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Effect of booster doses of poliovirus vaccine in previously vaccinated children, Clinical Trial Results 2013

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ABSTRACT

Background: Considering the current polio situation Pakistan needs vaccine combinations to reach maximum population level immunity. The trial assessed whether inactivated poliovirus vaccine (IPV) can be used to rapidly boost immunity among children in Pakistan.
Methods: A five-arm randomized clinical trial was conducted among children (6–24 months, 5–6 years and 10–11 years). Children were randomized in four intervention arms as per the vaccines they received (bOPV, IPV, bOPV + vitamin A, and bOPV + IPV) and a control arm which did not receive any vaccine. Baseline seroprevalence of poliovirus antibodies and serological immune response 28 days after intervention were assessed.
Results: The baseline seroprevalence was high for all serotypes and the three age groups [PV1: 97%, 100%, 96%, PV2: 86%, 100%, 99%, PV3: 83%, 95%, 87% for the three age groups respectively]. There was significantly higher rate of immune response observed in the study arms which included IPV (95–99%) compared with bOPV only arms (11–43%), [$p < 0.001$]; Vitamin A was not associated with improved immune response. Immune response rates in the IPV only arm and IPV + bOPV arm were similar [$p > 0.5$].
Conclusion: IPV has shown the ability to efficiently close existing immunity gaps in a vulnerable population of children in rural Pakistan.

1. Introduction

The goal to eradicate polioviruses worldwide was adopted in 1988 and since then the number of paralyzed persons due to polioviruses has decreased by over 99.9%. In 2014, the World Health Organization (WHO) reported 359 cases of paralytic poliomyelitis due to wild polioviruses worldwide [1]. In the end of 2015, the remaining endemic areas with wild poliovirus circulation were limited to security compromised parts of Pakistan and Afghanistan. In Nigeria, no new cases of polio have been reported in 2015, and in September 2015 Nigeria has been removed from the list of poliovirus endemic countries by WHO [2]. Despite the dramatic reduction in cases of poliomyelitis, it is proving difficult for the Global Polio Eradication Initiative (GPEI) to finally complete the eradication by interrupting the last chains of transmission in these endemic areas; and exportations of wild polioviruses from the endemic areas into polio-free countries have occurred in multiple occasions, sometimes causing large outbreaks of poliomyelitis [3].

In Pakistan, progress has been made in 2015 compared with 2014: as of October 2015, Pakistan had reported 36 cases of poliomyelitis caused by wild poliovirus; compared with 223 for the same period in 2014 [1]. Most of the success of the eradication program is due to large scale use of Oral Poliovirus Vaccine (OPV). The elimination of wild poliovirus type 2 in 1999, and possibly type 3 in 2013, as well as significant reduction of cases caused by wild poliovirus type 1 was achieved with OPV [4]. OPV has been proven to be an excellent vaccine with its ability to induce mucosal immunity; provide for secondary spread to contacts; ease of administration; and low price, however the vaccine has limitations such as low immunogenicity in some tropical countries [5,6]; and, in very rare circumstances, the live virus in OPV may cause paralysis to vaccine recipients (Vaccine Associated Paralytic Poliomyelitis or VAPP); in addition, OPV may genetically revert and regain neurovirulence and cause paralysis, this mutated virus with ability to spread within communicates is referred to as Circulating Vaccine Derived Poliovirus cVDPV [7,8]. To address the low OPV immunogenicity in

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certain settings, the GPEI developed new formulations of OPV, including monovalent and bivalent OPV (mOPV and bOPV) vaccines [9,10]. To overcome low OPV immunogenicity in some settings, GPEI has implemented multiple targeted campaigns with a combination of OPV and the Inactivated Poliovirus Vaccine (IPV) administered at the same time since 2013 [11].

IPV has been used for many decades in combination with OPV or on its own in routine immunization programs throughout the world. Its safety and high humoral immunogenicity is well established; and recent data demonstrated IPV's ability to boost mucosal immunity in individuals who had been immunized with OPV previously [12–14]. In this trial, we compared serological response to poliovirus vaccines administered to previously OPV immunized children with the objective to assess whether IPV can be used to rapidly close the immunity gap among children in Pakistan who live in areas of high poliovirus transmission risk. We also explored whether adding one dose of vitamin A administered together with OPV will improve immunogenicity.

2. Methods

The Ethical Review Committee of the Aga Khan University, the National Bioethics Committee of Pakistan and the Ethical Review Committee of the World Health Organization, Geneva granted the approval of this randomized controlled trial. We took written informed consent from the parents or care givers of the selected participants. All activities followed the guidelines of Good Clinical Practice; the trial protocol was registered with the Australian New Zealand Clinical Trials Registry bearing identifier ACTRN 12612000264886. The Aga Khan University, Pakistan conducted this study. The World Health Organization provided technical and financial support. Sera for antibody titers were tested at Centers of Disease Control and Prevention, Atlanta, USA.

