

Safety and immunogenicity of inactivated poliovirus vaccine when given with measles–rubella combined vaccine and yellow fever vaccine and when given via different administration routes: a phase 4, randomised, non-inferiority trial in The Gambia



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Summary

Background The introduction of the inactivated poliovirus vaccine (IPV) represents a crucial step in the polio eradication endgame. This trial examined the safety and immunogenicity of IPV given alongside the measles–rubella and yellow fever vaccines at 9 months and when given as a full or fractional dose using needle and syringe or disposable-syringe jet injector.

Methods We did a phase 4, randomised, non-inferiority trial at three periurban government clinics in west Gambia. Infants aged 9–10 months who had already received oral poliovirus vaccine were randomly assigned to receive the IPV, measles–rubella, and yellow fever vaccines, singularly or in combination. Separately, IPV was given as a full intramuscular or fractional intradermal dose by needle and syringe or disposable-syringe jet injector at a second visit. The primary outcomes were seroprevalence rates for poliovirus 4–6 weeks post-vaccination and the rate of seroconversion between baseline and post-vaccination serum samples for measles, rubella, and yellow fever; and the post-vaccination antibody titres generated against each component of the vaccines. We did a per-protocol analysis with a non-inferiority margin of 10% for poliovirus seroprevalence and measles, rubella, and yellow fever seroconversion, and ($1/3$) \log_2 for \log_2 -transformed antibody titres. This trial is registered with ClinicalTrials.gov, number NCT01847872.

Findings Between July 10, 2013, and May 8, 2014, we assessed 1662 infants for eligibility, of whom 1504 were enrolled into one of seven groups for vaccine interference and one of four groups for fractional dosing and alternative route of administration. The rubella and yellow fever antibody titres were reduced by co-administration but the seroconversion rates achieved non-inferiority in both cases (rubella, -4.5% [95% CI -9.5 to -0.1]; yellow fever, 1.2% [-2.9 to 5.5]). Measles and poliovirus responses were unaffected (measles, 6.8% [95% CI -1.4 to 14.9]; poliovirus serotype 1, 1.6% [-6.7 to 4.7]; serotype 2, 0.0% [-2.1 to 2.1]; serotype 3, 0.0% [-3.8 to 3.9]). Poliovirus seroprevalence was universally high ($>97\%$) after vaccination, but the antibody titres generated by fractional intradermal doses of IPV did not achieve non-inferiority compared with full dose. The number of infants who seroconverted or had a four-fold rise in titres was also lower by the intradermal route. There were no safety concerns.

Interpretation The data support the future co-administration of IPV, measles–rubella, and yellow fever vaccines within the Expanded Programme on Immunization schedule at 9 months. The administration of single fractional intradermal doses of IPV by needle and syringe or disposable-syringe jet injector compromises the immunity generated, although it results in a high post-vaccination poliovirus seroprevalence.

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Introduction

The World Health Assembly declared its commitment to global polio eradication in 1988, at a time when an estimated 350 000 people were paralysed annually as a result of the infection. Since then, major strides have been made and the incidence of polio has fallen by more than 99% to the point where fewer than 75 cases of paralytic polio associated with wild-type infection were reported worldwide in 2015.^{1,2}

In 2012, the Strategic Advisory Group of Experts on Immunisation (SAGE), the global policy-making body for vaccination, recommended the withdrawal of the type 2 component of the oral poliovirus vaccine (OPV) from routine immunisation, leading to the replacement of trivalent OPV with bivalent OPV in April, 2016.³ The switch comes after the eradication of wild-type 2 poliovirus in 1999 and represents a crucial step in the

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Research in context

Evidence before this study

We did a PubMed search to identify articles published in any language before Jan 31, 2016. We used the following terms with appropriate Boolean operators: [objective 1] "inactivated poliovirus vaccine", "measles", "rubella", "yellow fever", "vaccin*", "immun*", "co-administration", "concomitant", "interference"; [objective 2] "inactivated poliovirus vaccine", "intradermal", "fractional dose", "device", "jet inject*", "disposable syringe jet inject*". Reference lists were reviewed for additional publications. No trials or studies have examined the co-administration of the measles–rubella vaccine with the yellow fever vaccine or the co-administration of the single-component inactivated poliovirus vaccine (IPV) with either the measles–rubella or the yellow fever vaccine. Three studies, all undertaken in west and central Africa, have examined the co-administration of the single-component measles vaccine and the yellow fever vaccine. None demonstrated any interference between these vaccines in infants aged 6–12 months. By contrast, a single study undertaken in Brazil examined the co-administration of a three-component measles, mumps, and rubella (MMR) vaccine and the yellow fever vaccine; its findings showed decreased seroconversion for yellow fever, rubella, and mumps, but no effect on measles seroconversion associated with co-administration. Rubella and yellow fever geometric mean antibody titres were also reduced. No trials or studies have previously been reported from sub-Saharan Africa exploring either fractional doses of IPV or the use of disposable-syringe jet injector (DSJI) to administer IPV in any age group. Two trials, one undertaken in India and the other in Cuba, have examined fractional doses of IPV in oral poliovirus vaccine-primed infants. The trial in Cuba included groups who received IPV via needle and syringe, as well as groups with vaccine administered by DSJI, whereas the trial in India included only DSJI-based intradermal IPV administration. In both cases, the response to the fractional intradermal doses of IPV was lower than the responses to the full intramuscular dose. In the trial in Cuba, the responses to the needle and syringe and DSJI-based intradermal administration routes were similar. The use of an intramuscular DSJI to administer IPV has not been reported. To our knowledge,

this is the first report identified describing the use of the intramuscular DSJI to vaccinate children younger than 1 year.

Added value of this study

This study provides the first data for the safety and immunogenicity of co-administering the measles–rubella and yellow fever vaccines, and also on the additional effect of IPV co-administration in 9–10-month old infants. Although the antibody concentrations for rubella and yellow fever were reduced by vaccine co-administration, the seroconversion rates were consistently maintained within a –10% non-inferiority margin. Co-administration had no effect on the measles and poliovirus serological responses and there were no safety concerns. These are also the first data reported from sub-Saharan Africa on the administration of fractional intradermal doses of IPV. In this setting, such fractional doses of the vaccine result in lower antibody titres and few infants experiencing a four-fold rise compared with a full intramuscular dose. Nonetheless, most infants who remained seronegative after serial doses of OPV were likely to seroconvert. Full-dose IPV can be safely and effectively administered to children younger than 1 year using a DSJI.

Implications of all the available evidence

Our data open the way for the inclusion of a dose of IPV within the infant immunisation schedule alongside the measles–rubella and yellow fever vaccines at 9–12 months of age across sub-Saharan Africa and South America, and also for the addition of IPV to the measles–rubella vaccine administered to infants in those parts of the world in which yellow fever is non-endemic. A second dose of IPV at this age will probably induce more sustained protection than a second dose within the infant priming schedule, and thus is likely to be favoured if high coverage can be obtained. The supply benefits as well as reduced costs of administering fractional intradermal doses of IPV make such an approach attractive, although it will result in a compromise in the serological protection generated in the population. However, it should result in the seroconversion of most seronegative infants and may therefore be considered in campaigns and outbreak control.

endgame strategy, because more than 90% of circulating vaccine-derived polioviruses (and approximately 30% of vaccine-associated paralytic polio) are of this virus type.³ To maintain population priming against the type 2 virus, the switch has been accompanied by the introduction of a dose of the (trivalent) inactivated poliovirus (IPV). This is being given concomitantly with the third dose of bivalent OPV at 3–4 months of age in most countries that use the recommended Expanded Programme on Immunization (EPI) schedule.⁴ If a second dose is recommended, as is likely in countries at risk of outbreaks in advance of final OPV cessation, its administration alongside the measles–rubella

combined vaccine and the yellow fever vaccine at 9 months would be favourable given the availability of supportive safety and immunogenicity data.

