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# Intradermal fractional booster dose of inactivated poliomyelitis vaccine with a jet injector in healthy adults

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**ABSTRACT**

For global eradication of poliomyelitis, inactivated poliovirus vaccine (IPV) needs to become available in all countries. Using fractional-doses (reduced-doses) may impact affordability and optimize the utilization of the production capacity. Intradermal administration has the potential to lower the dose without reducing immunogenicity. A needle-free jet injector may be a reliable way to administer vaccines intradermally. The primary objective of this randomized controlled trial was to compare the immunogenicity and tolerability of fractional-dose intradermal IPV (Netherlands Vaccine Institute, NVI) booster vaccination administered with a jet injector (PharmaJet) to full-dose and fractional-dose intramuscular vaccination with a needle and syringe. Immunogenicity was assessed by comparing the differences in the post-vaccination $\log_2$ geometric mean concentrations of neutralizing antibodies (GMC) between the study groups. A total of 125 Dutch adult volunteers with a well-documented vaccination history were randomized to one of four groups: full-dose intramuscular needle (IM-NS-0.5), full-dose intramuscular jet injector (IM-JI-0.5), 1/5$^{th}$ dose intramuscular needle (IM-NS-0.1), 1/5$^{th}$ dose intradermal jet injector (ID-JI-0.1). Vaccination with the JI was less painful (87% no pain) than vaccination with a NS (60% no pain), but caused more transient erythema (JI 85%, NS 24%) and swelling (JI 50%, NS 5%). Intradermal vaccination caused less vaccination site soreness (ID 16%, IM 52%). At baseline all subjects had seroprotective antibody concentrations. After 28 days, GMC were slightly lower in the ID-JI-0.1 group than in the reference group (IM-NS-0.5). The differences were not statistically significant, but the stringent non-inferiority criterion (i.e. a difference of 1 serum dilution in the microneutralization assay) was not met. After one year, differences in GMC were no longer apparent. In contrast, intramuscular vaccination with a fractional dose administered with a needle (IM-NS-0.1) was statistically inferior to full-dose intramuscular vaccination. This shows that intradermal but not intramuscular delivery of fractional-dose IPV may be sufficient for routine polio vaccination.

## INTRODUCTION

The new Global Polio Eradication Initiative has set a target for complete interruption of the transmission of poliovirus [1]. After eradication, cessation of oral poliovirus vaccine (OPV) is needed to prevent outbreaks due to circulating vaccine derived poliovirus [2, 3]. Countries must then decide whether to stop all routine immunization against polio or to continue immunization with inactivated poliovirus vaccine (IPV). One of the prerequisites for cessation of the use of OPV is therefore to make IPV affordable and suitable for use in developing countries [4]. The worldwide production capacity for IPV is limited and the current weighted-average purchase price per dose of vaccine, when purchased by the United Nations Children's Fund, is $0.15 for trivalent OPV and approximately $3 for IPV [5]. Strategies to reduce this 20-fold cost increase include intradermal (ID) delivery of a fractional (reduced) antigen dose, intramuscular (IM) delivery of a fractional dose, or delivery of fewer doses. Administering vaccines intradermally is thought to enhance their immunogenicity because of the high density of antigen presenting cells in the dermis [6-9]. In a trial in the Philippines, a fractional dose of IPV administered intradermally with a needle at 6, 10 and 14 weeks and at 15–18 months, induced similar seroprotection rates but lower antibody titers than full-dose intramuscular IPV [10].

Intradermal vaccination with a needle and syringe can be difficult, particularly in small children. A needle-free jet injector may be a reliable way to administer vaccines intradermally. It requires little training and reduces the risk of needle-stick injuries. In a trial in Oman, a fractional dose of IPV administered intradermally with a needle-free jet injector (Biojector® 2000) at 2, 4 and 6 months of age induced similar seroconversion rates but lower antibody titers than three full intramuscular doses [5]. In a similar trial in Cuba, in which infants were vaccinated at 6, 10 and 14 weeks after birth, which is a suboptimal immunization schedule for IPV [11, 12], both the seroconversion rates and antibody titers were lower after fractional-dose intradermal vaccination than after full-dose intramuscular vaccination [13]. In both trials, parents preferred administration with a jet injector over injection with a needle [5, 13]. No data are yet available on long-term protection and booster responses after vaccination with fractional-doses in infants.

These studies could not distinguish whether the intradermal site of administration or the lower antigen dosage were responsible for the lower immunogenicity of fractional-doses, because the study design did not include a third arm with fractional-dose IPV given intramuscularly. In anticipation of subsequent trials in infants as the primary target for polio eradication, this trial was designed to compare the immunogenicity and safety in adult volunteers with a well-documented vaccination history of a fractional booster dose of IPV administered intradermally with PharmaJet injection system, to both full- and fractional-dose IPV (Netherlands Vaccine Institute, NVI) injected intramuscularly with a needle and/or jet injector. The PharmaJet injection system is a handheld spring-powered injector and therefore suitable for use in developing countries.

## METHODS

### *Ethics Statement*

All participants provided informed consent. The study was approved by the Dutch ethics committee, the Central Committee on Research Involving Human Subjects (protocol number NL29671.000.09; EU Clinical Trials Register EUDRACT 2009-015175-27; Netherlands Trial Register 2196).

### *Study design*

This was a single-center, randomized, controlled, non-inferiority trial conducted at Leiden University Medical Center in the Netherlands, between August 2010 and February 2012. Subjects were vaccinated between August 2010 and January 2011. The primary objective was to evaluate the tolerability (vaccination site and systemic reactions) and to compare the immunogenicity 28 days after vaccination of a fractional booster dose of IPV administered intradermally with a needle-free jet injector (ID-JI-0.1), with standard full-dose intramuscular vaccination administered with a needle and syringe (IM-NS-0.5). Secondary objectives were (i) to compare the safety and immunogenicity of full-dose intramuscular IPV booster vaccination administered with a jet injector (IM-JI-0.5), with IM-NS-0.5, and (ii) to compare the immunogenicity of ID-JI-0.1, with fractional-dose intramuscular IPV administered with a needle and syringe (IM-NS-0.1). Healthy Dutch adult volunteers who had received exactly 6 combined DTP-IPV vaccinations according to the National Immunization Program (i.e. at age 3 months, 4 months, 5 months, 11 months, 4 years and 9 years) were eligible. Exclusion criteria were: any IPV booster dose after 10 years of age, any OPV dose.

### *Vaccine and jet injector*

Per participant we used one vial of IPV (NVI, lot 814AB, 0.5 mL per vial, expiration date: 05 Nov 2011) containing formaldehyde-inactivated poliovirus (strains Mahoney, MEF-1 and Saukett), type 1, 2 and 3: 40:8:32 D-antigen units respectively, and formaldehyde: 0.025 mg in phosphate buffer. The jet injector that was used was the PharmaJet Needle-free Jet Injection System. Separate jet injectors and single-use needle-free syringes were used for intramuscular and intradermal administration. The ID injector used in this study was an investigational version of the FDA 510k-cleared v1.0 SC/IM device. Modifications to permit ID delivery included a smaller main spring, a longer ejection pin to limit syringe fill volume to 100µl, and the ability to continuously vary the main spring pressure through the use of spring preload system. With the exception of orifice diameter modifications, syringes were identical to SC/IM syringes (Photograph 1).