This was a five arm community based randomized controlled superiority trial in a Pakistani children residing in district of Matiari in Sindh province. The trial activities were conducted between March 2012 and August 2013. The primary outcome of the study was the immune response against the booster doses of polio vaccine given to previously vaccinated children. There were five arms in the study four of them were intervention arms while the fifth one was control arm. The arms were classified as (bOPV), (IPV), (bOPV + Vitamin A), (bOPV + IPV) and (Control) arms. We enrolled healthy children aged 6–24 months, 5–6 years and 10–11 years, permanently residing in the study area after having a written informed consent the parents. Children with known bleeding disorders, chronic illness, severe malnutrition and acute infections were excluded. Enrolled children were randomized into one of five study arms. All study personnel were trained in Good Clinical Practices (GCP).

For this study we obtained OPV and IPV from WHO-prequalified producers. IPV (lot number G0445-1) was procured from Novartis and bOPV (lot number H5328-1) was procured from Glaxo Smith Kline. The bOPV was formulated to contain at least $10^{6}CCID_{50}$ of Sabin poliovirus type 1 and at least $10^{5.8}CCID_{50}$ of Sabin poliovirus type 3. Each IPV dose (0.5 mL) is formulated to contain 40 D antigen units of type 1, 8 D antigen units of type 2, and 32 D antigen units of type 3 poliovirus.

We estimated the sample size by using the ANOVA Multiple comparison technique in a single factor ANOVA study. Sample size of 202 was calculated for each group assuming a baseline seroprevalence of 80%, power of 80% the between group difference of 20% at a significance level of 0.05. Assuming an attrition of 20%, the final sample size was set to be 1350 (270 in each study arm). The participants were randomized in one of the study Arm, the randomization was done after the formal consent procedure. The study supervisor did the randomization through hidden entry envelope randomization technique to assign the groups. Randomization lists and envelopes were prepared by an independent research officer at data management unit of Aga Khan University. The randomization numbers and groups were inserted in the envelopes starting from 0001 to 1590 having equal number of allocations in each group in the block of 30.

Following randomization we enrolled children in the study and data was collected on socio demographic indicators and prior vaccination history. Height and weights were also measured to establish the nutritional status of the children.

Blood sample (3 mL) was collected by trained phlebotomist using standard venipuncture techniques on Day 0 and Day 28. After collection the blood samples were allowed to clot, centrifuged to separate serum, and transported to the Nutrition Research Laboratory (NRL) at the Aga Khan University in Karachi under cold chain conditions where they were stored at −20 °C until shipment to the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA. Neutralizing antibodies were determined by the method recommended by the World Health Organization [15] at the Enterovirus Laboratory, CDC. Serial dilutions of serum (starting at 1:8 and ending at 1:1024) were incubated with 100 $TCID_{50}$ of poliovirus types 1, 2, and 3 at 36 °C for 3 h before 1–2 × 104 HEp-2 (Cincinnati) cells were added to each well. The HEp-2 (Cincinnati) cell line is particularly sensitive for polioviruses. We assigned unobserved titers values of less than 8 if they were less than the starting dilution, and of more than or equal to 1448 if they were more than the final dilution.

Vaccination history for OPV received through routine immunization was assessed from vaccination cards when available or by parental recall if card were not available. OPV doses received through Supplemental Immunization Activities (SIAs) were estimated by the number of SIA rounds that were conducted in the study area during the life of each child. Enrolled subjects were not vaccinated with any supplementary OPV doses during the study period. Adverse events following vaccination were identified by site investigators and reviewed by the principal investigator. Children were observed for 30 min following the administration of the vaccine for immediate adverse events; parents were instructed to immediately report back to the health centers if adverse events occurred. Serious adverse events were reported for review to the Data and Safety Monitoring Board, Ethical Review Committees of the Aga Khan University and the World Health Organization.

After the enrolment procedures the child was followed on Day 3 and Day 7 for any possible adverse event and then was brought again at the study clinic on day 28 for blood draw. This blood sample was drawn to assess the sero conversion and boosting that occurred in different vaccine combinations compared to the control group. The primary outcome measure for the study was the seroconversion and boosting in immunity. Seropositivity was defined as reciprocal titers of poliovirus neutralizing antibodies $\geqslant 8$; seroconversion was defined as the change from seronegative to seropositive (from reciprocal titer of <8 to $\geqslant 8$); and boosting was defined as $\geqslant$4-fold increase in titers. In this study, "immune response" combines both boosting and seroconversion. The analysis of immune response was restricted to infants with a baseline serological titer of $\leqslant 362$ to ensure that a 4-fold boosting response could be achieved since the highest titer tested was 1:1448 [16].

2.1. Data management and analysis

Data was dual entered on pre structured screens on visual fox pro. Demographic, clinical and Laboratory data were merged and the Statistical analysis was per-formed using STATA version 12. The proportion of seroconversion in different study arms was compared

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