At the time of widespread IPV introduction, fractional intradermal doses of IPV represent an important option to reduce both the manufacturing scale-up required and the costs involved. The delivery of the vaccine using a disposable-syringe jet injector also has the potential to facilitate rapid campaign-based delivery of IPV, for example in the context of an outbreak of type 2 circulating vaccine-derived poliovirus. An intramuscular booster dose of IPV after OPV priming has previously been shown to result in high seroconversion rates,

whereas the seroconversion rates and more particularly the antibody titres generated after fractional-dose IPV administration are reduced in most studies, which until now have all been done outside sub-Saharan Africa.^{5–12}

We undertook a randomised, controlled trial with two objectives. First, we aimed to assess for interference associated with the co-administration of IPV, measles–rubella vaccine, and yellow fever vaccine, and to confirm the safety of co-administration. Second, we aimed to compare the immunogenicity and safety of intramuscular full-dose (0·5 mL) IPV and intradermal fractional-dose (0·1 mL) IPV, delivered using either needle and syringe or disposable-syringe jet injector.

Given the logistical and cost benefits of co-administering IPV with the other vaccines at 9 months, and of fractional dosing and administration with disposable-syringe jet injector, a non-inferiority design was used to assess the primary immunogenicity endpoints.

Methods

Study design and participants

We did a phase 4, single-centre, randomised, laboratory-observer-blind, non-inferiority trial in the periurban west coast of The Gambia. Infants attending three typical government clinics for their EPI immunisations were recruited. Information regarding the trial was provided in these clinics and parents expressing an interest were invited to nearby clinical trial facilities for consent discussions.

To be eligible, infants had to be aged 9–10 months (inclusive); to have received at least three doses of trivalent OPV up to 28 days before recruitment; to have not received any measles, rubella, yellow fever, or inactivated poliovirus vaccines; and to be clinically healthy with no indications of clinically significant chronic health problems (appendix).

The study was approved by The Gambia Government/MRC Joint Ethics Committee and the Medicines Board of The Republic of The Gambia. It was conducted according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice and local ethical and regulatory requirements.

A parent provided written or thumb-printed informed consent for their offspring to take part in the study. Most parents were not literate in English, in which case an impartial witness was present throughout the informed consent discussion, undertaken in one of the local languages, and signed to attest to the completeness of the information given.

Randomisation and masking

Enrolled infants were randomly assigned into one of eight study groups using pre-prepared, sequentially numbered, sealed envelopes to maintain allocation concealment. The randomisation list was electronically generated with a block size of 32 and was stratified by

sex and by the clinic where the infant was recruited. Randomisation was undertaken by a study clinician after confirmation of eligibility. Neither the parents nor field team were masked to randomisation group, because double-dummy placebo injections (as would have been required to achieve blinding) were not considered to be ethically justified. Laboratory personnel generating and analysing serological data were masked to treatment allocation.

Procedures

At visit one, infants received the IPV, measles–rubella, and yellow fever vaccines either singularly, in combinations of two, or all three vaccines given together, according to the schedule outlined in figure 1 and the appendix. The measles–rubella and yellow fever vaccines were administered as single 0·5 mL intramuscular injections into the left thigh, and the IPV as a single 0·5 mL intramuscular injection into the right thigh using a 23G/25 mm needle.

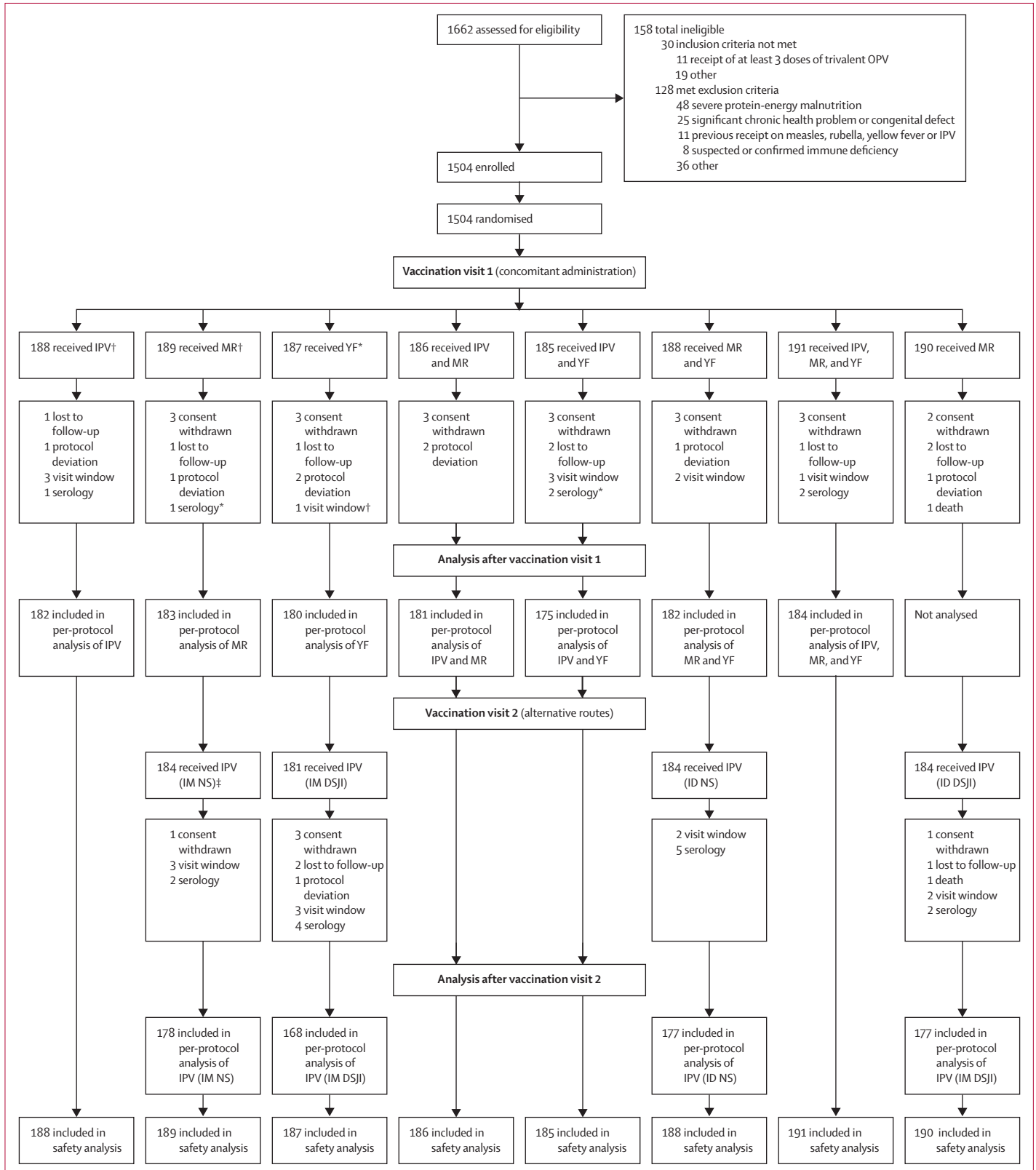
At visit two, those infants who had not received IPV at visit one received the vaccine into the right thigh either as a full-dose (0·5 mL) intramuscular injection using a 23G/25 mm needle; as a fractional-dose (0·1 mL) intradermal injection using a 26G/10 mm needle; as a full dose (0·5 mL) using an intramuscular disposable-syringe jet injector (Stratis; Pharmajet, Golden, CO, USA); or as a fractional dose (0·1 mL) using an intradermal disposable-syringe jet injector (Tropis; Pharmajet). Details of the vaccines are provided in the appendix.

Infants were observed for 30 min after vaccination and immediate reactogenicity data were collected. Reactogenicity data were also collected during home visits done on days one to three after vaccinations in which routes of IPV administration were investigated, and on day three after other vaccinations. Data on adverse events and serious adverse events were collected throughout the study.

Blood samples for baseline and post-vaccination serology were collected by peripheral venepuncture and separated and stored at –70°C within 6 h. Poliovirus, measles, and rubella serology was undertaken in the Virus Reference Department (Public Health England Laboratories, Colindale, UK). Yellow fever serology was undertaken at the Robert Koch Institute (Berlin, Germany).