### *Randomization and procedures*

The sponsor (NVI) prepared 125 sealed envelopes indicating allocation to one of the four treatment groups. The envelopes were numbered in random order using a random number

generator (www.random.org). The study was not blinded. A single investigator included and vaccinated all participants (D.S.). The reference group, IM-NS-0.5, received one full-dose vaccination with IPV (40:8:32 DU in 0.5 mL) administered intramuscularly with a 25-gauge needle and 1.0 mL syringe. Study group IM-JI-0.5 received one full-dose (0.5 mL) vaccination administered intramuscularly with a jet injector. Study group IM-NS-0.1 received one fractional-dose vaccination with IPV (8:1.6:6.4 DU in 0.1 mL) administered intramuscularly with a 25-gauge needle and 1.0 mL syringe. Study group ID-JI-0.1 received one fractional-dose vaccination (0.1 mL) administered intradermally with a jet injector. Vaccinations were injected into the deltoid muscle of the right arm, except for intradermal vaccinations, which were injected in the skin overlying the posterior deltoid (Photograph 2). In all study-groups, we measured residual moisture, defined as vaccine remaining on, rather than in the skin, with a quantitative filter paper. Blood samples were taken at baseline (immediately before vaccination) and at day 7 (6-8), day 28 (25-31) and day 365 (330-400) after vaccination. For four days, participants filled out a diary on vaccination site and systemic reactions and recorded use of medication. Participants measured the size of vaccination site redness, swelling and induration using a caliper that was designed to measure the size of skin reactions. Adverse events occurring after four days were collected by routinely inquiring after health-complaints at the 7- and 28-day blood collection.

### *Immunogenicity assay*

The titer of neutralizing antibodies against poliovirus types 1, 2 and 3 was determined by microneutralization assay [14]. Sera were diluted in 24 two-fold dilution steps and in duplicate. Dilutions were incubated for three hours at 36°C with 100$CCID_{50}$ (cell culture infectious dose 50%) of poliovirus type 1, 2 or 3 (strains Mahoney, MEF-1 and Saukett) followed by an overnight incubation at 5°C. Then, $2x10^5$ Vero cells/mL were added to the serum/virus mixtures. After a seven-day incubation at 36 °C (5% CO2) the results were read following fixation and staining with a crystal-violet solution with 5% formalin. The $\log_2$ titer was defined as the final serum dilution giving protection against 100$CCID_{50}$ of challenge virus in which no CPE is present, resulting in a completely stained monolayer. Titers were converted to IU/mL by comparison with the titer of an in-house reference serum (IHS) of known potency. The potency of the IHS in IU/mL was determined by comparison with the titer of an International Standard Serum (NIBSC code: 82/585) as described previously [14]. To allow comparison between the groups, a $\log_2$ transformation was performed on the antibody concentrations in IU/mL and the mean was calculated which is referred to as the $\log_2$ geometric mean antibody concentration ($\log_2$ GMC). Titers of 1:8 are considered seroprotective and this has been shown to correspond to 0.080 IU/mL for type 1, 0.0180 IU/mL for type 2 and 0.075 IU/mL for type 3 poliovirus [15].

### *Statistical analysis*

The primary immunogenicity endpoint was evaluated at day 28, by comparing the differences in the post-vaccination $\log_2$ GMC between group ID-JI-0.1 (minuend) and the reference

group, IM-NS-0.5 (subtrahend). Non-inferiority was to be concluded if the lower limit of the 95% Confidence Interval (95% CI) for the difference did not exceed -1, which corresponds to a difference of 1 serum dilution in the microneutralization assay. Only if the margin was not crossed for any of the three poliovirus strains (PV1, PV2, PV3), the overall verdict was 'non-inferior'. Based on a standard deviation of the $\log_2$ GMC of 2.0, a one-sided alpha of 0.025 and a beta of 0.8, the sample size for each study arm was 30. The non-inferiority margin was based upon a combination of statistical reasoning and clinical judgment [16]. We assumed that all participants would already have a titer well above the level that corresponds to seroprotection since they had received 6 previous polio vaccine doses [17, 18]. That is why the between-group difference in the $\log_2$ GMC at day 28 was chosen as the primary endpoint for immunogenicity. GMCs were analyzed in the per-protocol population with t-tests. Adverse events were described in the intention-to-treat population and analyzed with $\chi^2$ tests. Statistical significance was defined as a p-value <0.05. Analyses were done with IBM® SPSS®, Statistics, Version 20.0.

### *Role of the funding source*

IPV was produced and supplied by the NVI. Funding was provided by the ministry of Public Health, Welfare and Sport. The jet injectors and related materials were provided by PharmaJet®, which has a research and development agreement with NVI to support clinical trials *in kind*.

## RESULTS

A total of 125 adults were randomly assigned to one of four groups. One subject did not complete the visit at day 28 and was excluded from immunogenicity analyses, as were four subjects who followed a different childhood immunization program (Figure 1). These five subjects were included in the safety analysis but not in the immunogenicity analysis. One year after vaccination, 79 subjects submitted an additional sample. The remaining 41 subjects were not included at this time-point; 20 had received pre-travel DTP booster vaccinations, 20 were lost to follow-up and 1 had received chemotherapy. Baseline characteristics are described in Table 1.

### *Vaccine delivery and adverse events*

Intradermal delivery with the jet injector consistently produced blebs of 8 mm, which correspond to the diameter of the skin contact ring on the face of the needle-free syringe (Table 2). Vaccine residual moisture was minimal and more moisture was not associated with reduced immunogenicity. Of note, the measured residual moisture after vaccination with the jet injector was sometimes overestimated, as it also measured liquid adherent to the syringe face during filling, then transferred to the skin at the time of vaccine administration. Vaccination with a jet injector was less painful than vaccination with a needle (Table 2). Erythema, swelling and induration were more frequent after use of the jet injector. Soreness

and arms stiffness were considerably less frequent after intradermal delivery with the jet injector than after intramuscular delivery with either a needle or jet injector (Table 2).

### *Immunogenicity*

At baseline, all subjects had seroprotective antibody concentrations (Table 3). Baseline concentrations did not differ significantly between the groups. Seven days after vaccination, GMC increased for all poliovirus serotypes with a further increase at day 28 (Table 3). Reverse cumulative distribution curves of antibody titers, before and 28 days after vaccination are depicted in Figure 2.

The primary immunogenicity endpoint was the between-group difference in the post-vaccination $\log_2$ GMC for each of the three poliovirus strains. At day 28, $\log_2$ GMC did not differ significantly between group ID-JI-0.1 and the reference group. The difference between ID-JI-0.1 (minuend) and IM-NS-0.5 (subtrahend) was -0.20 (95% CI -1.38 – 0.98) for PV1, -0.42 (95% CI -1.64 – 0.82) for PV2, and -1.07 (95% CI -2.31 – 0.17) for PV3 (Figure 3). The lower limit of the 95% confidence intervals crossed -1, meaning that the pre-defined criterion for non-inferiority was not met. Formally the result can be classified as inconclusive regarding the question of non-inferiority [19]. Skin fold measurement, body mass index and spillage were not associated with the magnitude of the immune response (data not shown).

