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Randomized controlled study of fractional doses of inactivated poliovirus vaccine administered intradermally with a needle in the Philippines☆

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SUMMARY

Objective: Comparison of a fractional inactivated poliovirus vaccine (IPV) dose administered intradermally (ID) to a full dose administered intramuscularly (IM).
Methods: Healthy Filipino infants were randomized to receive IPV as either a fractional ($1/5^{th}$) dose ID by needle injection or a full dose IM at 6, 10, and 14 weeks and a booster at 15–18 months of age. Pre- and post-vaccination anti-polio 1, 2, and 3 titers were estimated. Adverse events were monitored throughout the study.
Results: Following primary series vaccination, anti-polio 1, 2, and 3 titers were ≥8 (1/dil) in 99–100% of participants, and the ID route was non-inferior to the IM route. Depending on the study group, antibody persistence was detected in 83–100% of participants, and the booster dose resulted in a strong anamnestic response in all groups. The incidence of adverse events in each group was similar, except for injection-site erythema (higher in the ID group).
Conclusions: Primary series and booster vaccination of a fractional IPV dose administered by the ID route was highly immunogenic and well tolerated. These data confirm the medical validity of using fractional ID doses of IPV. The programmatic feasibility of implementing affordable mass vaccination programs based on this delivery mode has yet to be established.

1. Introduction

The oral poliovirus vaccine (OPV) has been an important tool in moving towards the World Health Organization (WHO) goal of global eradication of poliomyelitis.[1] However, its use is linked to the occurrence of vaccine-associated paralytic poliomyelitis (VAPP), with several recent outbreaks due to circulating virus-derived polioviruses (cVDPV) having been identified in countries using OPV.[2,3] In 2007, the Advisory Committee on Polio Eradication recommended that efforts should be made to develop affordable inactivated poliovirus vaccine (IPV) as one of the alternatives towards discontinuation of OPV that would be practical for use in low-income settings.[4] Currently, numerous cost-reduction approaches are being promoted by the WHO and are being evaluated, including reduction in the number of administrations (reduced schedule), reduction in the antigen content by use of adjuvants, and optimization of vaccine production processes or use of poliovirus seed strains that are less infectious or not infectious at all.[5] In addition, intradermal delivery of a reduced dose of IPV is envisaged as a way to reduce the cost of the polio vaccine. While such a dose-reduction approach has previously been validated in terms of immunogenicity for numerous vaccines,[6–8] its proof-of-concept and programmatic feasibility in polio vaccination with modern IPVs has not been fully established.

The first reports of the immunogenicity of IPV administered intradermally (ID) in adults and children were by Salk in 1953.[9,10] Soon after the availability of the first commercial IPVs in 1955, several European and American vaccination programs relied for a while on vaccinations with IPV administered ID by the Mantoux technique (using a needle).[11–17] Later, with the availability of the modern IPV (the so-called enhanced-potency IPV), three separate proof-of-concept studies were carried out in India in the 1990s, in which a fractional dose of IPV administered by the ID route demonstrated that one-fifth of the intramuscular (IM) volume is immunogenic when delivered ID with needles. None of these studies, however, was randomized versus IM.[18–20] ID administration by the Mantoux technique has several disadvantages, including the inability to precisely determine the volume of the administered vaccine due to leakage at the site of injection, the necessity for training and skill, and the time needed to perform the injection. The development and use of multi-use nozzle jet injectors (MUNJIs) has been tainted by subject-to-subject blood-borne contamination. Now the envisaged approach is to use

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disposable syringe jet injectors (DSJIs), with either disposable, pre-filled syringes to be inserted in the injectors, or disposable syringes that are inserted into the injector device for administration after filling at the time of use from a vaccine vial presentation.[21] Various manufacturers are currently developing affordable DSJIs.

Recently, the WHO sponsored two studies in Cuba and in Oman with two different IPV vaccines used with two different schedules (6–10–14 weeks in Cuba and 2–4–6 months in Oman).[22,23] The vaccines were administered either ID using a DSJI filled at the time of use (Biojector® 2000 (Bioject), customized for an ID administration) or by IM route using a regular syringe and needle. The primary objective of these WHO-sponsored studies was to demonstrate non-inferiority in terms of seroconversion for the ID route compared to the IM route. Although both studies demonstrated clinically relevant immunogenicity of the vaccines following ID administration, non-inferiority was not demonstrated in the Cuban study. The overall response (seroconversion and median titers) was lower for the 6–10–14 week schedule compared to the 2–4–6 month schedule, and lower in the ID groups compared to the IM groups.