Neutralising antibody titres against poliovirus types 1, 2, and 3 were assessed using neutralisation assays as previously described.¹³ Serial two-fold dilutions from a starting dilution of one in eight were undertaken until an endpoint titre was attained. Seropositivity was defined as a reciprocal neutralising antibody titre of eight or more. Measles and rubella IgG antibody concentrations were determined using a commercial enzyme-linked immunosorbent assay (Enzygnost anti-measles and anti-rubella virus IgG; Siemens, Munich, Germany). Seropositivity for measles was defined as an IgG

See Online for appendix



concentration of 150 IU/mL or more and for rubella as an IgG concentration of 4 IU/mL or more. Yellow fever neutralisation titres were determined using the microneutralisation test as previously described.¹⁴ Serial two-fold dilutions were undertaken from a starting dilution of one in four, up to a dilution of one in 256. Seropositivity for yellow fever was defined as a reciprocal neutralising antibody titre of eight or more.

Outcomes

The effects of vaccine co-administration (objective one) were assessed through the vaccines administered at visit one. Interference was identified by comparing the study groups which received IPV, measles–rubella vaccine, or yellow fever vaccine alone with those in which the vaccines were given in combination. Baseline serum samples were taken before vaccination and post-vaccination samples were taken at visit two, 4–6 weeks later.

The response to IPV administered as a full intramuscular dose or as a fractional intradermal dose, using either needle and syringe or disposable-syringe jet injector (objective two), was assessed through the vaccines administered at visit two. Infants in groups that did not receive IPV at visit one had a baseline sample for poliovirus serology taken at visit two, before IPV administration, and a post-vaccination sample taken at visit three, 4–6 weeks later.

Baseline and post-vaccination seroprevalence, rates of seroconversion (seronegative to seropositive), and the number of seropositive infants who had a four-fold rise in antibodies after vaccination were generated for each vaccine antigen. The total response, combining the percentage of infants who seroconverted and the percentage who experienced a four-fold antibody rise, was also calculated.

The primary endpoints for the assessment of non-inferiority were the post-vaccination seroprevalence rates for poliovirus and the rate of seroconversion between the baseline and the post-vaccination sample for

measles, rubella, and yellow fever (S); and also the post-vaccination antibody titres (T) generated against each component of the vaccines. For the purposes of assessing vaccine interference the reference responses (S_{REF} and T_{REF}) against which non-inferiority was assessed were those generated when each of the vaccines was administered on its own. When assessing the alternative modes of IPV delivery, the responses generated after 0.5 mL intramuscular needle and syringe-based administration at visit two represented the reference. The responses generated after vaccine co-administration and after fractional-dose intradermal IPV administration with needle and syringe as the primary analyses, and IPV administration with disposable-syringe jet injector as secondary analyses, represented the investigational responses (S_{INV} and T_{INV}). A secondary non-inferiority analysis was also undertaken on the total response data.

The primary safety outcomes were the occurrence of serious adverse events throughout an infant's enrolment in the trial; local and systemic adverse reactions collected on days zero to three after administration via disposable-syringe jet injector, and comparator IPV administration with needle and syringe; also on day zero and day three after the singularly and co-administered vaccines.

Statistical analysis

The non-inferiority analysis was undertaken on the per-protocol population described in figure 1. Non-inferiority of the response to each vaccine component was declared if the lower limit of the 95% CI of the difference in responses ($S_{INV} - S_{REF}$) was greater than the –10% non-inferiority margin. The margin was determined on the basis of considered public health effects of such a reduction compared with the potential logistical and cost benefits of co-administration and of the alternative modes of IPV delivery, and is consistent with available regulatory guidance.^{15,16}

We calculated that 188 infants per group (1504 infants in total) would be required to provide 80% power to demonstrate non-inferiority. This was based on a reference and investigational group response rate of 90% taken from published reports,^{5,17} a one-sided α of 0.025, and a 20% margin for participant attrition. This sample size provided 92% power to determine the non-inferiority of the antibody titres if the lower limit of the 95% CI for the difference between \log_2 -transformed titres ($T_{INV} - T_{REF}$) was greater than the $(1/3)$ \log_2 non-inferiority margin assuming a non-parametric Mann-Whitney test. The 95% CIs for the point difference ($S_{INV} - S_{REF}$) were estimated using the Wilson score interval.¹⁸ The titre data were \log_2 -transformed and if normality and constant variance assumptions were satisfactory the 95% CI for the differences between the mean \log_2 -transformed titres ($T_{INV} - T_{REF}$) were estimated via the pooled variance from a two-sample *t* test. The non-inferiority inference was corroborated by estimating non-parametric CIs on the basis of the Hodges-Lehman

Figure 1: Trial profile

At visit one, infants received IPV, measles–rubella vaccine, and yellow fever vaccine either singularly, in combinations of two (IPV and measles–rubella, IPV and yellow fever, or measles–rubella and yellow fever) or all three vaccines given together.

This allowed interference between the vaccines associated with co-administration to be assessed (objective one). An eighth group, who received the measles–rubella vaccine at visit one, was required to provide four groups at visit two who had not previously received IPV. This allowed the alternative routes of administration and the disposable-syringe jet injector devices to be assessed (objective two).

The additional group was not included in the immunogenicity assessment for objective one. At visit two, infants in the four groups for IPV administration route received the vaccine either as a full (0.5 mL) intramuscular dose or as a fractional (0.1 mL) intradermal dose, using either a needle and syringe or a disposable-syringe jet injector device. IPV=inactivated poliovirus vaccine. MR=measles–rubella. YF=yellow fever. IM=intramuscular. NS=needle and syringe. ID=intradermal. DSJI=disposable-syringe jet injector. *Excluded from the per-protocol population for vaccine co-administration due to missing a visit window (n=1) or as a result of not having a complete set of serology results (n=3), but included in the analysis related to the alternative routes (the deviations had no effect on the assessment of the second objective). †Reference groups for objective one. ‡Reference group for objective two.

median difference. Interval regression was done to test for non-inferiority of the measles antibody concentrations given the proportion of left-censored seronegative data. Responses were declared inferior if the upper limit of the 95% CI for the differences between the investigational and reference responses were below the non-inferiority margin.

Objectives one and two are distinct and do not affect each other, therefore correction for multiplicity between these objectives was not required. To reflect the expected requirement for the responses to each vaccine antigen to be maintained for their future co-administration to be recommended, individual non-inferiority tests were subsequently combined using the intersection union test.¹⁹ Thus, for global non-inferiority to be declared for a given vaccine combination, non-inferiority had to be achieved individually for each component of the co-administered vaccines. This is conservative in terms of the type I error rate. No formal power calculation was undertaken for this intersection union test approach because the dependence structure between the within-subject serological responses was unknown, and an independence assumption was highly unlikely. However, the margin for participant attrition and the group response rates used in calculating the power of individual non-inferiority tests were conservative.

For objective two, a primary comparison was undertaken between the intramuscular and intradermal administration routes based on needle and syringe, reflecting the key policy decision in the field currently. Comparisons between the needle and syringe route, versus the disposable-syringe jet injector route, were secondary analyses.

Data were extracted using SQL queries and summary statistics and analyses were generated in Matlab (release R2014b) and Stata (release 12.1). A data and safety monitoring board (DSMB) reviewed safety data throughout the trial. The trial was registered with ClinicalTrials.gov, number NCT01847872, where the trial protocol is available.

Role of the funding source

The trial was sponsored by the Medical Research Council and funded by the Bill & Melinda Gates Foundation (BMGF). A BMGF employee (ASB) participated in the study design, data interpretation, and decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The first infant was enrolled on July 10, 2013, and the last infant completed the study on May 8, 2014. Enrolment was temporarily halted between Oct 22 and Dec 2, 2013, after a national trivalent OPV campaign including infants enrolled in the trial within the target age group. No infants enrolled in the study at the time received a dose of trivalent OPV during the campaign and any effect of environmental exposure on systemic immunity is likely to be minimal in the context of a recent dose of IPV; any effect would also be evenly distributed between groups.

