Immunogenicity and safety of a novel monovalent high-dose inactivated poliovirus type 2 vaccine in infants: a comparative, observer-blind, randomised, controlled trial

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Summary

Background Following the proposed worldwide switch from trivalent oral poliovirus vaccine (tOPV) to bivalent types 1 and 3 OPV (bOPV) in 2016, inactivated poliovirus vaccine (IPV) will be the only source of protection against poliovirus type 2. With most countries opting for one dose of IPV in routine immunisation schedules during this transition because of cost and manufacturing constraints, optimisation of protection against all poliovirus types will be a priority of the global eradication programme. We assessed the immunogenicity and safety of a novel monovalent high-dose inactivated poliovirus type 2 vaccine (mIPV2HD) in infants.

Methods This observer-blind, comparative, randomised controlled trial was done in a single centre in Panama. We enrolled healthy infants who had not received any previous vaccination against poliovirus. Infants were randomly assigned (1:1) by computer-generated randomisation sequence to receive a single dose of either mIPV2HD or standard trivalent IPV given concurrently with a third dose of bOPV at 14 weeks of age. At 18 weeks, all infants were challenged with one dose of monovalent type 2 OPV (mOPV2). Primary endpoints were seroconversion and median antibody titres to type 2 poliovirus 4 weeks after vaccination with mIPV2HD or IPV; and safety (as determined by the proportion and nature of serious adverse events and important medical events for 8 weeks after vaccination). The primary immunogenicity analyses included all participants for whom a post-vaccination blood sample was available. All randomised participants were included in the safety analyses. This trial is registered with ClinicalTrials.gov, number NCT02111135.

Findings Between April 14 and May 9, 2014, 233 children were enrolled and randomly assigned to receive mIPV2HD (117 infants) or IPV (116 infants). 4 weeks after vaccination with mIPV2HD or IPV, seroconversion to poliovirus type 2 was recorded in 107 (93·0%, 95% CI 86·8–96·9) of 115 infants in the mIPV2HD group compared with 86 (74·8%, 65·8–82·4) of 115 infants in the IPV group (difference between groups 18·3%, 95% CI 5·0–31·1; p<0·0001), and median antibody titres against poliovirus type 2 were 181 (95% CI 72·0–362·0) in the mIPV2HD group and 36 (18·0–113·8) in the IPV group (difference between groups 98·8, 95% CI 60·7–136·9; p<0·0001). Serious adverse events were reported for six (5%) of 117 infants in the mIPV2HD group and seven (6%) of 116 infants in the IPV group during the 8-week period after vaccination; none were related to vaccination. No important medical events were reported.

Interpretation Our findings lend support to the use of mIPV2HD as an option for stockpiling for outbreak response or primary protection in selected areas at risk for emergence of poliovirus type 2 during the next phase of the polio eradication plan.

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Introduction

The worldwide eradication of polio is closer than ever, with the number of cases caused by wildtype poliovirus decreasing substantially in recent years.[1] Currently, only two countries, Pakistan and Afghanistan, are regarded as endemic for polio, where transmission of wild poliovirus has never been interrupted.[2] Also, of the three serotypes of wild poliovirus, only type 1 is currently circulating in these endemic countries. Wild poliovirus type 2 is deemed eradicated because the last naturally occurring case was seen in 1999. However, Sabin poliovirus type 2 accounts for roughly 97% of recent circulating vaccine-derived poliovirus outbreaks that typically occur in areas with low immunisation coverage and about 26–31% of cases of vaccine-associated paralytic poliomyelitis.[3] No cases of wild poliovirus type 3 have been reported since November, 2012, the longest period ever for interruption of type 3 circulation.

With such historic progress being made in interrupting transmission of wild poliovirus, estimates suggest that the current burden of vaccine-related poliomyelitis is probably greater than that caused by wild poliovirus.[1] The overall worldwide risk of vaccine-associated paralytic poliomyelitis is estimated to be 4·7 cases per million livebirths, which means an annual incidence of about 498 cases.[3] Additionally, the mean number of reported