To complete these recent investigations, we conducted a randomized controlled trial in the Philippines to compare the primary series and booster immunogenicity of IPV by ID administration using the Mantoux technique to the IM route when used with the most challenging (least immunogenic) schedule (i.e. at 6–10–14 weeks of age – the Expanded Programme on Immunization (EPI) schedule). The ID route remains unlicensed as a route of administration for polio vaccine, and the primary objective of the primary series part of our study was to assess the non-inferiority of the fractional dose of IPV administered ID in comparison to the full dose administered IM, in terms of seroprotection (percentage of subjects with antibody titers $\geq$8 (1/dil)), using the non-inferiority definition used by most National Regulatory Agencies (NRAs) for licensure purposes, defined as the lower limit of the two-tailed 95% confidence interval (CI) of the observed difference between the fractional ID group versus the full dose IM group being $<$5 percentage points. The immunogenicity endpoints for the booster part of the study were to check for antibody persistence a year after the primary vaccination and to describe the immunogenicity and safety of the booster dose administered ID or IM. We also assessed the safety and reactogenicity of IPV administration by both routes.

2. Materials and methods

2.1. Study design and participants

The primary series vaccination study was a randomized, controlled, open-label, phase II study conducted at the University of the East Ramon Magsaysay Memorial Medical Center, Manila, Philippines. Healthy infants were randomized to receive either a fractional (1/5th of the IM volume) dose of IPV by the ID route or a full dose via the IM route, as per the EPI schedule at 6, 10, and 14 weeks of age. Participants were excluded either at the time of screening (0 to 7 days after birth, at which time the study was explained) or at the first vaccination (6 weeks of age) if they had illnesses or health issues (established by clinical examination and/or medical history), which could have interfered with the study, or a congenital or acquired immunodeficiency, or human immunodeficiency virus, hepatitis B antigen, or hepatitis C seropositivity.

Study participants who completed the primary vaccination series and returned for the booster study then received the same fractional ID or full IM dose of IPV as was received in the primary series.

Study protocols for the primary series study and the booster vaccination study were approved by the ethics committee at the study center and the studies were conducted in accordance with the Edinburgh revision of the Declaration of Helsinki, Good Clinical Practice (GCP), International Conference on Harmonisation (ICH) guidelines and the European Directive 2001/20/EC for clinical studies conducted outside the European Union. A signed informed consent form was obtained from the parent or other legally acceptable representative of each participant before any study procedure was performed.

2.2. Study vaccines and administration

The IPV vaccine, IMOVAX® Polio, batch numbers A0190-1 and A0427-2 for the primary vaccination and batch numbers D0051-1 and B0281-5 for the booster vaccination, was manufactured and supplied by Sanofi Pasteur, Lyon, France. The vaccine for ID administration was supplied as 5-ml vials, with each 0.1-ml dose containing 8, 1.6, and 6.4 D antigen units of types 1, 2, and 3 poliovirus, respectively. The vaccine for IM administration was supplied as 0.5-ml pre-filled syringes, with each dose containing 40, 8, and 32 D antigen units of types 1, 2, and 3 poliovirus, respectively. The fractional dose was administered ID in the right upper arm with a syringe mounted with a 13-mm 30-gauge needle, and the full dose was administered IM in the anterolateral area of the right thigh with a syringe equipped with a 16-mm 25-gauge needle.

Concomitantly in the study, participants received, free of charge, commercially available diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b (DTwP–Hib; 2, 4, 6 months of age) and hepatitis B (0, 1, 6 months of age) vaccines $\geq$10 days before or after the IPV vaccination (not assessed as part of our study).

2.3. Immunogenicity assessment

During the primary series vaccination, blood samples for the immunogenicity assessments were collected just before the first dose and 1 month after the third dose. For the booster study, blood samples were collected just before the booster dose and 1 month later.