A total of 1662 infants were assessed for eligibility. After screening, 158 infants were deemed to be ineligible and 1504 infants were randomised (figure 1). Immunogenicity was analysed in the per-protocol

	IPV at visit 1 (n=188)	Measles-rubella at visit 1, IPV (IM NS) at visit 2 (n=189)	Yellow fever at visit 1, IPV (IM DSJI) at visit 2 (n=187)	IPV and measles-rubella at visit 1 (n=186)	IPV and yellow fever at visit 1 (n=185)	Measles-rubella and yellow fever at visit 1, IPV (ID NS) at visit 2 (n=188)	IPV, measles-rubella, and yellow fever at visit 1 (n=191)	IPV (ID DSJI) at visit 2 (n=190)	Overall (n=1504)
Age, months	9.6 (9.0-11.0)	9.6 (9.0-11.0)	9.6 (9.0-11.0)	9.7 (9.0-11.0)	9.5 (9.0-11.0)	9.7 (9.0-11.0)	9.6 (9.0-11.0)	9.5 (9.0-11.0)	9.6 (9.0-11.0)
Male sex	89 (47%)	92 (49%)	90 (48%)	91 (49%)	90 (49%)	92 (49%)	94 (49%)	92 (48%)	730 (49%)
Weight, kg	8.1 (6.0-12.9)	8.1 (6.2-12.4)	8.1 (6.1-11.5)	8.2 (6.2-11.9)	8.2 (6.0-10.9)	8.1 (6.1-10.7)	8.1 (6.0-11.9)	8.2 (6.2-11.7)	8.2 (6.0-12.4)
Length, cm	70.4 (63.0-77.0)	70.7 (62.0-78.0)	70.5 (63.0-78.0)	70.8 (63.0-78.0)	70.7 (63.0-77.0)	70.4 (65.0-76.0)	70.5 (64.0-79.0)	70.6 (64.0-78.0)	70.6 (62.0-79.0)
Number of previous OPV doses*	4.9 (4.0-6.0)	5.0 (4.0-6.0)	4.8 (4.0-7.0)	5.0 (4.0-7.0)	4.9 (4.0-6.0)	4.9 (4.0-6.0)	4.9 (4.0-6.0)	4.9 (4.0-6.0)	4.9 (4.0-7.0)
Time since last OPV dose, days*	83.6 (29.0-192.0)	81.5 (29.0-190.0)	86.7 (28.0-191.0)	85.1 (20.0-222.0)	84.2 (34.0-182.0)	83.1 (31.0-192.0)	84.5 (30.0-190.0)	87.1 (28.0-196.0)	84.5 (20.0-222.0)
Mother's tribe									
Mandinka	102 (54%)	101 (53%)	105 (56%)	107 (58%)	100 (54%)	107 (57%)	96 (50%)	94 (49%)	812 (54%)
Wolof	23 (12%)	22 (12%)	20 (11%)	23 (12%)	24 (13%)	21 (11%)	21 (11%)	23 (12%)	177 (12%)
Fula	13 (7%)	14 (7%)	14 (7%)	11 (6%)	15 (8%)	13 (7%)	18 (9%)	21 (11%)	119 (8%)
Other	50 (27%)	52 (28%)	48 (26%)	45 (24%)	46 (25%)	47 (25%)	56 (29%)	52 (27%)	396 (26%)

Data are mean (range) or n (%). IPV=inactivated poliovirus vaccine. IM=intramuscular. NS=needle and syringe. DSJI=disposable-syringe jet injector. ID=intradermal. OPV=oral poliovirus vaccine. *Based on information recorded on the parent-held infant welfare card for routine doses and parent recall associated with knowledge of dates of national OPV campaigns for campaign-based doses.

Table 1: Baseline characteristics

	IPV	Measles-rubella	Yellow fever	IPV and measles-rubella	IPV and yellow fever	Measles-rubella and yellow fever	IPV, measles-rubella, and yellow fever
Poliovirus type 1							
Seroprevalence	160/182, 87.9% (82.4–91.9)	162/181, 89.5% (84.2–93.2)	162/176, 92.0% (87.1–95.2)	..	159/184, 86.4% (80.7–90.6)
Antibody titres	64 (64–128)	64 (64–64)	128 (64–128)	..	64 (64–114)
Poliovirus type 2							
Seroprevalence	174/182, 95.6% (91.6–97.8)	174/181, 96.1% (92.2–98.1)	171/176, 97.2% (93.5–98.8)	..	178/184, 96.7% (93.1–98.5)
Antibody titres	64 (64–128)	128 (64–128)	128 (64–128)	..	64 (64–128)
Poliovirus type 3							
Seroprevalence	130/182, 71.4% (64.5–77.5)	139/181, 76.8% (70.1–82.3)	151/176, 85.8% (79.9–90.2)	..	133/184, 72.3% (65.4–78.2)
Antibody titres	32 (16–64)	32 (16–32)	64 (32–64)	..	32 (16–32)
Measles							
Seroprevalence	..	1/183, 0.5% (0.1–3.0)	..	2/181, 1.1% (0.3–3.9)	..	2/182, 1.1% (0.3–3.9)	0/185, 0.0% (0.0–2.0)
Antibody titres	..	<150 (<150–<150)	..	<150 (<150–<150)	..	<150 (<150–<150)	<150 (<150–<150)
Rubella							
Seroprevalence	..	16/183, 8.7% (5.5–13.7)	..	20/181, 11.0% (7.3–16.5)	..	25/182, 13.7% (9.5–19.5)	24/185, 13.0% (8.9–18.6)
Antibody titres	..	<4 (<4–<4)	..	<4 (<4–<4)	..	<4 (<4–<4)	<4 (<4–<4)
Yellow fever							
Seroprevalence	4/180, 2.2% (0.9–5.6)	..	3/175, 1.7% (0.6–4.9)	5/182, 2.7% (1.2–6.3)	3/185, 1.6% (0.6–4.7)
Antibody titres	<4 (<4–<4)	..	<4 (<4–<4)	<4 (<4–<4)	<4 (<4–<4)

Data are median (95% CI) or n/N, % (95% CI). Seroprevalence is defined as follows: poliovirus types 1, 2, and 3, reciprocal neutralising antibody titre ≥ 8 ; measles, antibody concentration ≥ 150 IU/mL; rubella, antibody concentration ≥ 4 IU/mL; yellow fever, reciprocal neutralising antibody titre ≥ 8 . Denominators differ from number of infants due to missing serological results for one or other antigen. IPV=inactivated poliovirus vaccine.

Table 2: Baseline serology in the per-protocol population examined for vaccine interference

population, after exclusion of participants due to consent withdrawal (parent withdrew consent for continued study participation after randomisation; n=25), loss to follow-up (all contact with family lost; n=11), protocol deviation (any deviation from the protocol which could, in theory, affect the immunogenicity results obtained—eg, vaccines received outside protocol; n=3), ineligibility for randomisation (n=3), vaccination error (n=2), randomisation error (n=1), serum sample obtained outside the visit window period (n=20), required serology results not obtained for any reason (n=19), or death of infant during study participation (n=1). Of the 1314 infants in one of the seven groups included in the assessment of vaccine co-administration (objective one), 1267 (96%) were included in the per-protocol analysis. Of the 754 infants in one of the four groups in which the alternative modes of IPV delivery were subsequently assessed (objective two), 700 (93%) were included in the per-protocol analysis.

The demographic characteristics of the 1504-randomised infants are provided in table 1. 730 (49%) were male and all had received at least four doses of OPV. The baseline serological data in the seven groups considered in

the assessment of vaccine interference are provided in table 2. Poliovirus seroprevalence rates ranged from 86% to 92% for type 1, 96% to 97% for type 2, and 71% to 86% for type 3 (table 2). Seroprevalence for measles ranged from zero to 1%, for yellow fever from 2% to 3%, and for rubella from 9% to 14% (table 2).