Research in context

Evidence before this study

In 2012, to phase out the use of live type 2 poliovirus vaccine, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recommended that trivalent oral polio vaccine (tOPV) be replaced with bivalent oral polio vaccine (bOPV) containing only poliovirus types 1 and 3 in all countries by 2016. This change is to be preceded by the introduction of at least one dose of conventional trivalent inactivated poliovirus vaccine (IPV) in routine immunisation programmes to provide immunity to poliovirus type 2. However, a dose of inactivated poliovirus type 2 higher than the standard dose (8 D-Ag units) may be needed to ensure adequate immunity. With the aim of improving type 2 immunogenicity with a single dose, a new monovalent high-dose inactivated poliovirus vaccine (mIPV2HD), which contains four times the standard dose of inactivated poliovirus type 2 (32 D-Ag units), was formulated. Higher D-Ag content of IPV was investigated by Salk and co-workers in a series of dose-ranging studies several decades ago. We searched PubMed for papers published between Jan 1, 1955, and Feb 28, 2013, with the terms "IPV", "high-dose", "poliovirus", and/or "type 2" and identified several published reports of clinical trials investigating high-dose IPV formulated from inactivated Sabin strains of poliovirus. However, we are not aware of any other published study in which a monovalent high-dose inactivated vaccine was compared with trivalent IPV in a mixed bOPV-IPV schedule, and where mOPV2 was used to assess intestinal immunity in such schedules.

Added value of this study

To our knowledge, this study is the first to report data for safety and humoral and intestinal immunogenicity of mIPV2HD formulation in a naive infant population using a mixed bOPV-IPV schedule. The humoral immune response to poliovirus type 2 with mIPV2HD was superior to that of IPV and the intestinal immunity to poliovirus type 2 was similar in both groups. These results provide evidence that mIPV2HD can be safely used in infants and show that a combined bOPV-mIPV2HD schedule would adequately protect against all three poliovirus types.

Implications of all the available evidence

With the upcoming worldwide switch from tOPV to bOPV, the only protection against poliovirus type 2 will come from IPV. In view of the supply and cost constraints of IPV, higher immunogenicity against poliovirus type 2 from a single dose of a monovalent high-dose formulation could be of advantage in settings at risk of emergence of this serotype. Our study showed an excellent safety and immunogenicity profile of mIPV2HD compared with currently available IPV and therefore is an important addition to the clinical evidence base for vaccine options for the polio endgame.

cases of circulating vaccine-derived poliovirus has been 76 per year during the period between 2005 and 2013.[1] By contrast, the total number of polio cases caused by wildtype strains was 416 in 2013 and 359 in 2014.[4] Therefore, vaccination policies for the eradication programme need to ensure that adequate focus is given to the elimination of all types of polioviruses to achieve and sustain polio eradication in the long term.

With this epidemiological backdrop, the Polio Eradication and Endgame Strategic Plan 2013–2018 was developed by the Global Polio Eradication Initiative (GPEI) in 2013 with the aim of wiping out the last cases of polio from all causes by 2018.[5] As a first step towards eliminating vaccine-related polio disease, the Endgame Plan recommends replacement of trivalent oral poliovirus vaccine (tOPV, which protects against types 1, 2, and 3), with bivalent oral poliovirus vaccine (bOPV, which protects against types 1 and 3), by April, 2016, preceded by the introduction of at least one dose of inactivated poliovirus vaccine (IPV) in routine immunisation programmes worldwide. From 2016 onwards, a mixed bOPV-IPV regimen in the Expanded Program on Immunization schedule is recommended, in which the one dose of IPV would be used with the primary intent to prime the population for immunity against poliovirus type 2. Additionally, this dose of IPV will boost immunity against types 1 and 3. The final step of the Endgame Plan would be to stop all OPV use after 2018–19 and to use only IPV for protection against polio.[5,6] This strategy was endorsed by the Strategic Advisory Group of Experts on immunization (SAGE) in October, 2015.[7]

The current formulation of IPV with D-antigen (D-Ag) content of 40, 8, and 32 units for poliovirus types 1, 2, and 3, respectively, in IPV stand-alone or combination vaccines was established on the basis of a series of pivotal studies by Salk and his co-workers.[8–12] Although the formulations containing 320-32-64 and 80-8-16 D-Ag units produced higher rates of seroconversion, the 40-8-32 D-Ag unit formulation was chosen because it induced sufficient immune response in infants after administration in full primary series of three or more doses and could be manufactured in adequate quantities.[13] The immune response from IPV to poliovirus type 2 is low and might be related to its sensitivity to formalin inactivation.[14] When given at or after 2 months of age, currently available IPV provides 32–77% seroconversion against poliovirus type 2.[15–18] Achieving better protection against poliovirus type 2 from a single dose of inactivated vaccine could have substantial public health benefit, particularly during the period when tOPV will be replaced by bOPV worldwide, putting type 2 protection at some risk.

With the aim of improving type 2 immunogenicity with a single dose, monovalent high-dose inactivated