The seroneutralization assay to determine the anti-polio 1, 2, and 3 antibody titers was conducted by Focus Diagnostics, Inc.[24] This assay measures the viability of poliovirus-sensitive Vero cells that are exposed to neutralizing antibodies in the serum sample mixed with poliovirus strains 1, 2, and 3, which act as a challenge virus. For this trial, wild-type poliovirus strains 1, 2, and 3 (Mahoney, MEF-1, and Saukett, respectively) were used instead of the Sabin strains used by most laboratories because of containment concerns. The Karber method was used to determine the serial dilution that neutralized 50% of the challenge virus. Results were expressed as titers (1/dil). The lower limit of quantification for the assay was 4 (1/dil).

The primary endpoint for the primary series study was the seroprotection rate (% of subjects with anti-polio antibody titer $\geq$8 (1/dil)) 1 month after primary series, with secondary endpoints being the geometric mean titer (GMT) for anti-polio 1, 2, and 3 in each group. In addition, as a post-hoc analysis to make the results of this study comparable with the two WHO-sponsored studies, the seroconversion rates were estimated descriptively for both the primary series and booster vaccinations. Seroconversion was defined as a $\geq$4-fold increase in post-primary series antibody titers over the expected titer at that time, calculated taking into account the decline of maternally derived antibodies measured in the pre-primary series sample. An anti-polio antibody half-life of 28 days was assumed.[25] The endpoints for the booster phase were similar to those used in the primary series study.

2.4. Safety assessment

All participants were included in the evaluation of reactogenicity and safety. After each vaccination, participants were observed for 30 min to monitor immediate events; their relationship to the vaccination was assessed by the Investigator. For the following 7 days, the participant's parent(s)/legal guardian recorded the start, end, and intensity of pre-defined (solicited) injection site reactions (tenderness, erythema, and swelling) and solicited systemic reactions (fever, vomiting, abnormal crying, drowsiness, loss of appetite, and irritability) on diary cards, daily. Unsolicited events observed during the period between the time of injection and the next visit were also recorded by the parent(s)/guardian using the diary card; unsolicited systemic events were assessed by the Investigator for their relationship to the vaccination, whereas unsolicited injection site events were considered as related to the IPV vaccine. Serious adverse events were collected throughout the study.

2.5. Statistical analysis

The sample size calculation was based on the non-inferiority hypothesis of primary series immunogenicity and performed using the Farrington and Manning formula[26] to give the study a global power of >90% with a clinically acceptable limit for non-inferiority of 5%. Based on this, 236 infants (118 per group) were enrolled. For each polio type, non-inferiority was demonstrated if the 95% CI of the difference in the seroprotection rates between the ID fractional dose group and the IM full dose group lay entirely above the clinically acceptable limit for non-inferiority (−5%) (one-sided test, alpha = 2.5%). The 95% CI was calculated based on the Wilson score method without continuity correction, as described by Newcombe.[27] Seroprotection rates, GMTs, and seroconversion rates were calculated with their 95% CI. For the safety evaluation, the percentage and 95% CI of participants was calculated for each solicited adverse event.

3. Results

3.1. Demographics

Between February and July 2008, a total of 118 participants were enrolled in the primary series vaccination study in each group. Of these, 115 participants in each group completed the study. Overall participant disposition is presented in Figure 1. Participant withdrawal was voluntary, except for one case of non-compliance. The age of participants in both groups was similar (mean of 45.5 days at inclusion in both groups); males and females were equally split in the ID fractional dose group, while the IM full dose group had more females than males (63% vs. 37%), although this was not considered to be of clinical importance.

The booster study was conducted between April and July 2009. Of 225 participants who returned for the booster vaccination, 113 from the ID fractional dose group and 111 from the IM full dose group completed the booster phase, with one voluntary withdrawal from the latter group.

3.2. Immunogenicity

3.2.1. Primary series vaccination

The non-inferiority analysis for the primary series is presented in Table 1, and parameters for assessment of immunogenicity – seroprotection, GMTs, and seroconversion for anti-polio 1, 2, and 3 – are presented in Table 2. The pre-primary series seroprotection rates were 56–60%, 69–72%, and 41–45% for polioviruses 1, 2, and 3, respectively, in both groups. Following primary series vaccination, seroprotection was achieved in 100% of participants for anti-polio 1 and 2 antibodies, and in 99.1% of participants for anti-polio 3 antibodies in the group receiving the ID fractional dose of IPV. The seroprotection rate against all three polio types was 100% in the group receiving the IM full dose of IPV. For each polio type, the 95% CI of the difference between the two groups lay above the clinically acceptable limit of −5%, demonstrating the non-inferiority of fractional dosing by the ID route in terms of immunogenicity.

