full 3-dose schedule (doses administered at 6, 10, and 14 weeks) or any 2-dose schedule (doses administered at 6 and 10 weeks or at 10 and 14 weeks). The half-life of antibody decay was assumed to be 28 days. For subjects whose test results were seronegative, a change to a seropositive result in a successive specimen (ie, a reciprocal titer ≥ 8) was considered to be seroconversion.

Statistical analyses were performed using R (version; R Foundation) [42], and SAS statistical packages (version 9.13; SAS Institute) [43]. Comparisons of the proportion of subjects with seroconversion were performed with the (Yates-corrected) χ^2 test. Differences in the distribution of antibody titers were tested using the Kolmogorov-Smirnov nonparametric method [44]. The 95% confidence intervals (CI) of median values were derived by simulation [45].

RESULTS

Study population. A total of 673 parents consented to participate in this study; of these, cord blood was collected from 606 newborns. Of these, 135 subjects were excluded before randomization. A total of 471 infants were randomized to the 2 study groups, and 391 subjects completed the study; the final study group consists of 364 (77.3%) subjects who completed the study requirements (Figure 1).

Table 4. Type of Adverse Events, by Study Arm and Vaccine Dose, Fractional Inactivated Poliovirus Vaccine (IPV) Clinical Trial, Cuba, 2006–2007

Study arm, dose	Temperature		Redness	Induration	Local pain	Combination ^a	Intermittent crying for <1 h
	37.0°C–37.9°C	>37.9°C					
Arm A (n = 187)							
Dose 1	38 (20)	1 (0.5)	25 (13) ^b	4 (2.1)	1 (0.5)	26 (14) ^c	3 (1.5)
Dose 2	21 (11)	0 (0)	8 (4)	3 (1.6)	1 (0.5)	1 (0.5)	1 (0.5)
Dose 3	11 (6)	0 (0)	19 (1) ^d	5 (2.6)	0 (0)	1 (0.5)	0 (0)
Arm B (n = 177)							
Dose 1	32 (18)	2 (1)	8 (4)	2 (1)	1 (0.5)	9 (5)	4 (2)
Dose 2	41 (23) ^e	0 (0)	3 (1.6)	0 (0)	1 (0.5)	0 (0)	2 (1)
Dose 3	28 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

NOTE. Data are no. (%) of participants, unless otherwise indicated. Subjects in arm A received fractional-dose IPV administered intradermally. Subjects in arm B received full-dose IPV administered intramuscularly.

^a Combination of local signs and symptoms (redness, induration, and pain).

^b $\chi = 8.73$, $P = .003$.

^c $\chi = 8.23$, $P = .004$.

^d $\chi = 19.07$, $P < .001$.

^e Fisher Z: -2.52 , $P = .013$.

Immunogenicity of birth dose. After randomization, the 2 study arms (fractional-dose IPV or full-dose IPV) did not differ with respect to baseline attributes, type-specific seroprevalence, or poliovirus antibody titers. Poliovirus seroprevalence ranged from 83.1% to 88.8% for type 1, from 85.6% to 91.0% for type 2, and from 40.1% to 44.1% for type 3 (Table 1).

Seroconversion with the 3-dose IPV schedule was 53.9%, 85.0%, and 69.0% for poliovirus types 1, 2, and 3, respectively, in the fractional-dose IPV arm, compared with 89.3%, 95.5%, and 98.9% in the full-dose IPV arm (all comparisons, $P < .001$; Table 2). Among subjects that seroconverted, there were significant differences in median titers by study arm (Table 2). In the fractional-dose IPV arm, the overall median reciprocal titers remained stable at 9 at 6 weeks of age and 11 at 18 weeks of age for type 1, increased from 9 to 45 for type 2, and increased from <8 to 13 for type 3. In the full-dose IPV arm, the overall median reciprocal titers increased from 11 at 6 weeks of age to 74 at 18 weeks of age for type 1, from 11 to 214 for type 2, and from <8 to 295 for type 3 (Figure 2).

The dose-specific seroconversion rates by study arm are shown in Table 3. Full-dose intramuscular IPV was more immunogenic after each dose than was fractional dose IPV; subjects in the fractional-dose IPV arm seroconverted at significantly lower levels than those subjects in the full-dose arm (except for dose 3 for poliovirus type 2 and type 3).

A high level of maternally derived antibody was a risk factor for failure to seroconvert to all 3 poliovirus serotypes in both arms. On the basis of the antibody distribution, we stratified the subjects according to maternally derived antibody level in quartiles and then calculated the stratified seroconversion rates for each quartile by study arm. For each poliovirus serotype, there was a strong association between a higher-level quartile and a lower seroconversion rate. Seroconversion was not affected by birth weight or sex.

Adverse events following vaccination. No moderate or serious adverse effects were recorded. Minor local adverse effects were frequent, especially induration, pain, and redness at the inoculation site. In the fractional-dose IPV arm, 63 (33.5%) of 187 subjects had 98 adverse events following the first dose, 36 (19.0%) of 187 subjects had 60 adverse events after the second dose, and 29 (15.4%) of 187 subjects had 49 adverse events after the third dose. In the full-dose IPV arm, 46 (25.7%) of 177 subjects had 95 adverse events following the first dose, 36 (20.0%) of 177 subjects had 51 adverse events after the second dose, and 17 (9.5%) of 177 subjects had 289 adverse events after the third dose. Only the difference after the third doses was significant (Fisher Z , $P = .03$). The prevalence of these events was significantly higher in the fractional-dose IPV arm than among the full-dose IPV arm (Table 4).