Summary statistics for the reference and investigational groups after vaccination are provided in table 3. Post-vaccination poliovirus seroprevalence ranged from 98% to 100% for type 1, was consistently 100% for type 2, and ranged from 97% to 99% for type 3. The lower limit of the 95% CI ($S_{INV}-S_{REF}$) was above the -10% non-inferiority margin in all cases and non-inferiority was thus demonstrated (rubella, -4.5% [95% CI -9.5 to -0.1]; yellow fever, 1.2% [-2.9 to 5.5]; measles, 6.8% [95% CI -1.4 to 14.9]; poliovirus serotype 1, 1.6% [-6.7 to 4.7]; serotype 2, 0.0% [-2.1 to 2.1]; serotype 3, 0.0% [-3.8 to 3.9]; figure 2, appendix). The median antibody titre increased to 512 for poliovirus types 1 and 2 across all groups and to between 768 and 1024 for poliovirus type 3. The corresponding non-inferiority analysis for differences in antibody titre ($T_{INV}-T_{REF}$) is illustrated in figure 2; the corresponding figures are given in the

	IPV (n=182)	Measles-rubella (n=183)	Yellow fever (n=180)	IPV and measles-rubella (n=181)	IPV and yellow fever (n=175)	Measles-rubella and yellow fever (n=182)	IPV, measles-rubella, and yellow fever (n=184)
Poliovirus type 1							
Seroprevalence	179/182, 98.4% (95.3-99.4)	178/181, 98.3% (95.2-99.4)	175/175, 100.0% (97.9-100.0)	..	184/184, 100.0% (98.0-100.0)
Antibody titres	512 (512-512)	512 (512-512)	512 (512-512)	..	512 (512-512)
Seroconversion	19/22, 86.4% (66.7-95.3)	16/19, 84.2% (62.4-94.5)	14/14, 100.0% (78.5-100.0)	..	25/25, 100.0% (86.7-100.0)
Four-fold rise	100/160, 62.5% (54.8-69.6)	117/162, 72.2% (64.9-78.5)	98/161, 60.9% (53.2-68.1)	..	103/159, 64.8% (57.1-71.8)
Total response	119/182, 65.4% (58.2-71.9)	133/181, 73.5% (66.6-79.4)	112/175, 64.0% (56.7-70.7)	..	128/184, 69.6% (62.6-75.8)
Poliovirus type 2							
Seroprevalence	182/182, 100.0% (97.9-100.0)	181/181, 100.0% (97.9-100.0)	175/175, 100.0% (97.9-100.0)	..	184/184, 100.0% (98.0-100.0)
Antibody titres	512 (512-512)	512 (256-512)	512 (512-512)	..	512 (512-512)
Seroconversion	8/8, 100.0% (67.6-100.0)	7/7, 100.0% (64.6-100.0)	5/5, 100.0% (56.6-100.0)	..	6/6, 100.0% (61.0-100.0)
Four-fold rise	121/174, 69.5% (62.3-75.9)	113/174, 64.9% (57.6-71.6)	111/170, 65.3% (57.9-72.0)	..	119/178, 66.9% (59.6-73.3)
Total response	129/182, 70.9% (63.9-77.0)	120/181, 66.3% (59.1-72.8)	116/175, 66.3% (59.0-72.9)	..	125/184, 67.9% (60.9-74.3)
Poliovirus type 3							
Seroprevalence	177/182, 97.3% (93.7-98.8)	178/181, 98.3% (95.2-99.4)	174/175, 99.4% (96.8-99.9)	..	179/184, 97.3% (93.8-98.8)
Antibody titres	768 (512-1024)	1024 (512-1024)	1024 (1024-1024)	..	1024 (512-1024)
Seroconversion	47/52, 90.4% (79.4-95.8)	39/42, 92.9% (81.0-97.5)	24/25, 96.0% (80.5-99.3)	..	46/51, 90.2% (79.0-95.7)
Four-fold rise	109/130, 83.8% (76.6-89.2)	115/139, 82.7% (75.6-88.1)	121/150, 80.7% (73.6-86.2)	..	115/133, 86.5% (79.6-91.3)
Total response	156/182, 85.7% (79.9-90.1)	154/181, 85.1% (79.2-89.5)	145/175, 82.9% (76.6-87.7)	..	161/184, 87.5% (81.9-91.5)
Measles							
Seroprevalence	..	141/183, 77.0% (70.4-82.5)	..	141/181, 77.9% (71.3-83.3)	..	143/182, 78.6% (72.1-83.9)	154/184, 83.7% (77.7-88.3)
Antibody titres	..	250 (230-280)	..	240 (220-260)	..	270 (243-310)	250 (230-290)
Seroconversion	..	140/182, 76.9% (70.3-82.4)	..	139/179, 77.7% (71.0-83.1)	..	142/180, 78.9% (72.4-84.2)	154/184, 83.7% (77.7-88.3)
Four-fold rise	..	1/1, 100.0% (20.7-100.0)	..	0/2, 0.0% (0.0-65.8)	..	0/2, 0.0% (0.0-65.8)	0/0
Total response	..	83/141, 77.0% (70.4-82.5)	..	81/139, 76.8% (70.1-82.3)	..	82/142, 78.0% (71.5-83.4)	84/154, 83.7% (77.7-88.3)
Rubella							
Seroprevalence	..	180/183, 98.4% (95.3-99.4)	..	174/181, 96.1% (92.2-98.1)	..	176/182, 96.7% (93.0-98.5)	174/184, 94.6% (90.3-97.0)
Antibody titres	..	31 (27-36)	..	27 (21-33)	..	27 (24-31)	24 (20-29)
Seroconversion	..	164/167, 98.2% (94.9-99.4)	..	154/161, 95.7% (91.3-97.9)	..	152/157, 96.8% (92.8-98.6)	150/160, 93.8% (88.9-96.6)
Four-fold rise	..	0/16, 0.0% (0.0-19.4)	..	0/20, 0.0% (0.0-16.1)	..	0/25, 0.0% (0.0-13.3)	0/24, 0.0% (0.0-13.8)
Total response	..	83/164, 89.6% (84.4-93.3)	..	81/154, 85.1% (79.2-89.5)	..	82/152, 83.5% (77.4-88.2)	84/150, 81.5% (75.3-86.5)
Yellow fever							
Seroprevalence	173/180, 96.1% (92.2-98.1)	..	169/175, 96.6% (92.7-98.4)	173/182, 95.1% (90.9-97.4)	179/184, 97.3% (93.8-98.8)
Antibody titres	128 (91-128)	..	91 (91-128)	64 (64-91)	64 (45-64)

(Table 3 continues on next page)

	IPV (n=182)	Measles-rubella (n=183)	Yellow fever (n=180)	IPV and measles-rubella (n=181)	IPV and yellow fever (n=175)	Measles-rubella and yellow fever (n=182)	IPV, measles-rubella, and yellow fever (n=184)
(Continued from previous page)							
Seroconversion	169/176, 96.0% (92.0-98.1)	..	166/172, 96.5% (92.6-98.4)	168/177, 94.9% (90.6-97.3)	176/181, 97.2% (93.7-98.8)
Four-fold rise	3/4, 75.0% (30.1-95.4)	..	2/3, 66.7% (20.8-93.9)	4/5, 80.0% (37.6-96.4)	2/3, 66.7% (20.8-93.9)
Total response	172/180, 95.6% (91.5-97.7)	..	168/175, 96.0% (92.0-98.0)	172/182, 94.5% (90.2-97.0)	178/184, 96.7% (93.1-98.5)

Data are median (95% CI) or n/N, % (95% CI). Seroprevalence is defined as follows: poliovirus types 1, 2, and 3, reciprocal neutralising antibody titre ≥ 8 ; measles, antibody concentration ≥ 150 IU/mL; rubella, antibody concentration ≥ 4 IU/mL; yellow fever, reciprocal neutralising antibody titre ≥ 8 ; seroconversion is defined for all antigens as a change from seronegative baseline to seropositive after vaccination and is expressed as a percentage of those individuals who were seronegative at baseline. Four-fold rise is defined as follows: poliovirus types 1, 2, and 3, a four-fold rise in antibody titres amongst those infants who were seropositive at baseline; measles and rubella, a four-fold rise in antibody concentrations amongst those infants who were seropositive at baseline; yellow fever, a four-fold rise in antibody titres amongst those infants who were seropositive at baseline with an antibody titre of ≤ 64 . Total response includes the number of subjects who underwent seroconversion and the number who had a four-fold rise (as previously defined). IPV=inactivated poliovirus vaccine.