The GMTs for anti-polio 1, 2, and 3 increased in both groups following the primary series vaccination, and were approximately two-fold higher in the IM full dose group (Figure 2), but no formal statistical test was performed. Seroconversion, after adjustment for maternal antibody decay, was similarly high in the two groups: 99.1%, 94.5%, and 95.4% in the ID fractional dose group seroconverted and 98.2%, 98.2%, and 100% in the IM full dose group seroconverted against poliovirus 1, 2, and 3, respectively.

3.2.2. Booster vaccination

The GMTs were lower in both groups at 12–15 months than the post-primary series levels (Figure 2). However, seroprotective antibody titers (≥8 (1/dil)) against poliovirus 1, 2, and 3 were observed in 95.5%, 95.5%, and 88.3% of the participants in the ID fractional dose group and 100%, 98.2%, and 96.4% in the IM full dose group.

Following booster vaccination, GMTs for anti-polio 1, 2, and 3 increased considerably in both groups, displaying an anamnestic response to the previously administered IPV (Figure 2). Post booster, seroprotection rates were 100% against each polio type, including those participants whose antibody titers after the primary series or at pre-booster were below seroprotective levels.

3.3. Safety

Solicited injection site and systemic reactions are presented in Table 3 for the primary series and booster vaccinations. No adverse event in either study led to discontinuation, and no deaths were reported in either study.

3.3.1. Primary series vaccination

The incidence of at least one solicited reaction (in terms of the number of participants experiencing a reaction) was 89.8% in the ID fractional dose group and 77.7% in the IM full dose group. Solicited injection site reactions were more frequent among participants in the ID fractional dose group than in those in the IM full dose group (83.1% vs. 59.8%). Unsolicited events were reported in 71.2% of the participants in the ID fractional dose group and 75.2% of those in the IM full dose group; these were mostly systemic, the most common being pyrexia (in 7.6% and 6.8% of participants in the ID fractional dose and the IM full dose groups, respectively). Three participants in the ID fractional dose group and one participant in the IM full dose group had an unsolicited injection site reaction that the Investigator assessed as related to the vaccination (hematoma in the ID fractional dose group and induration in the IM full dose group). There were two episodes of gastroenteritis that were reported as serious adverse events in the ID fractional dose group (neither was considered by the Investigator to be related to the study vaccine or procedures) and none in the IM full dose group.

3.3.2. Booster vaccination

The incidence of at least one solicited reaction was 54.5% in the ID fractional dose group and 42.5% in the IM full dose group. As for the primary vaccination, solicited injection site reactions were more frequent among participants in the ID fractional dose group (49.1%) compared with those in the IM full dose group (30.1%).