At day 28, $\log_2$ GMC were significantly lower in group IM-NS-0.1 (minuend) than in group IM-NS-0.5 (subtrahend): -1.08 (95% CI -2.07 – -0.09) for PV1, -1.59 (95% CI -2.82 – -0.37) for PV2, -1.65 (95% CI -3.13 – -0.17) for PV3 (Figure 3). At day 28, $\log_2$ GMC did not differ significantly between group IM-JI-0.5 (minuend) and group IM-NS-0.5 (subtrahend): -0.79 (95% CI -1.67 – 0.08) for PV1, -0.58 (95% CI -1.69 – 0.53) for PV2 and -0.82 (95% CI -2.11 – 0.47) for PV3 (Figure 3).

After one year, GMC remained high in all groups (Table 3). Antibody concentrations declined by less than one serum dilution for PV1 and PV3 and by approximately two serum dilutions for PV2. The rate at which antibody concentrations declined was similar in all four groups.

## DISCUSSION

Intradermal vaccination with a jet injector was less painful and caused less vaccination site soreness than vaccination with a needle. The jet injector caused more transient vaccination site erythema and swelling. This is in line with previous reports [20]. Fractional-dose intradermal vaccination was immunogenic, but titers were somewhat lower than after standard full-dose intramuscular vaccination. The differences were not statistically significant. After one year, the differences were no longer apparent. In contrast, intramuscular injection of fractional-dose IPV induced significantly lower titers than full-dose IPV.

The immunogenicity results are in line with previous studies in Oman and Cuba [5, 13]. They are also in line with another recent trial in Cuba, in which infants who had not been

vaccinated before received two ID fractional doses of IPV, delivered with a jet injector [21]. A single fractional dose produced seroconversion in almost half the infants and a priming response in almost all of those who did not undergo seroconversion. The authors argue, that for the post-eradication era, two doses of IPV given at the ages of 4 and 8 months could suffice. However, in another recent trial among Indian infants, supplemental fractional-dose ID IPV, delivered with an investigational PharmaJet injector was significantly less effective than full-dose IM vaccination [22]. Excessive undelivered vaccine as a result of marginal investigational device performance likely contributed to the low seroconversion and antibody titers in the ID group.

Our study shows that fractional-dose intramuscular IPV was significantly less immunogenic than full-dose IPV, even when used as a booster vaccination. Based on this result and the results of other studies, we conclude that dose reduction lowers immunogenicity but that fractional-dose intradermal vaccination is more immunogenic than fractional-dose intramuscular vaccination. The D-antigen content in IPV is not as superfluous for poliovirus type 3 as it is for type 1 and 2 [23, 24]. This may be the reason why the response to type 3 poliovirus seemed weaker than to type 1 and 2 after intradermal vaccination.

The sample-size in preliminary studies is commonly based on a rule-of-thumb rather than a formal calculation. By using a non-inferiority design, we forced ourselves to pre-define the criterion by which fractional-dose IPV was to be judged vis-à-vis full-dose IPV. The pre-defined criterion for non-inferiority was not met. Ideally, one would want to base the primary outcome and non-inferiority margin on a clinically relevant endpoint such as the seroprotection rate. As expected, most participants in this study had baseline titers well above the level that corresponds to seroprotection. That is why the primary outcome and non-inferiority margin was based on the $\log_2$ GMC. We found that baseline antibody concentrations were higher and that the variance in antibody concentrations was larger than expected at the design stage of the study. This is exemplified by the fact that, even at baseline the confidence intervals for the between-group differences in antibody concentrations exceeded the pre-defined non-inferiority margin of one $\log_2$ GMC difference, i.e. one dilution step in the neutralization assay.

This study has a number of strengths. Firstly, the study population was homogenous and all participants had completed the same childhood vaccination schedule without any additional booster vaccinations. This increased the validity of the comparisons. Secondly, the study design made it possible to distinguish to what extent the route of administration and to what extent the dose was responsible for lower immunogenicity of fractional-doses. Furthermore, vaccination technique, residual moisture, bleb size and local vaccination site reactions were well documented. Lastly, results were reported in IU/mL, which facilitates comparison with other studies.

This study also has limitations. First, it was not blinded, which may have influenced results. Although Simon et al. describe a method with which blinding of such a trial is possible, this

289 could not be done in our study, in which we used a different site for intradermal vaccination
290 than for intramuscular vaccination [20]. Second, baseline antibody concentrations were higher
291 than we had expected which influenced the statistical evaluation for non-inferiority. Third, the
292 mean baseline antibody concentration for PV1 was somewhat higher in the group that
293 received fractional-dose intramuscular IPV. It seems unlikely that this influenced results in a
294 significant manner, as the immune response to all three poliovirus strains was weaker in this
295 group. Finally, all vaccines were delivered by a single user. Although this increases the
296 validity of the comparisons by minimizing between-user differences in vaccine delivery, it
297 limits the generalizability to real life practice.

298 **CONCLUSION**

299 Fractional-dose intradermal IPV booster vaccination using a PharmaJet injection system was
300 well tolerated and immunogenic. Antibody titers in the fractional-dose intradermal group were
301 slightly lower than after standard full-dose intramuscular vaccination. After one year,
302 differences in antibody titers were no longer apparent. In contrast, one-fifth of a standard
303 dose administered intramuscularly with a needle was statistically inferior to full-dose
304 intramuscular vaccination.