Table 3: Post-vaccination serology in the per-protocol population examined for vaccine interference

appendix. Finally, examining the total response, including the proportion of infants who seroconverted and the proportion who had a four-fold rise in antibody titres (table 3), gave no indication that vaccine co-administration interfered with the poliovirus-specific responses.

Seroconversion rates for measles ranged from 77% to 84%. There was no evidence that vaccine co-administration negatively affected either the seroconversion rates or the post-vaccination measles antibody concentrations. For both outcomes, non-inferiority of the responses against the prespecified margins was demonstrated (figure 2, appendix). In total, 98% of infants who received the measles-rubella vaccine alone seroconverted to rubella, whereas 94% seroconverted when all three vaccines were administered together. Non-inferiority was nonetheless demonstrated against the -10% non-inferiority margin. Rubella-specific antibody concentrations were reduced by vaccine co-administration and did not achieve non-inferiority, irrespective of whether measles-rubella vaccine was co-administered with one or both of the additional vaccines; although interference was most marked when all three vaccines were given together (figure 2, appendix).

The seroconversion rates for yellow fever vaccine ranged from 95% to 97%, and were unaffected by vaccine co-administration. However, the yellow fever median antibody titre was 128 (95% CI 91-128) when the vaccine was administered on its own, while it was only 64 (95% CI 45-64) and was inferior when all three vaccines were administered together (figure 2, appendix). The same trend was demonstrated when yellow fever vaccine was administered with either the IPV vaccine or the measles-rubella vaccine alone, and non-inferiority was not demonstrated for any combination.

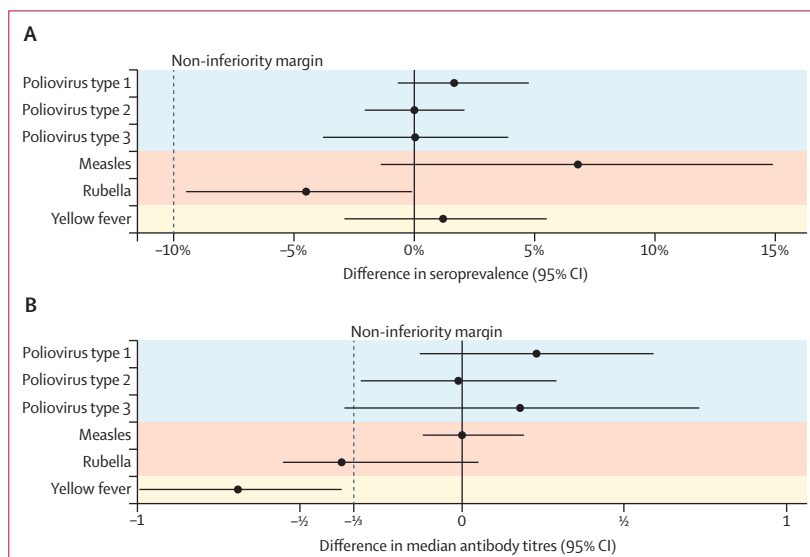


Figure 2: Vaccine co-administration (objective one)

(A) Differences in the seroprevalence for poliovirus types 1, 2, and 3 seroconversion for measles, rubella, and yellow fever, comparing each of the vaccines administered on its own with the combination of all three vaccines administered together. Circles represent the point estimate, lines are 95% CIs. (B) Difference in the antibody titres comparing each of the vaccines administered on its own with the combination of all three vaccines administered together. Circles represent the point estimate, lines are 95% CIs.

Applying the intersection union test,¹⁹ global non-inferiority was demonstrated for all vaccine combinations when examining seroprevalence and seroconversion rates. By contrast, when examining antibody titres, no vaccine combination achieved global non-inferiority, reflecting the reduction in both the rubella and yellow fever titres associated with co-administration.

The baseline and post-vaccination serological data for the four groups considered in the assessment of the fractional dosing and IPV administration with disposable-syringe jet injector (objective two) are provided in tables 4 and 5, respectively. Post-vaccination

seroprevalence ranged from 97% to 99% for type 1 and from 99% to 100% for type 2. The three alternative routes of administration were consistently non-inferior for these outcomes (figure 3, appendix). Poliovirus serotype 3 seroprevalence achieved non-inferiority for the intradermal needle and syringe administration but did not achieve non-inferiority after intradermal administration using the disposable-syringe jet injector ($S_{INV} - S_{REF} -5.66\%$ [95% CI -10.60 to -1.31]). Non-inferiority of the median antibody titres was not

achieved by any of the alternative routes (figure 3B, appendix). Furthermore, the titres generated after the primary analysis of intradermal needle and syringe administration were inferior for serotype 3 and after the analysis of intradermal administration with disposable-syringe jet injector were inferior for all serotypes. Overall, two-thirds of infants either seroconverted or had a four-fold rise in antibody titres after intramuscular needle and syringe (67%) or disposable-syringe jet injector (66%) administration, compared with 56% and 44% after the equivalent intradermal routes. The same pattern was seen for the type 2 and type 3 polioviruses (table 5). A secondary non-inferiority analysis of these total responses is provided in the appendix.

A modified intention-to-treat analysis (including 1277 [97%] of 1314 infants for analysis of objective one; and 711 [94%] of 754 infants for analysis of objective two) was done in all infants in whom serological endpoints were measured outside the specified visit windows any other minor protocol deviations resulted in the same statistical inference as the per-protocol analysis (data not shown).

A total of 36 serious adverse events occurred in 35 infants enrolled in the trial. Three infants died, two of whom were hospitalised at the time. None of the deaths were deemed related to vaccination by the data safety and monitoring board. One serious adverse event was defined as possibly related to yellow fever vaccination. The infant developed a significant rash

	IPV intramuscular, needle and syringe (n=178)	IPV intramuscular, disposable-syringe jet injector (n=168)	IPV intradermal, needle and syringe (n=177)	IPV intradermal, disposable-syringe jet injector (n=177)
Poliovirus type 1				
Seroprevalence	155/178, 87.1% (81.4-91.2)	151/168, 89.9% (84.4-93.6)	152/177, 85.9% (80.0-90.2)	159/177, 89.8% (84.5-93.5)
Antibody titres	64 (46-128)	64 (32-64)	64 (64-128)	64 (64-128)
Poliovirus type 2				
Seroprevalence	171/178, 96.1% (92.1-98.1)	166/168, 98.8% (95.8-99.7)	173/177, 97.7% (94.3-99.1)	175/177, 98.9% (96.0-99.7)
Antibody titres	64 (64-128)	128 (64-128)	64 (64-128)	64 (64-65)
Poliovirus type 3				
Seroprevalence	142/178, 79.8% (73.3-85.0)	139/168, 82.7% (76.3-87.7)	131/177, 74.0% (67.1-79.9)	134/177, 75.7% (68.9-81.4)
Antibody titres	32 (32-32)	32 (32-64)	16 (16-32)	32 (16-64)

Data are median (95% CI) or n/N, % (95% CI). Seroprevalence is defined as a reciprocal neutralising antibody titre ≥ 8 .