Half-life decay of maternally derived antibody. The half-life of maternally derived antibody was calculated using the

cord blood and the 6-week results of antibody titers. To be included in this calculation, both samples had to have reciprocal antibody titer >8 . The half-life was estimated at 30.1 days ($n = 237$) for poliovirus type 1, 29.2 days for poliovirus type 2 ($n = 217$), and 34.6 days for poliovirus type 3 ($n = 50$).

DISCUSSION

This trial in Cuba represents the first large-scale assessment of fractional-dose IPV administered by needle-free device. The trial was strengthened by (1) no secondary exposure of poliovirus into the IPV study arms (because this was shown to be a problem in other studies [46, 47]) and (2) standardized intradermal administration of fractional-dose IPV by a needle-free device. Our findings demonstrate that fractional-dose IPV given intradermally by needle-free device results in significantly lower seroconversion rates than does full-dose IPV given intramuscularly for all poliovirus serotypes. In addition, after each dose of IPV, the rate of seroconversion in the fractional-dose IPV arm was significantly or substantially lower than the rate in the full-dose IPV arm. Both routes of administration were well tolerated, and only minor adverse events were reported.

In contrast to other trials, we can rule out the following potential causes for the low immunogenicity: (1) variation in intradermal administration, because all doses were administered in a standardized approach using a needle-free device; (2) low immunogenicity of IPV [46], because the seroconversion rates after intramuscular administration were comparable or substantially higher than those reported previously from IPV trials with vaccine from a different manufacturer conducted in Cuba [33] and in Puerto Rico [34]; (3) the influence of maternally derived antibody, because the levels in Cuba were low to all 3 serotypes compared with recent levels in countries where polio is endemic (suggesting a higher immune response would be expected in Cuba) [48, 49]; and (4) no likely effect on our results by secondary transmission of Sabin virus, because this study was conducted during a period when Cuba was not using tOPV (and very few study subjects seroconverted between birth and age 6 weeks) [36].

These findings are probably sufficiently robust to negate several hypotheses surrounding intradermal administration of IPV on this early schedule. It is apparent that the suboptimal performance of fractional-dose IPV occurred despite deposition of the antigen into a highly enriched environment for immunocompetent cells (dermis); and use of the intradermal route did not overcome the inhibitory effect of maternally derived antibody.

The possibility for reducing costs by use of fractional-dose IPV is tantalizing. Three fractional doses of 0.1 mL (1/5 of a full dose) cost less than a full dose (3/5 the cost of a full dose). In retrospect, it would have been useful to evaluate the impact of a fourth fractional dose of IPV administered at 9 months

of age (perhaps simultaneously with measles vaccine) to determine whether some of the nonseroconverting subjects had been primed and would have responded with a booster reaction. In terms of costs, even a 4-dose fractional schedule would require less antigen than a full dose of IPV.

Our study confirmed the excellent safety profile of IPV and extended this to fractional-dose IPV. There were no moderate or serious adverse reactions reported, and although significantly more minor local reactions were reported from the fractional-dose IPV arm, these reactions were very minor (induration, redness, and pain). In addition, a questionnaire administered to parents demonstrated a strong preference for intradermal administration. And when asked why, many parents responded with “the baby does not cry.”

The results of the half-life decay analyses of maternally derived antibody confirmed earlier studies conducted in the United States and elsewhere [32, 41] and provided additional reassurance for the use of a 28-day half-life of maternally derived antibody in our definition of seroconversion.

The study has limitations. Our study cannot distinguish whether the site of administration or the dosing was responsible for the lower immunogenicity of fractional doses, because the study design did not include a third arm with fractional-IPV given intramuscularly. In addition, we did not conduct a dose-finding study; thus, we cannot make any inference whether a higher antigen dose administered intradermally would have resulted in a higher immunogenicity. And finally, because subjects falling below the 10th percentile for height-to-weight ratio at any study visit were excluded, the results may not be completely representative.

Our results only partially confirmed earlier evaluations of intradermal administration of fractional-dose IPV [21–23]. The reasons for this are several-fold but may include the following: (1) the previous trials were conducted in a country (India) where tOPV use was widespread, which could have led to substantial secondary exposure of the study infants [46, 47] and thus may have masked differences between the groups; (2) IPV may have been administered subcutaneously (because needle and syringe were used for intradermal administration); (3) the vaccine was less immunogenic; or less likely, (4) genetic differences in the study populations were responsible for the response to presentation of antigen into the skin.

Our study demonstrates the feasibility of using fractional dose IPV as an antigen-sparing strategy. Additional gains in immunogenicity with fractional-dose IPV should be achievable by increasing the potency of the vaccine, because we observed significant differences in immunogenicity by virus type. However, administration of fractional-dose IPV as a priming strategy is unlikely to serve as an optimal antigen-sparing strategy when given at routine ages of 6, 10, and 14 weeks, in accordance with the Expanded Program of Immunization schedule. Given the

well-characterized interference of maternally derived antibody with IPV immunogenicity [48, 49], fractional dose IPV should be evaluated using a schedule that administers the first dose at 2 months of age and subsequent doses at intervals of 2 months.

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