305



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311

312

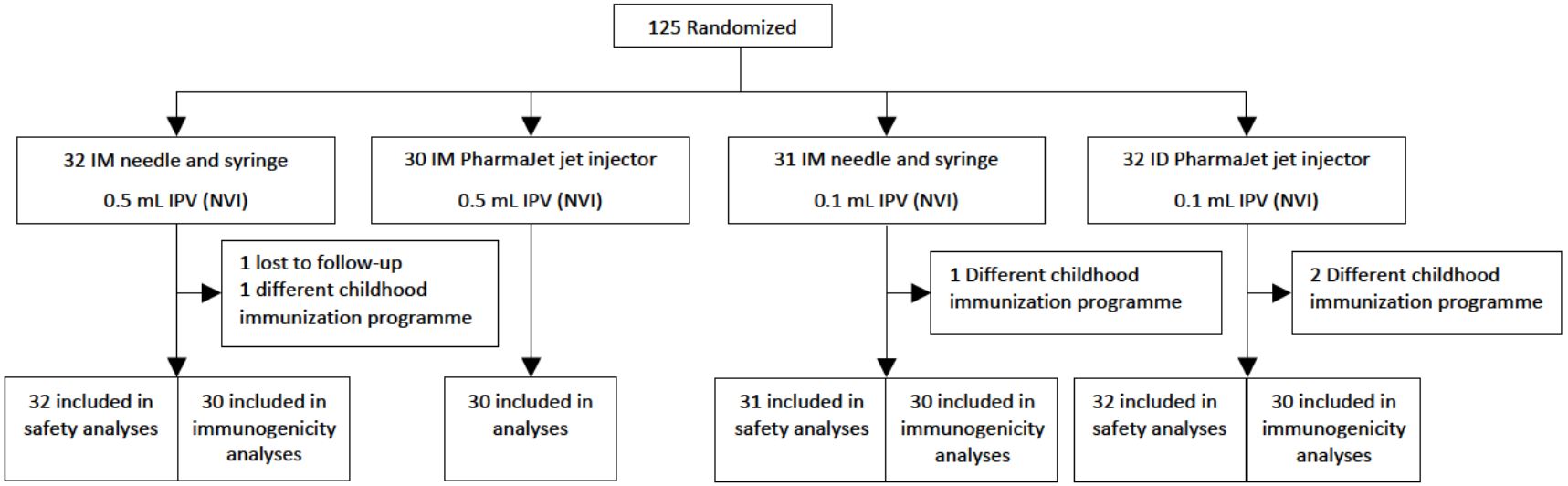
313 Authors' contributions:

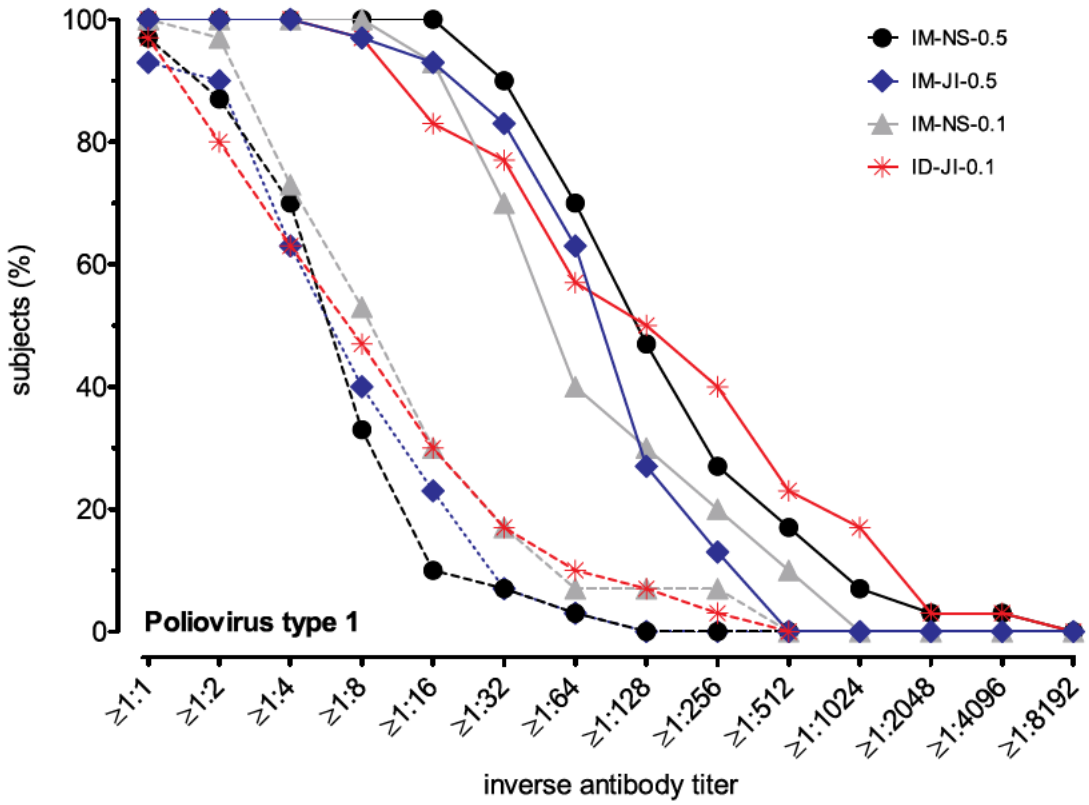
314 DS, PV, AW, NR and LV designed the study. DS recruited the participants and conducted the
315 study visits. DS, PV and AW were involved in data collection. PK performed the neutralization
316 assay. DS did the data analysis. DS, PV, NR and LV drafted the manuscript. CB facilitated
317 the study and reviewed and approved the manuscript. All authors gave final approval to the
318 manuscript.

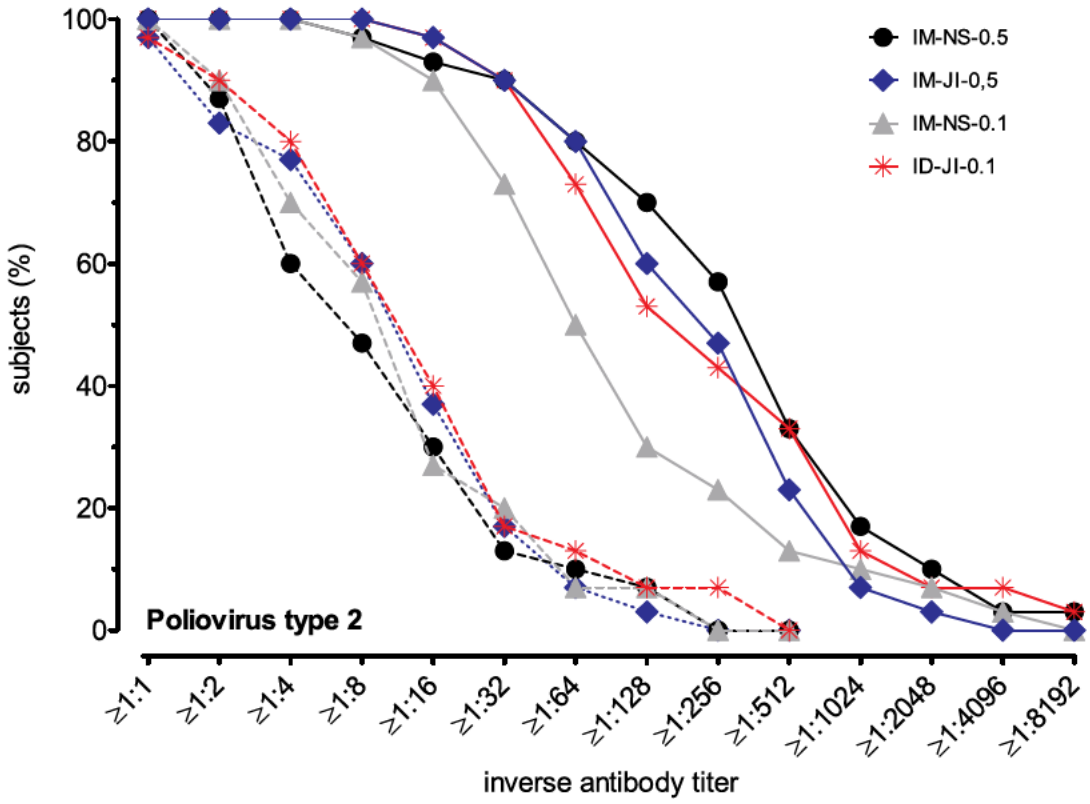
## TABLES AND FIGURES

**Figure 1: Trial profile.** IM=intramuscular. ID=intradermal. IPV=inactivated poliovirus vaccine. NVI=Netherlands Vaccine Institute.