Table 4: Baseline serology in the per-protocol population comparing routes of administration

	IPV intramuscular, needle and syringe (n=178)	IPV intramuscular, disposable-syringe jet injector (n=168)	IPV intradermal, needle and syringe (n=177)	IPV intradermal, disposable-syringe jet injector (n=177)
Poliovirus type 1				
Seroprevalence	175/178; 98.3% (95.2-99.4)	167/168; 99.4% (96.7-99.9)	174/177; 98.3% (95.1-99.4)	172/177; 97.2% (93.6-98.8)
Antibody titres	512 (256-512)	512 (256-512)	256 (256-256)	256 (128-256)
Seroconversion	20/23; 87.0% (67.9-95.5)	16/17; 94.1% (73.0-99.0)	22/25; 88.0% (70.0-95.8)	13/18; 72.2% (49.1-87.5)
Four-fold rise	99/155; 63.9% (56.1-71.0)	95/151; 62.9% (55.0-70.2)	77/152; 50.7% (42.8-58.5)	64/159; 40.3% (32.9-48.0)
Total response	119/178; 66.9% (59.6-73.3)	111/168; 66.1% (58.6-72.8)	99/177; 55.9% (48.6-63.0)	77/177; 43.5% (36.4-50.9)
Poliovirus type 2				
Seroprevalence	177/178; 99.4% (96.9-99.9)	168/168; 100.0% (97.8-100.0)	175/177; 98.9% (96.0-99.7)	177/177; 100.0% (97.9-100.0)
Antibody titres	512 (512-512)	512 (256-512)	256 (256-512)	256 (128-256)
Seroconversion	6/7; 85.7% (48.7-97.4)	2/2; 100.0% (34.2-100.0)	2/4; 50.0% (15.0-85.0)	2/2; 100.0% (34.2-100.0)
Four-fold rise	123/171; 71.9% (64.8-78.1)	98/166; 59.0% (51.4-66.2)	101/173; 58.4% (50.9-65.5)	72/175; 41.1% (34.1-48.5)
Total response	129/178; 72.5% (65.5-78.5)	100/168; 59.5% (52.0-66.7)	103/177; 58.2% (50.8-65.2)	74/177; 41.8% (34.8-49.2)
Poliovirus type 3				
Seroprevalence	175/178; 98.3% (95.2-99.4)	162/168; 96.4% (92.4-98.4)	167/177; 94.4% (89.9-96.9)	164/177; 92.7% (87.8-95.7)
Antibody titres	1024 (512-1024)	512 (512-1024)	512 (512-512)	256 (256-512)
Seroconversion	33/36; 91.7% (78.2-97.1)	23/29; 79.3% (61.6-90.2)	37/46; 80.4% (66.8-89.3)	30/43; 69.8% (54.9-81.4)
Four-fold rise	114/142; 80.3% (73.0-86.0)	113/139; 81.3% (74.0-86.9)	105/131; 80.2% (72.5-86.1)	93/134; 69.4% (61.2-76.6)
Total response	147/178; 82.6% (76.3-87.5)	136/168; 81.0% (74.3-86.2)	142/177; 80.2% (73.7-85.4)	123/177; 69.5% (62.4-75.8)

Data are median (95% CI) or n/N, % (95% CI). Seroprevalence is defined as a reciprocal neutralising antibody titre ≥ 8 ; seroconversion is defined as a change from seronegative at baseline to seropositive after vaccination and is expressed as a percentage of those individuals who were seronegative at baseline; four-fold rise is defined as a four-fold rise in antibody titres amongst those infants who were seropositive at baseline; total response includes the number of participants who underwent seroconversion and the number who had a four-fold rise (as previously defined).

Table 5: Post-vaccination serology in the per-protocol population comparing routes of administration

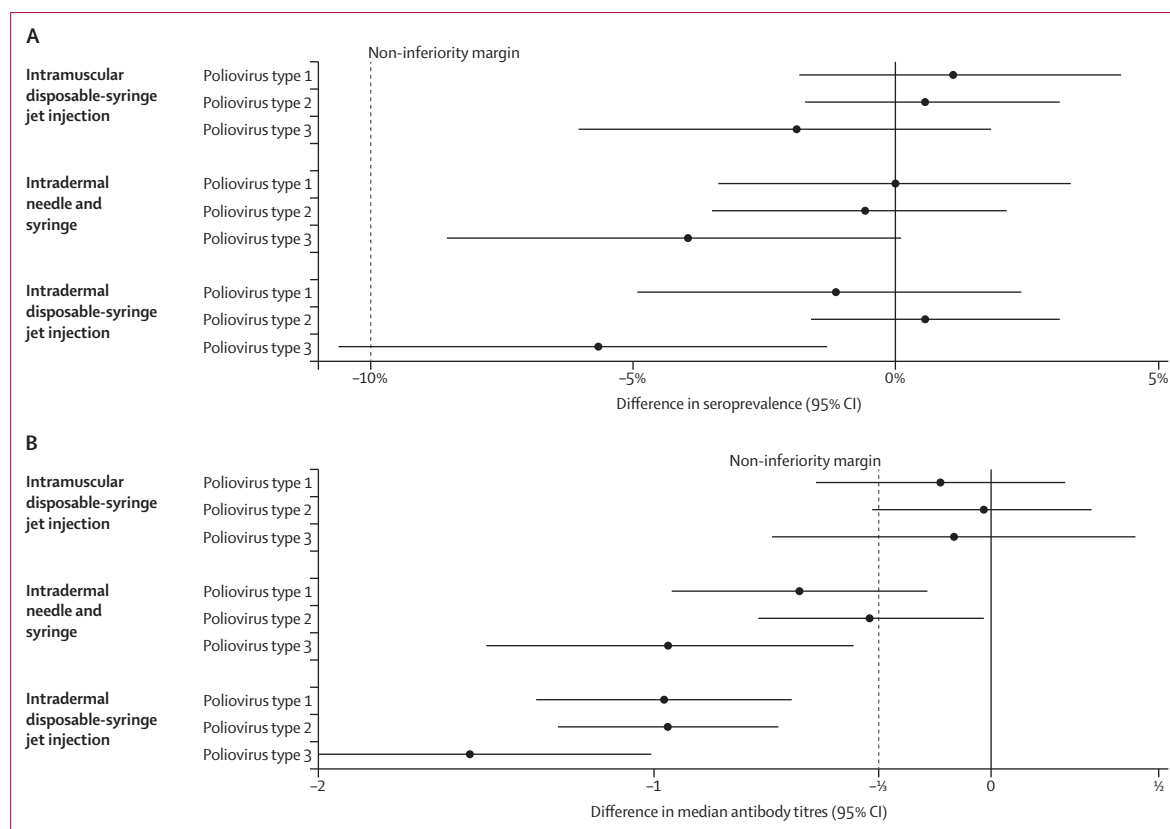


Figure 3: Alternative routes of administration (objective two)

(A) Differences in the seroprevalence for poliovirus types 1, 2, and 3 comparing full-dose IPV administered intramuscularly with a needle and syringe to the administration of a full dose of the same vaccine intramuscularly using a disposable-syringe jet injector, a fractional (0.1 mL) dose intradermally using a needle and syringe, and a fractional dose intradermally using a disposable-syringe jet injector. Circles represent the point estimate. (B) Difference in the median antibody titres comparing the same alternative routes of administration with the reference full dose (administration intramuscularly with needle and syringe). Circles represent the point estimate.

within 24 h of vaccination, although contact dermatitis related to an antiseptic wash was ultimately judged to be more likely.

All vaccinations were well tolerated, with a low level of local and systemic reactogenicity being recorded overall. At the day three home visit after visit one, redness, swelling, or tenderness occurred in nine infants after IPV, six infants after measles–rubella, and five infants after yellow fever vaccine administration. At visit two, there were no clinically significant immediate local reactions related to IPV delivery, irrespective of delivery route. Both devices were easy to use and reliable. Over the first 3 days, redness, swelling, or tenderness was recorded in two infants who received the intramuscular vaccine using a needle and syringe, five who received it intramuscularly using the disposable-syringe jet injector, three who received it intradermally using a needle and syringe, and three who received it intradermally using the disposable-syringe jet injector. All local reactogenicity was mild and had resolved by the day three home visit. All systemic reactogenicity was mild or moderate (appendix), and there were no notable differences related to treatment group.