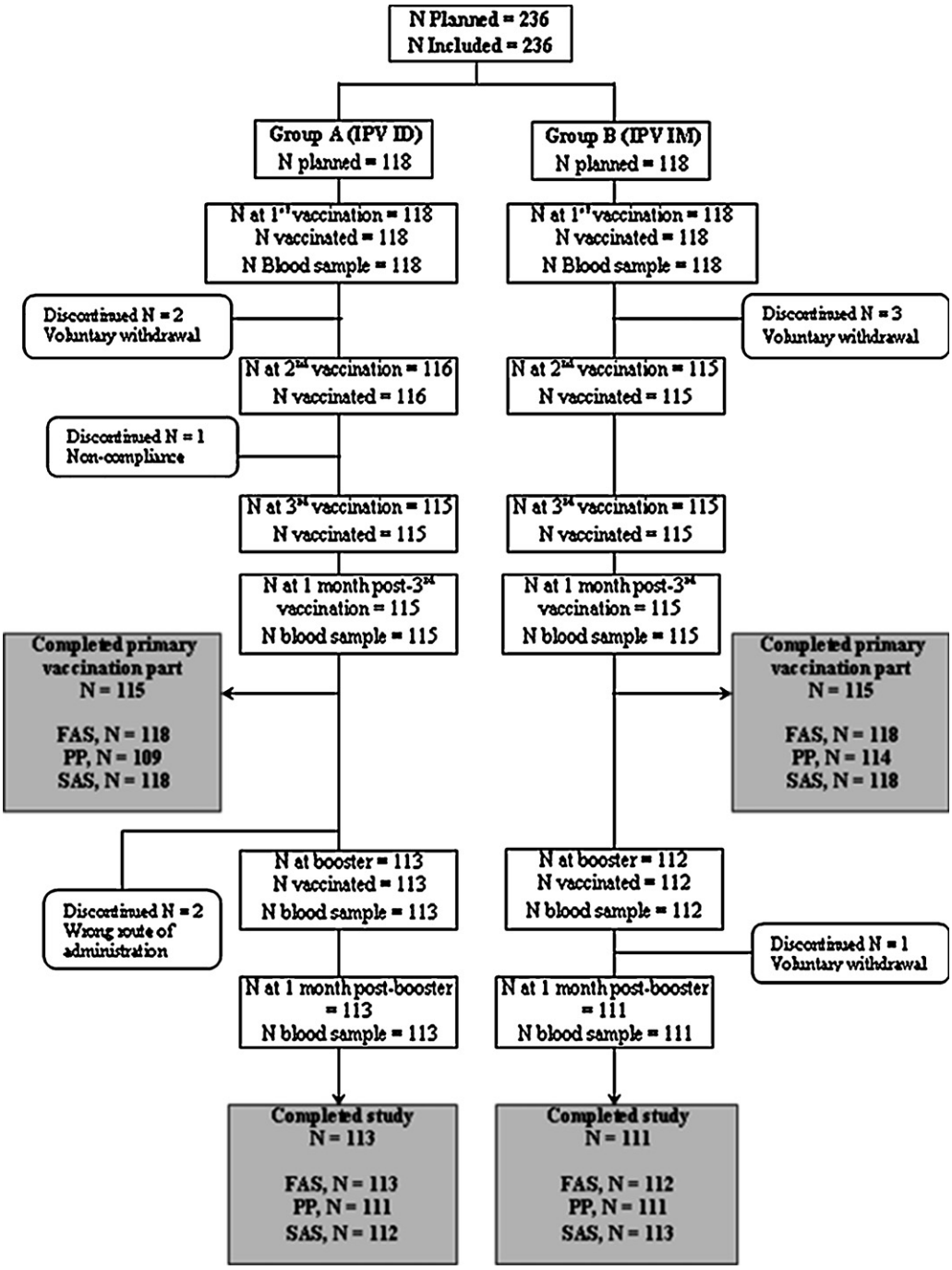

Figure 1. Disposition of participants in the primary and booster vaccination studies (IPV, inactivated polio vaccine; ID, intradermal; IM, intramuscular; FAS, full analysis set, participants who received at least one dose of IPV; PP, per-protocol, participants who completed the study without any protocol violation; SAS, safety analysis set, participants who received at least one dose of IPV and for whom safety data were collected).

Table 1
Non-inferiority analysis for primary vaccination series seroprotection data

Vaccination response (SP)	ID fractional dose (n = 109), % (95% CI)	IM full dose (n = 114), % (95% CI)	ID fractional dose − IM full dose, difference (95% CI)
Anti-polio 1, ≥8 (1/dil)	100.0 (96.7; 100.0)	100.0 (96.8; 100.0)	0.00 (−3.40; 3.26)
Anti-polio 2, ≥8 (1/dil)	100.0 (96.7; 100.0)	100.0 (96.8; 100.0)	0.00 (−3.40; 3.26)
Anti-polio 3, ≥8 (1/dil)	99.1 (95.0; 100.0)	100.0 (96.8; 100.0)	−0.92 (−5.01; 2.43)

SP, seroprotection; ID, intradermal; IM, intramuscular; CI, confidence interval.
Non-inferiority was demonstrated when the 95% confidence interval of the group difference lay entirely above the clinically acceptable limit for non-inferiority (−5%).

Table 2
Seroprotection, geometric mean titers, and seroconversion of anti-polio antibodies in the per-protocol analysis set, before and 1 month after injection with inactivated polio vaccine for the primary series and the booster vaccination