**Figure 1**


125 Randomized
32 IM needle and syringe
0.5 mL IPV (NVI)
30 IM PharmaJet jet injector
0.5 mL IPV (NVI)
31 IM needle and syringe
0.1 mL IPV (NVI)
32 ID PharmaJet jet injector
0.1 mL IPV (NVI)
1 lost to follow-up
1 different childhood immunization programme
1 Different childhood immunization programme
2 Different childhood immunization programme
32 included in safety analyses
30 included in immunogenicity analyses
30 included in analyses
31 included in safety analyses
30 included in immunogenicity analyses
32 included in safety analyses
30 included in immunogenicity analyses



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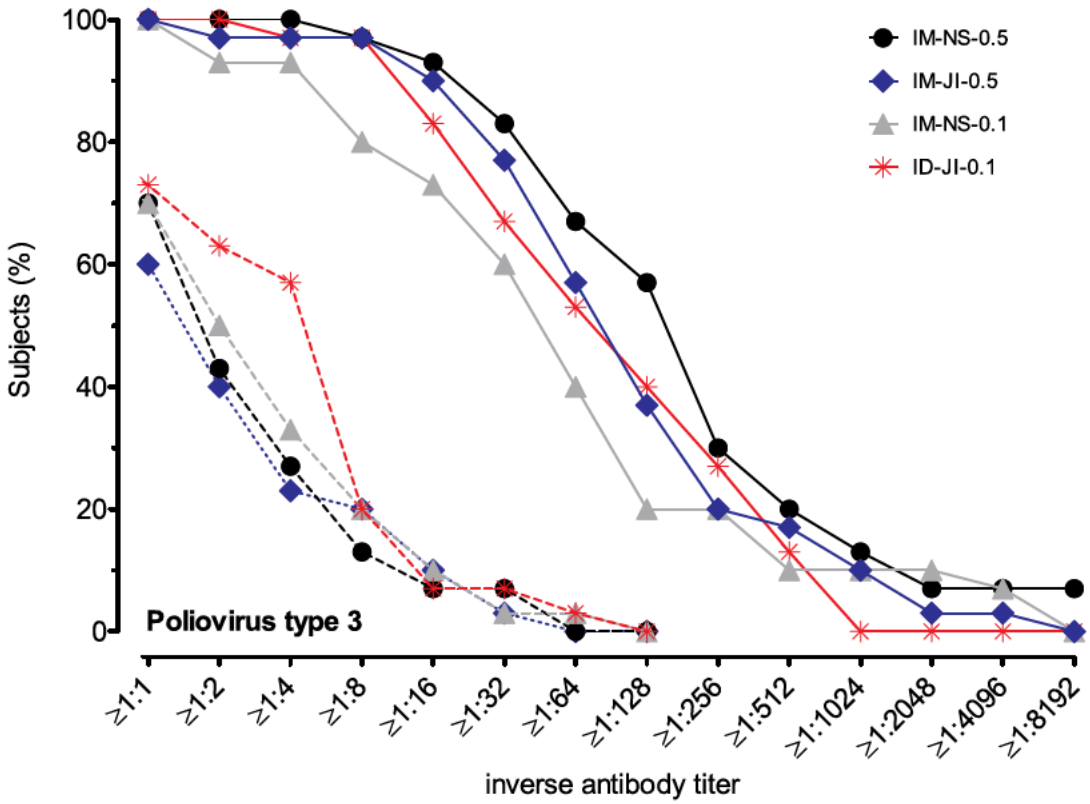


**Figure 2: Reverse cumulative distribution curves of antibody titers at baseline and at day 28.** Dashed lines: baseline titers. Smooth lines: titers at day 28.



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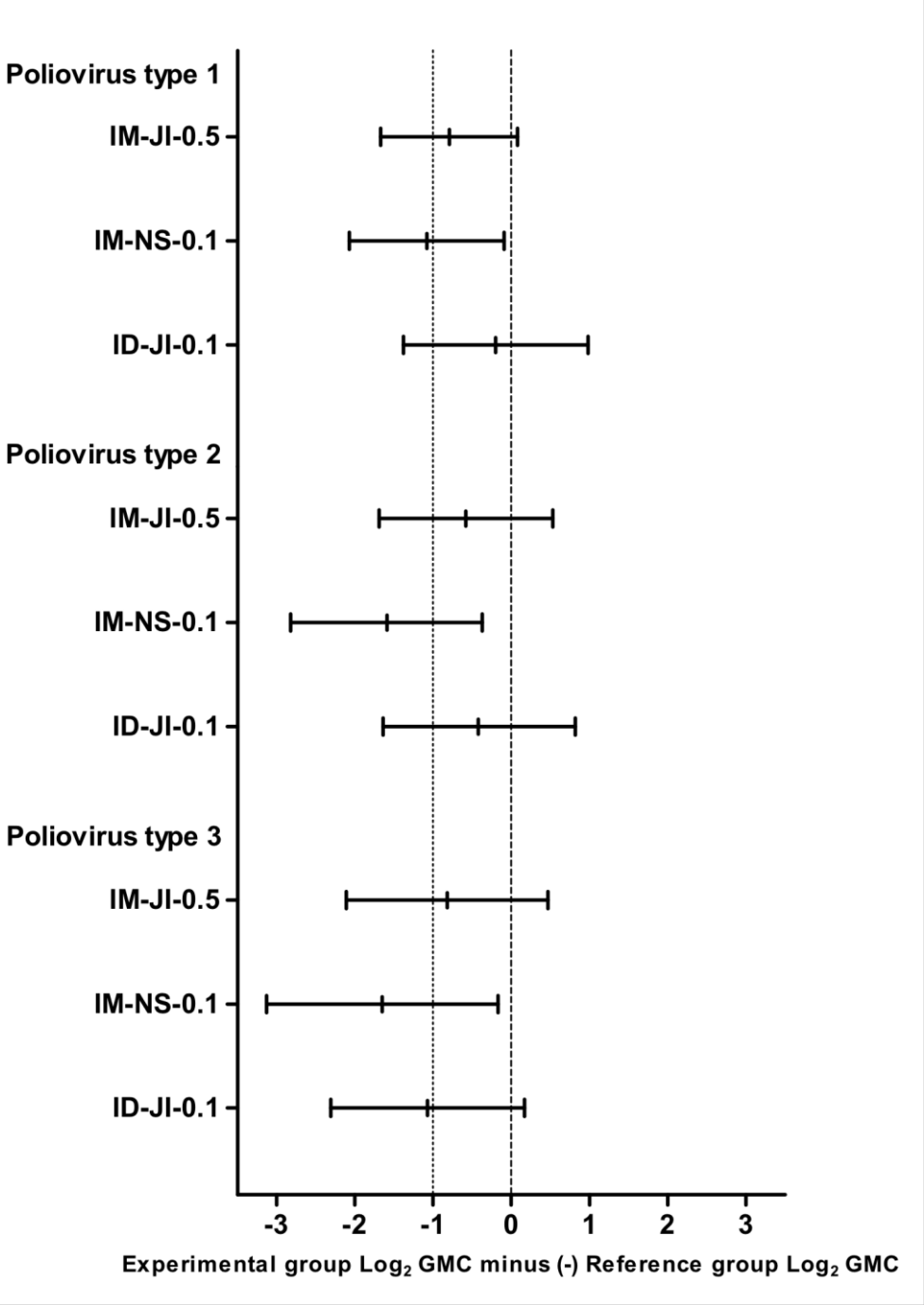


