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 (⅓) $\log_2$ 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

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,