	ID fractional dose				IM full dose			
	Primary series		Booster		Primary series		Booster	
	Pre-primary	Post-primary	Pre-booster	Post-booster	Pre-primary	Post-primary	Pre-booster	Post-booster
Anti-polio 1								
≥8 (1/dil) %	59.6 (49.8; 68.9)	100.0 (96.7; 100.0)	95.5 (89.8; 98.5)	100.0 (96.7; 100.0)	56.1 (46.5; 65.4)	100.0 (96.8; 100.0)	100.0 (96.7; 100.0)	100.0 (96.7; 100.0)
GMT	10.4 (8.0; 13.4)	221 (188; 259)	48.2 (38.7; 59.9)	2833 (2392; 3356)	11.7 (8.9; 15.4)	585 (482; 710)	109.8 (84.3; 143.2)	6666 (5613; 7916)
SC %	99.1[a] (95.0; 100.0)		95.5 (89.8; 98.5)		98.2[a] (93.8; 99.8)		96.4 (91.0; 99.0)	
Anti-polio 2								
≥8 (1/dil) %	71.6 (62.1; 79.8)	100.0 (96.7; 100.0)	95.5 (89.8; 98.5)	100.0 (96.7; 100.0)	69.3 (60.0; 77.6)	100.0 (96.8; 100.0)	98.2 (93.6; 99.8)	100.0 (96.7; 100.0)
GMT	16.5 (12.9; 21.1)	234 (186; 294)	94.0 (65.8; 134.2)	3210 (2672; 3857)	16.7 (12.8; 21.6)	795 (638; 992)	132.5 (98.4; 178.3)	6522 (5540; 7678)
SC %	94.5[a] (88.4; 98.0)		83.8 (75.6; 90.1)		98.2[a] (93.8; 99.8)		88.3 (80.8; 93.6)	
Anti-polio 3								
≥8 (1/dil) %	45.0 (35.4; 54.8)	99.1 (95.0; 100.0)	88.3 (80.8; 93.6)	100.0 (96.7; 100.0)	41.2 (32.1; 50.8)	100.0 (96.8; 100.0)	96.4 (91.0; 97.0)	100.0 (96.7; 100.0)
GMT	7.8 (6.0; 10.0)	194 (157; 240)	50.3 (37.6; 67.4)	4498 (3608; 5607)	6.7 (5.2; 8.6)	774 (622; 963)	136 (103; 181)	11 952 (10 046; 14 220)
SC %	95.4[a] (89.6; 98.5)		94.6 (88.6; 98.0)		100.0[a] (96.8; 100.0)		94.6 (88.6; 98.0)	

ID, intradermal; IM, intramuscular; GMT, geometric mean of titers; SC, seroconversion.
Numbers in brackets are 95% CI.
[a] Calculated after adjustment of individual pre-primary series antibody titers to account for maternal antibody decay.