340
341 **Figure 3: Differences in the post-vaccination $log_2$ geometric mean antibody concentration at day**
342 **28 in the study groups (minuend) in comparison with the reference group (IM-NS-0.5)**
343 **(subtrahend).** Mean differences with 95% confidence intervals. Zero indicates no difference. The non-inferiority
344 margin was set at -1 (i.e. one titration step in the neutralization assay). Only if the margin was not crossed for any of
345 the three poliovirus strains (PV1, PV2, PV3) the overall verdict was non-inferior.
346

**Figure 4: PharmaJet Needle-free Jet Injection System for intradermal delivery**. The ID injector used in this study was an investigational version of the FDA 510k-cleared v1.0 SC/IM device.

**Figure 4**

**Figure 5: Intradermal vaccination in skin overlying the posterior deltoid.**



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**Figure 5**

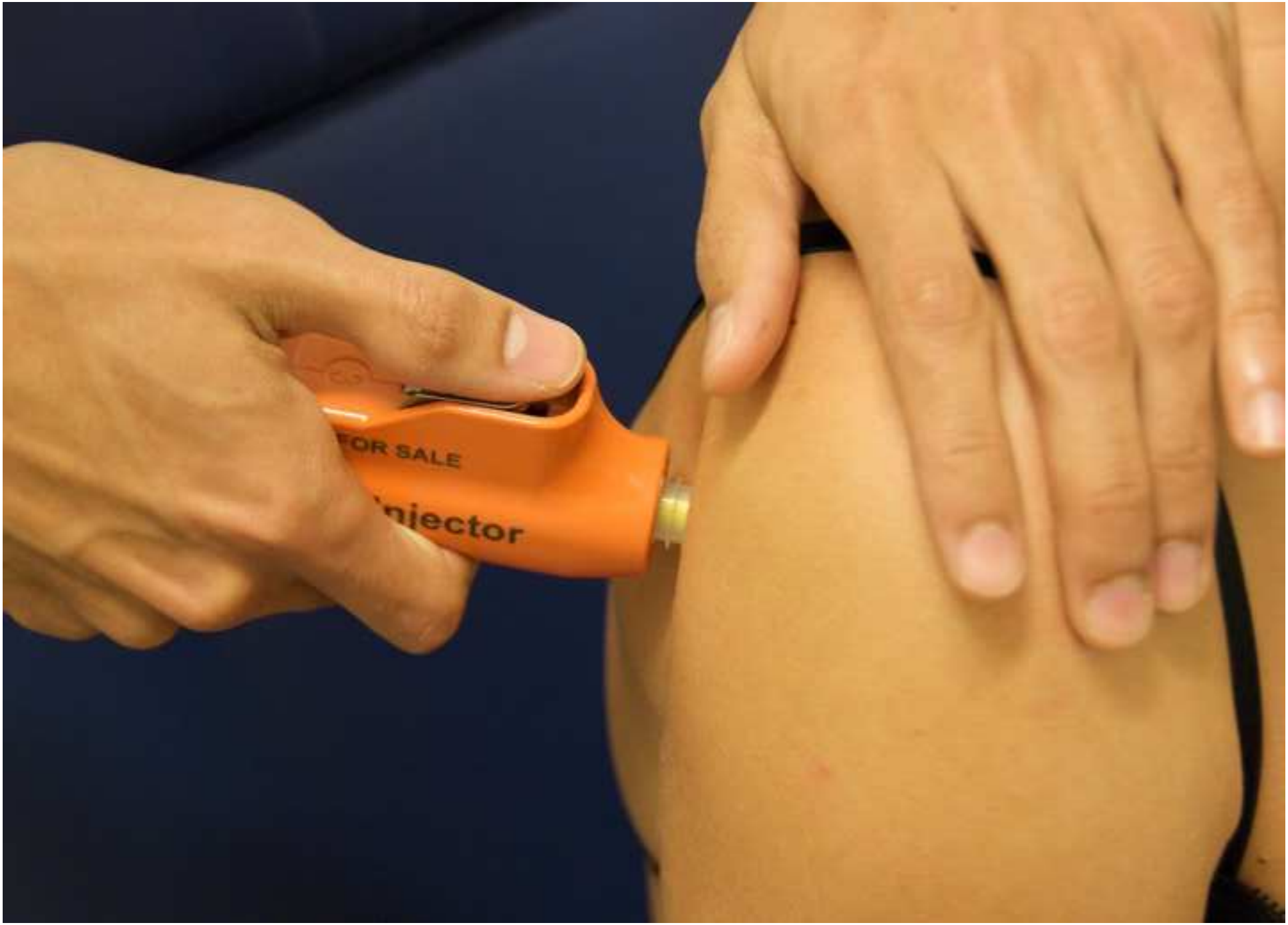

**Table 1**

Demographic characteristics of volunteers assigned to full- (0.5 mL) or fractional-dose (0.1 mL) inactivated poliovirus booster vaccination, injected intramuscularly (IM) or intradermally (ID), with a needle and syringe (NS) or a jet injector (JI).

| Characteristic | IM-NS-0.5 (n=32) | IM-JI-0.5 (n=30) | IM-NS-0.1 (n=31) | ID-JI-0.1 (n=32) |
|---|---|---|---|---|
| Female sex - n (%) | 20 (63) | 18 (60) | 23 (74) | 21 (66) |
| Mean age - years (SE) | 21.1 (0.5) | 21.8 (0.8) | 21.6 (0.7) | 21.5 (0.4) |
| Mean Body Mass Index (SE) | 22.2 (0.4) | 22.0 (0.6) | 22.4 (0.4) | 22.3 (0.5) |
| Mean skin fold measurement – mm (SE)* | 17.6 (1.4) | 18.2 (1.6) | 19.4 (1.3) | 15.0 (1.0) |
| Current smoker - n (%) | 4 (13) | 7 (23) | 4 (13) | 5 (16) |

The skin fold was measured at the injection site. Vaccinations were injected into the deltoid muscle of the right arm, except for intradermal vaccinations which were injected in the skin overlying the posterior deltoid. SE=standard error