Discussion

To our knowledge, this is the first trial to examine the co-administration of IPV with the measles–rubella and yellow fever vaccines, or to examine co-administration of the measles–rubella and yellow fever vaccines together. It provides the key data required before any future introduction of IPV into the EPI schedule alongside the measles–rubella and yellow fever vaccines at 9 months of age. Although co-administration resulted in a significant reduction in the antibody titres generated against both rubella and yellow fever, seroconversion rates were maintained above the –10% non-inferiority margin in both cases. There was no evidence of interference with the immunity generated against either the polioviruses or the measles component of the combined vaccine and there were no safety concerns.

The measles–rubella vaccine is universally recommended by WHO for infants aged 9–12 months. The switch from the single-component measles vaccine is currently underway across sub-Saharan Africa and has recently occurred in The Gambia. The yellow fever vaccine is recommended for all children living in endemic countries across sub-Saharan Africa and

South America. Thus, the data generated in this trial, representing a typical setting and population in west Africa, have direct implications for vaccine policy across these parts of the world, most of which currently also include OPV within their EPI schedule. Findings from a meta-analysis suggest that a single dose of IPV given at around 4 months of age will protect about half of recipients, whereas two doses given at an interval will provide at least 80% protection and hence is expected to be recommended before final OPV cessation.⁴ The administration of the second dose of IPV at 9 months of age, alongside the measles–rubella and yellow fever vaccines, is likely to generate more sustained protection than two doses given within the infant priming schedule.²⁰

Reduced seroconversion rates to yellow fever and rubella have been demonstrated following the co-administration of the three-component measles, mumps, and rubella vaccine with the yellow fever vaccine.²¹ By contrast, those studies examining the co-administration of the single-component measles vaccine and the yellow fever vaccine have consistently demonstrated a lack of interference in the same age group.^{13,17,18} Findings from this study demonstrate that, although measles–rubella and yellow fever vaccine co-administration is associated with a reduction in the rubella and yellow fever antibody levels, which are further compromised on the addition of IPV, seroconversion rates are maintained to both antigens.

Mathematical modelling suggests that the risk of congenital rubella syndrome might be increased, through shifting the age of infection in susceptible females into their childbearing years, as a result of suboptimal vaccine coverage or response rates.²² The 9–14% baseline rubella seroprevalence in 9–10-month-old infants in this study suggests significant levels of rubella infection over the first year of life in The Gambia. This is also likely to reflect maternal exposure over the same time period when further pregnancies are also common. Nonetheless, in view of the relative maintenance of the rubella seroconversion rates and the booster dose of the measles–rubella vaccine recommended in the second year of life, the reduced antibody concentrations in isolation do not seem to preclude future co-administration.

Primary yellow fever vaccine failure is exceptionally rare and, in view of the seroconversion rates demonstrated in all groups, is unlikely to be affected by co-administration. The long-term stability of the yellow fever antibody titres generated by vaccination means that secondary failures are also currently almost unheard of.²³ Whether the reduction in titres demonstrated will compromise the lifelong immunity needed in light of the recent WHO recommendation that only a single dose of the vaccine be included within the EPI schedule at 9 months necessitates monitoring if such a schedule becomes established.²³

Irrespective of timing, supply constraints and the cost of the vaccine make fractional dosing and disposable-syringe jet-injector administration attractive options for both campaign and programmatic delivery.¹ In the context of a high baseline seroprevalence, reflecting previous OPV immunisation, the post-vaccination seroprevalence rates were non-inferior to full-dose intramuscular needle and syringe administration, with the exception of the intradermal disposable-syringe jet injector for the type 3 poliovirus. By contrast, the neutralising antibody titres did not achieve non-inferiority for any comparison with the full-dose intramuscular IPV. The proportion of infants who either seroconverted or who had a four-fold rise in antibody titres was also consistently lower by the intradermal route.

This is the first trial to explore the use of fractional doses of IPV in sub-Saharan Africa and provides key data relevant to this setting. The findings are consistent with trials that have examined the use of fractional doses of IPV in OPV-primed toddlers elsewhere.^{5,9} A single fractional intradermal dose of IPV in an OPV-vaccinated population will result in seroconversion in most infants who remain seronegative despite multiple doses of OPV. This may be adequate for outbreak control or campaign use, when injector-based administration might also offer practical advantages. Although the neutralising antibody titres generated by IPV could be maintained for more than 30 years, this is likely to be compromised by lower initial titres.²⁴ Memory responses persist even in the absence of detectable antibody, but it is unknown whether these translate into sustained protection.⁴ Thus, research aiming to enhance IPV immunogenicity through, for example, the use of novel adjuvants and new technologies (eg, dissolvable microneedles) remains a priority if fractional dosing is to become routine.

Several limitations of the trial and the future application of the results should be considered. First, the study was undertaken in a trivalent OPV primed population rather than a population primed with bivalent OPV and IPV. Although the post-vaccination seroprevalence rates were high after the fractional intradermal doses of IPV and after the injector-based administration, data indicate these figures and the resulting antibody titres are likely to be a conservative estimate of the response to a booster, rather than a primary IPV dose.^{10,25} Second, when examining the poliovirus titres, there are a number of examples where non-inferiority was not demonstrated despite the point estimate for the difference being close to zero. Thus, care must be exercised in interpreting the outcome of non-inferiority testing in isolation without examining the associated titre differences. Similarly, a number of chance differences in baseline poliovirus titres are present and should be noted. Thirdly, safety data was not collected in a blinded fashion and although the context and absence of any consistent trends suggests substantial

bias is unlikely, this possibility should nonetheless be recognised. Finally, the trial design did not include a second randomisation step at visit two. Thus, the possibility of some residual effect of the vaccines administered at visit one on the responses to IPV administered at visit two is acknowledged. We are not aware of data to indicate that this possibility is anything more than a theoretical concern.

In conclusion, our trial findings have direct policy implications for the polio eradication endgame given the expected need to introduce a second dose of IPV into the schedule in those parts of the world at risk of outbreaks after OPV cessation. In view of the global non-inferiority of the response rates demonstrated and the lack of safety signals, the findings support the future co-administration of the IPV, measles–rubella, and yellow fever vaccines, although ongoing monitoring of rubella and yellow fever seroprevalence is warranted if such a programme becomes established. The use of fractional intradermal doses of IPV, irrespective of method of administration, will result in a high post-vaccination seroprevalence and, as recently endorsed by WHO,²⁶ remains an option for an outbreak response. However, such approaches substantially compromise the polio-specific immunity generated and—supply constraints and costs acknowledged—are not supported as a single dose routine approach on the basis of these findings.

Contributors

EC contributed to the trial design, oversaw the trial implementation, data analysis, and data interpretation, and wrote the initial draft of the clinical trial protocol and trial report; YS, JUA, IA, AOB, MBH, NM-A, AU, PMC, and MEO contributed to and coordinated the planning and implementation of the trial including all infant recruitment and data collection; DJJ contributed to the design of the trial, undertook all statistical analysis, and contributed to data interpretation; KEB, MN, PRC, and ER undertook laboratory analysis and contributed to data interpretation; BK contributed to the design and implementation of the trial and to data interpretation; JM oversaw the sponsorship responsibilities for the trial. ASB and RC contributed to the design of the study, advised on aspects of trial implementation, and contributed to data interpretation. All authors provided input into the drafting and critical revision of the final report and gave final approval of the version to be published.

Declaration of interests

ASB is an employee of the Bill & Melinda Gates Foundation who provided grant funding for the trial. RC has received grants from the Bill and Melinda Gates Foundation during the conduct of this trial. BK has previously received grant funding from GSK and Pfizer to conduct vaccine research at the MRC Unit in The Gambia, although not for vaccines in any way related to the vaccines used in this trial. MN and PRC have previously received grants from Sanofi-Pasteur unrelated to this trial. All other authors declare no competing interests

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