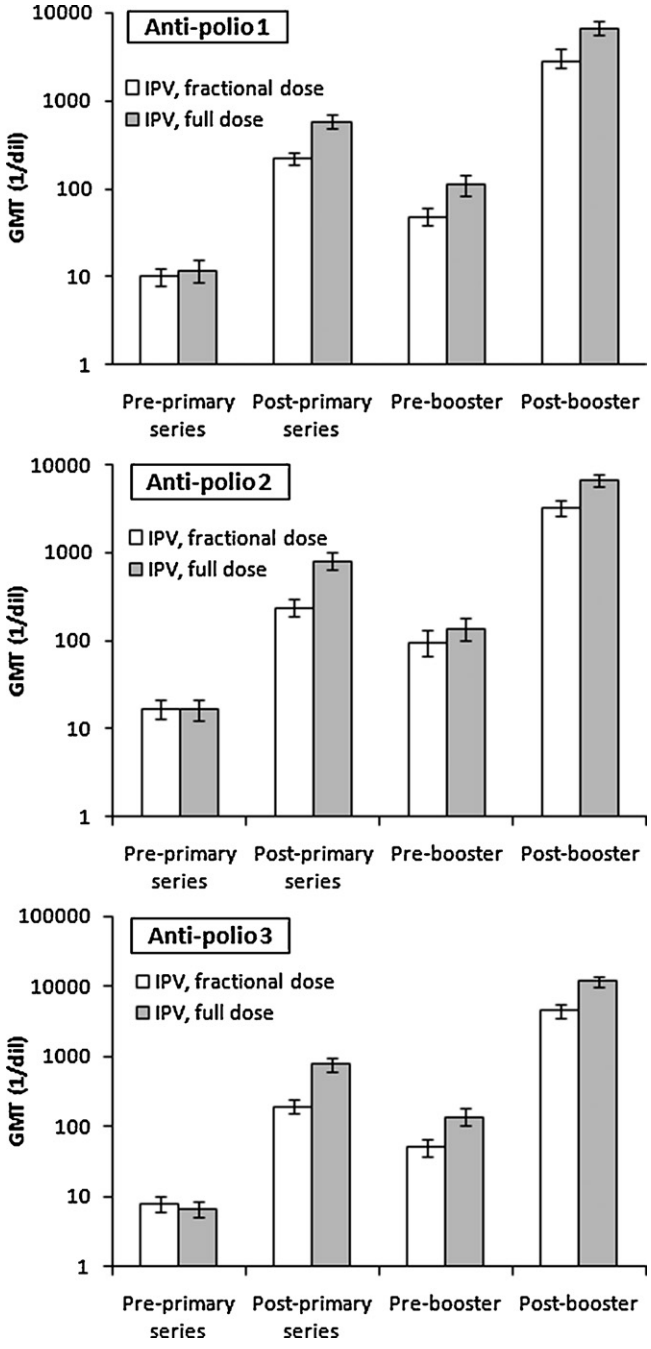

Figure 2. Geometric mean titers (GMTs) of anti-polio antibodies before and after the primary series and the booster vaccination (GMT, geometric mean of titers, IPV, inactivated polio vaccine); Y-error bars are 95% CI for the calculated GMT.

Unsolicited events were reported in 39.3% of the participants in the ID fractional dose group and in 45.1% of those in the IM full dose group, and all were assessed to be unrelated to the vaccination. There were two serious adverse events of bronchopneumonia in the IM full dose group, both of which were considered by the Investigator to be unrelated to the study vaccine or procedures.

4. Discussion

Historically, IPV administration by the ID route has been used for mass vaccination alongside other injection routes – IM and subcutaneous. Vaccination programs carried out in Europe in the 1960s showed ID IPV to be of relatively good effectiveness.[11–17]

Table 3
Incidence of solicited injection site and systemic reactions within 8 days following vaccine injection during the primary series and the booster stage in the safety analysis set

	Primary vaccination		Booster	
	ID fractional dose	IM full dose	ID fractional dose	IM full dose
	% (*n*)	% (*n*)	% (*n*)	% (*n*)
Solicited injection site reactions				
Tenderness	60.2 (71)	50.4 (59)	28.6 (32)	21.2 (24)
Erythema	69.5 (82)	29.1 (34)	38.4 (43)	11.5 (13)
Swelling	21.2 (25)	9.4 (11)	8.9 (10)	1.8 (2)
Solicited systemic reactions				
Fever	5.9 (7)	10.3 (12)	8.0 (9)	15.0 (17)
Vomiting	15.3 (18)	21.4 (25)	3.6 (4)	5.3 (6)
Crying abnormal	33.9 (40)	30.8 (36)	2.7 (3)	3.5 (4)
Drowsiness	37.3 (44)	35.0 (41)	5.4 (6)	8.0 (9)
Appetite lost	16.1 (19)	19.7 (23)	8.0 (9)	7.1 (8)
Irritability	49.2 (58)	43.6 (51)	6.3 (7)	9.7 (11)

ID, intradermal; IM, intramuscular.

However, given the inability to estimate the precise amount of polio antigen in these historical IPV vaccines, these results have a limited consequence relative to the current situation. Following the (re-)development and licensure of the modern IPV during the mid-1980s, three small-scale proof-of-concept studies carried out in the 1990s in India did establish that a fractional dose of IPV that had a defined antigen content for polio 1, 2, and 3, administered ID by the Mantoux technique, was immunogenic. An inherent drawback of these studies was the lack of a control group of study subjects receiving a full dose by IM route.[18–20] Our study, through its randomized controlled design, confirms the immunogenic potential of a fractional dose of IPV administered ID via the Mantoux technique and establishes beyond doubt the medical validity of the concept.