**Table 2**
Adverse events following administration of full- (0.5 mL) or fractional-dose (0.1 mL) inactivated poliovirus vaccine, injected intramuscularly (IM) or intradermally (ID), with a needle and syringe (NS) or a jet injector (JI).

| | IM-NS-0.5 (n=32) | IM-JI-0.5 (n=30) | IM-NS-0.1 (n=31) | ID-JI-0.1 (n=32) |
|---|---|---|---|---|
| **Vaccine delivery** | | | | |
| Pain – n (%) | 13 (41) | 6 (20) | 12 (39) | 2 (6) |
| Vagal reaction | 0 | 0 | 1 (3) | 0 |
| Bleb diameter in mm – median (IQR) | NA | NA | NA | 8 (8-8) |
| Spillage on skin in μl – median (IQR) | 0 (0-17) | 12 (2-45) | 0 (0-2) | 13 (8-40) |
| **Systemic adverse events** | | | | |
| Fever – n (%) | 0 | 0 | 1 (3) | 0 |
| Myalgia – n (%) | 2 (6) | 3 (10) | 4 (13) | 3 (9) |
| Fatigue – n (%) | 8 (25) | 6 (20) | 10 (32) | 10 (31) |
| Headache – n (%) | 6 (19) | 6 (20) | 9 (29) | 8 (25) |
| **Vaccination site adverse events** | | | | |
| Erythema – n (%) | 9 (28) | 25 (83)[c] | 6 (19) | 28 (88)[c] |
| Maximum size in mm – median (IQR) | 5 (5-15) | 25 (15-35) | 5 (5-6) | 15 (10-15) |
| Duration in days– median (IQR) | 2 (1-2) | 3 (2-4) | 1 (1-1.3) | 4 (2.3-4) |
| Swelling – n (%) | 0 | 12 (40)[c] | 3 (10) | 19 (59)[c] |
| Maximum size in mm – median (IQR) [range] | 0 | 15 (11-33) | 10 [5-65] | 10 (10-15) |
| Duration in days– median (IQR) [range] | 0 | 2.5 (2-3) | 1 [1-2] | 2 (2-4) |
| Induration – n (%) | 3 (9) | 11 (37)[d] | 3 (10) | 11 (34)[d] |
| Maximum size in mm – median (IQR) [range] | 10 [5-25] | 20 (10-20) | 5 [5-65] | 15 (10-20) |
| Duration in days– median (IQR) [range] | 2 [2-3] | 2 (2-3) | 1 [1-2] | 2 (1-3) |
| Soreness vaccination site – n (%) | 16 (50) | 17 (57) | 15 (48) | 5 (16)[c] |
| Arm stiffness – n (%) | 13 (41) | 9 (30) | 11 (35) | 5 (16)[d] |

NA: Not applicable. Medians, interquartile ranges (IQR) and ranges pertain to proportions that had the adverse event. p values for the comparison with the reference group: 0.09[a], 0.002[b], <0.005[c], 0.02[d] ($\chi^2$ tests).



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**Table 3**

$Log_2$ geometric mean antibody concentrations (GMC in IU/mL) at baseline and 7, 28 and 365 days after full- (0.5 mL) or fractional-dose (0.1 mL) intramuscular (IM) or intradermal (ID) inactivated poliovirus booster vaccination, administered with a needle and syringe (NS) or a jet injector (JI).

| | IM-NS-0.5 | IM-JI-0.5 | IM-NS-0.1 | ID-JI-0.1 |
|---|---|---|---|---|
| **At day 0 (baseline)** | **n=30** | **n=30** | **n=30** | **n=30** |
| poliovirus type 1 | 2.57 (2.04-3.11) | 2.72 (2.12-3.31) | 3.42 (2.74-4.11)[b] | 2.98 (2.15-3.81) |
| poliovirus type 2 | 3.12 (2.41-3.82) | 3.28 (2.61-3.95) | 3.30 (2.61-3.98) | 3.58 (2.80-4.36) |
| poliovirus type 3 | 0.87 (0.13-1.61) | 0.59 (-0.29-1.47) | 1.13 (0.35-1.91) | 1.53 (0.63-2.42) |
| **At day 7** | **n=30** | **n=30** | **n=30** | **n=30** |
| poliovirus type 1 | 5.74 (5.11–6.37) | 5.13 (4.55-5.72) | 5.25 (4.60-5.89) | 5.29 (4.54-6.04) |
| poliovirus type 2 | 6.82 (6.06-7.58) | 5.93 (5.31-6.56)[b] | 5.27 (4.47-6.08)[a] | 6.08 (5.46-6.70) |
| poliovirus type 3 | 5.88 (4.60-7.16) | 4.62 (3.58-5.67) | 3.86 (2.81-4.91)[a] | 4.38 (3.74-5.02)[a] |
| **At day 28** | **n=30** | **n=30** | **n=30** | **n=30** |
| poliovirus type 1 | 7.14 (6.45 – 7.83) | 6.35 (5.83-6.86)[b] | 6.06 (5.39-6.74)[a] | 6.94 (6.02-7.87) |
| poliovirus type 2 | 8.13 (7.27-9.00) | 7.55 (6.89-8.21) | 6.54 (5.70-7.38)[a] | 7.71 (6.88-8.55) |
| poliovirus type 3 | 7.26 (6.32-8.21) | 6.44 (5.60-7.28) | 5.61 (4.52-6.71)[a] | 6.19 (5.43-6.95)[b] |
| **At day 365** | **n=22** | **n=21** | **n=17** | **n=19** |
| poliovirus type 1 | 6.70 (5.87–7.62) | 6.52 (5.70–7.34) | 5.31 (4.48– 6.14)[a] | 6.71 (5.85–7.57) |
| poliovirus type 2 | 5.87 (5.17–6.57) | 5.57 (4.78 – 6.36) | 4.44 (3.46–5.41)[a] | 5.95 (5.14–6.76) |
| poliovirus type 3 | 6.53 (5.66–7.40) | 6.21 (5.26–7.15) | 5.04 (4.10–5.98) [a] | 5.92 (5.21 –6.63) |

p value for the difference in GMC in comparison with reference group (IM-NS-0.5): [0.01-0.05][a], [0.06-0.09][b].
Mean $log_2$ GMC with 95% confidence interval.



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## References


[1] Global Polio Eradication Initiative – Strategic Plan 2010-2012. WHO, 2010 (Last accessed: August 07, 2012). Available from http://www.polioeradication.org/content/publications/GPEI.StrategicPlan.2010-2012.ENG.May.2010.pdf

[2] Minor P. Vaccine-derived poliovirus (VDPV): Impact on poliomyelitis eradication. Vaccine 2009; 27:2649-52.

[3] Aylward RB, Sutter RW and Heymann DL. Policy. OPV cessation--the final step to a "polio-free" world. Science 2005; 310:625-6.

[4] Conclusions and recommendations of the Advisory Committee on Poliomyelitis Eradication, Geneva, 27-28 November 2007. Wkly Epidemiol Rec 2008; 83:25-35.

[5] Mohammed AJ, AlAwaidy S, Bawikar S, Kurup PJ, Elamir E, Shaban MM, et al. Fractional doses of inactivated poliovirus vaccine in Oman. N Engl J Med 2010; 362:2351-9.

[6] Kupper TS and Fuhlbrigge RC. Immune surveillance in the skin: mechanisms and clinical consequences. Nat Rev Immunol 2004; 4:211-22.

[7] Nicolas JF and Guy B. Intradermal, epidermal and transcutaneous vaccination: from immunology to clinical practice. Expert Rev Vaccines 2008; 7:1201-14.

[8] Redfield RR, Innis BL, Scott RM, Cannon HG and Bancroft WH. Clinical evaluation of low-dose intradermally administered hepatitis B virus vaccine. A cost reduction strategy. Jama 1985; 254:3203-6.

[9] Nelson KS, Janssen JM, Troy SB and Maldonado Y. Intradermal fractional dose inactivated polio vaccine: a review of the literature. Vaccine 2012; 30:121-5.

[10] Cadorna-Carlos J, Vidor E and Bonnet MC. Randomized controlled study of fractional doses of inactivated poliovirus vaccine administered intradermally with a needle in the Philippines. Int J Infect Dis 2012; 16:e110-6.

[11] Dayan GH, Thorley M, Yamamura Y, Rodriguez N, McLaughlin S, Torres LM, et al. Serologic response to inactivated poliovirus vaccine: a randomized clinical trial comparing 2 vaccination schedules in Puerto Rico. J Infect Dis 2007; 195:12-20.

[12] Krishnan R, Jadhav M and John TJ. Efficacy of inactivated poliovirus vaccine in India. Bull World Health Organ 1983; 61:689-92.

[13] Resik S, Tejeda A, Lago PM, Diaz M, Carmenates A, Sarmiento L, 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.

[14] Manual for the virological investigation of polio. WHO/EPI/GEN 97.01. WHO; 1997.

[15] Diedrich S, Claus H and Schreier E. Immunity status against poliomyelitis in Germany: determination of cut-off values in International Units. BMC Infect Dis 2002; 2:2.

[16] Committee for Medicinal Products for Human Use (CHMP) guideline on the choice of the non-inferiority margin. Stat Med 2006; 25:1628-38.

[17] Rumke H, Labadie J, Elzinga-Gholizadea N and Mensinga T. IPV-Vero vaccine induces a strong booster reaction and is well tolerated in adults. Scand J Infect Dis 1998; 30:535-8.

[18] Grimprel E, von Sonnenburg F, Sanger R, Abitbol V, Wolter JM and Schuerman LM. Combined reduced-antigen-content diphtheria-tetanus-acellular pertussis and polio vaccine (dTpa-IPV) for booster vaccination of adults. Vaccine 2005; 23:3657-67.

[19] Piaggio G, Elbourne DR, Altman DG, Pocock SJ and Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006; 295:1152-60.

[20] Simon JK, Carter M, Pasetti MF, Sztein MB, Kotloff KL, Weniger BG, et al. Safety, tolerability, and immunogenicity of inactivated trivalent seasonal influenza vaccine administered with a needle-free disposable-syringe jet injector. Vaccine 2011; 29:9544-50.

[21] Resik S, Tejeda A, Sutter RW, Diaz M, Sarmiento L, Alemañi N, et al. Priming after a fractional dose of inactivated poliovirus vaccine. N Engl J Med 2013; 368:416-24.

[22] Estivariz CF, Jafari H, Sutter RW, John TJ, Jain V, Agarwal A, et al. Immunogenicity of supplemental doses of poliovirus vaccine for children aged 6-9 months in Moradabad, India: a community-based, randomised controlled trial. Lancet Infect Dis 2012; 12:128-35.

[22] Salk J. One-dose immunization against paralytic poliomyelitis using a noninfectious vaccine. Rev Infect Dis 1984; 6 Suppl 2:S444-50.

[23] Salk D, van Wezel AL and Salk J. Induction of long-term immunity to paralytic poliomyelitis by use of non-infectious vaccine. Lancet 1984; 2:1317-21.

**Supplemental Files**

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**Table S1**
$Log_2$ of the median antibody concentrations in IU/mL at baseline and 7, 28 and 365 days after full- (0.5 mL) or fractional-dose (0.1 mL) intramuscular (IM) or intradermal (ID) inactivated poliovirus booster vaccination, administered with a needle and syringe (NS) or a jet injector (JI).

| | **IM-NS-0.5** | **IM-JI-0.5** | **IM-NS-0.1** | **ID-JI-0.1** |
|---|---|---|---|---|
| **At day 0 (baseline)** | **n=30** | **n=30** | **n=30** | **n=30** |
| poliovirus type 1 | 2.74 (1.89-3.23) | 2.64 (1.45-3.89) | 3.08 (1.95-4.57) | 2.51(1.08-4.55) |
| poliovirus type 2 | 2.95 (1.61-4.47) | 3.73 (2.05-4.35) | 3.26 (1.75-4.69) | 3.58 (2.26-4.69) |
| poliovirus type 3 | 0.60 (-0.18-2.20) | 0.57 (-0.47-1.77) | 0.90 (-0.43-2.27) | 2.40 (-0.36-2.88) |
| **At day 7** | **n=30** | **n=30** | **n=30** | **n=30** |
| poliovirus type 1 | 5.64 (4.29–6.71) | 4.95 (4.36-5.85) | 5.42 (3.92-6.07) | 5.19 (4.04-6.48) |
| poliovirus type 2 | 6.83 (5.42-8.29) | 5.82 (4.82-7.29) | 5.26 (3.66-6.17) | 6.17 (5.09-7.08) |
| poliovirus type 3 | 5.41 (3.77-7.11) | 3.94 (3.02-6.23) | 3.38 (2.13-4.58) | 4.22 (3.13-5.45) |
| **At day 28** | **n=30** | **n=30** | **n=30** | **n=30** |
| poliovirus type 1 | 6.89 (5.84–8.30) | 6.39 (5.53-7.45) | 5.45 (4.86-7.10) | 6.74 (5.01-8.88) |
| poliovirus type 2 | 8.23 (6.76-9.41) | 7.83 (6.19-8.92) | 6.05 (4.82-7.96) | 7.61 (5.71-9.32) |
| poliovirus type 3 | 7.13 (5.13-8.36) | 6.36 (5.02-7.63) | 5.48 (3.56-6.70) | 6.22 (4.50-8.15) |
| **At day 365** | **n=22** | **n=21** | **n=17** | **N=19** |
| poliovirus type 1 | 6.47 (4.93–8.61) | 6.54 (4.93–7.68) | 5.29 (4.09–5.93) | 6.79 (6.04–7.80) |
| poliovirus type 2 | 5.75 (4.75–6.75) | 5.75 (4.00 – 6.99) | 4.17 (3.25–5.21) | 6.17 (4.25–7.17) |
| poliovirus type 3 | 6.29 (5.09–8.57) | 6.29 (3.95–7.84) | 5.09 (3.70–6.07) | 5.78 (4.81 –7.29) |

Median antibody concentrations in IU/mL, inter quartile range in brackets.