Our data on fractional dosing for primary series polio vaccination add to those from the WHO studies in Oman and Cuba.[22,23] However there are several differences between our study and the two sponsored by the WHO that should be taken into account. First are the endpoint used for non-inferiority demonstration and the non-inferiority criteria definitions. The WHO studies compared the seroconversion rates (defined as the % of subjects with a $\geq$4-fold increase over adjusted pre-vaccination titers) using the overlap of the 95% CI of the observed seroconversion rates, while we compared the seroprotection rates (defined as the % of subjects with antibody titers $\geq$8 (1/dil), and known to be influenced by maternally derived antibodies that could still be present at that time) by testing the lower limit of the 95% CI between the observed seroprotection rates using a non-inferiority limit of 5%. Second, and perhaps more importantly, is the type of serological assay used in the studies. The assay used in the WHO studies was based on the Sabin strains, whereas our assay was based on wild-type Salk strains. Sabin strains are antigenically different to Salk strains, particularly in terms of the antigenic sites responsible for the induction of the neutralizing antibodies, thereby potentially affecting the overall levels detected.[28] Furthermore, assay performance is also dependent on factors such as the type of cells (HEp-2 or Vero) used to grow the target virus, the size of the viral inoculum, the duration and temperature of the serum–virus interaction before cell culture, and the number of serial dilutions of the tested sera.[29,30] The type of assay (cytopathic effect or micro-metabolic inhibition test) can also influence the assay results. Despite numerous attempts to standardize the assay, the evaluation of the effect of the viral strain relative to other variables has never been thoroughly described particularly for the evaluation of neutralizing antibodies induced by IPV, and there is still no widely established international standard assay.[31] Moreover, unpublished data from Sanofi Pasteur indicate that the use of Sabin strains for the seroneutralization assay results in a significant underestimation of the antibody titers induced by IPV, thereby possibly skewing the conclusions of the WHO-sponsored studies. It is therefore very important to consider the characteristics of the assay used when comparing immunogenicity data between trials.

In our study, the seroconversion rates observed in the context of a relatively high prevalence of maternal antibodies was quite high (>94.5%) for each poliovirus type, and the post-primary antibody levels cannot be accounted for solely by the pre-primary series maternally-derived antibodies (56–60%, 69–72%, and 41–45% for polioviruses type 1, 2, and 3, respectively). The prevalence of maternally derived antibodies was higher in the Cuban study (83–88%, 85–91%, and 40–44% for polioviruses type 1, 2, and 3, respectively) than in the present study.

Finally, the WHO studies reported overall responses in terms of median titer (with an assay based on dilution range of samples ending at 1024); this is known to overestimate the results compared to a geometric estimation of the means. Also, the median titers were calculated only from seroconverted individuals, further complicating the comparison of the titers between studies. It is nevertheless true that the overall immunogenicity of the ID fractional dose is lower than the IM full dose, as evidenced by the lower mean titers in the ID fractional dose group. This creates doubt regarding the persistence of good immunological memory, and so brings into question the duration of protection afforded by the use of a fractional dose of IPV. We consider, however, that this should not be used as an argument against the medical validity of the concept. Good antibody persistence until 4–5 years of age has been shown after a three-dose primary series without a booster during the second year of life.[32,33]

While our study reinforces previous observations and proves the medical validity of fractional dose IPV administered ID, the question remains whether a DSJI can be developed, manufactured, and affordably deployed for mass vaccination, as the mass usage of needle ID injections is not foreseeable. Further evaluation will be needed to translate the concept of fractional dosing of IPV by ID route into a more cost-effective strategy in the ongoing campaign for polio eradication in low-income nations.

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Conflict of interest: JCC has acted as a principal investigator for Sanofi Pasteur for several clinical studies and has received honoraria from Sanofi Pasteur for congress attendance and the presentation of data other than those included in this manuscript. As the study sponsor, Sanofi Pasteur paid for the conduct of the studies described in this manuscript, although JCC received no direct payment from Sanofi Pasteur for conducting these studies and has no financial ties to Sanofi Pasteur.

MCB is employed by Sanofi Pasteur as a Medical Franchise Leader, and EV is employed by Sanofi Pasteur as Head, Global Medical Affairs.

Role of the funding source: The study sponsor, Sanofi Pasteur, developed the study protocol in conjunction with the principal investigator (JCC), processed the data collected during the study, was responsible for initial data interpretation and production of the clinical study report (with the study investigators), and initiated the decision to produce this article and to submit for publication.

Ethical approval: Study protocols for the primary series study and the booster vaccination study were approved by the ethics committee at the study center and the studies were conducted in accordance with Edinburgh revision of the Declaration of Helsinki, Good Clinical Practice (GCP), International Conference on Harmonisation (ICH) guidelines and the European Directive 2001/20/EC for clinical studies conducted outside the European Union. A signed informed consent form was obtained from the parent or other legally acceptable representative of each participant before any study procedure was performed.

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