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Effect of substituting IPV for tOPV on immunity to poliovirus in Bangladeshi infants: An open-label randomized controlled trial

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ABSTRACT

Background: The Polio Endgame strategy includes phased withdrawal of oral poliovirus vaccines (OPV) coordinated with introduction of inactivated poliovirus vaccine (IPV) to ensure population immunity. The impact of IPV introduction into a primary OPV series of immunizations in a developing country is uncertain.

Methods: Between May 2011 and November 2012, we enrolled 700 Bangladeshi infant-mother dyads from Dhaka slums into an open-label randomized controlled trial to test whether substituting an injected IPV dose for the standard Expanded Program on Immunization (EPI) fourth tOPV dose at infant age 39 weeks would reduce fecal shedding and enhance systemic immunity. The primary endpoint was mucosal immunity to poliovirus at age one year, measured by fecal excretion of any Sabin virus at five time points up to 25 days post-52 week tOPV challenge, analyzed by the intention to treat principle.

Findings: We randomized 350 families to the tOPV and IPV vaccination arms. Neither study arm resulted in superior intestinal protection at 52 weeks measured by the prevalence of infants shedding any of three poliovirus serotypes, but the IPV dose induced significantly higher seroprevalence and seroconversion rates. This result was identical for poliovirus detection by cell culture or RT-qPCR. The non-significant estimated culture-based shedding risk difference was −3% favoring IPV, and the two vaccination schedules were inferred to be equivalent within a 95% confidence margin of −10% to +4%. Results for shedding analyses stratified by poliovirus type were similar.

Conclusions: Neither of the vaccination regimens is superior to the other in enhancing intestinal immunity as measured by poliovirus shedding at 52 weeks of age and the IPV regimen provides similar intestinal immunity to the four tOPV series, although the IPV regimen strongly enhances humoral immunity. The IPV-modified regimen may be considered for vaccination programs without loss of intestinal protection.

1. Introduction

Global eradication of virulent poliovirus appears tantalizingly close as measured by the total incidence of polio cases per year, but challenges remain in the pursuit of this public health landmark. Oral poliovirus vaccine (OPV) provides excellent intestinal immunity and is highly effective at reducing viral fecal-oral transmission but contains live attenuated poliovirus, which can result in vaccine-associated paralytic poliomyelitis and reversion to a virulent circulating vaccine-derived strain. To eliminate that risk, a global switch to an inactivated poliovirus vaccine will be necessary. Injected inactivated poliovirus vaccine (IPV) induces excellent

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systemic immunity and does not revert to neurovirulence, but has a complex effect on intestinal immunity. IPV-only regimens are apparently inferior as measured by fecal transmission after challenge, but may depend on whether IPV is administered subsequent to doses of OPV [1–5]. Since a single coordinated global transition to solely administering inactivated vaccine is infeasible, and mass campaigns need repetition, primary vaccination schedules that blend doses of OPV with IPV will be necessary during the transition period. The optimal schedule to maintain individual immunity while minimizing transmission of active poliovirus is unknown and is likely to vary by region. Very recently in 2015, the Bangladesh government announced that it would incorporate an IPV dose into the existing four dose Expanded Program on Immunization (EPI) schedule and hence data on the effects of these substitutions will be critical for public health decision-makers.

We designed a randomized clinical trial to test the intestinal immune response and immunogenicity of a modified Bangladesh Expanded Program on Immunization (EPI) vaccination regimen with injected IPV substituted for the fourth trivalent OPV (tOPV) dose, administered at 39 weeks of age in this trial. Based on previous studies that suggested IPV can enhance intestinal immunity and reduce poliovirus transmission by fecal shedding, we hypothesized that infants receiving the IPV dose after OPV intestinal priming would enjoy enhanced intestinal and humoral immunity with lowered susceptibility to viral shedding.

2. Materials and methods

2.1. Study population and design

Seven hundred (700) eligible neonatal infant–mother dyads were enrolled into the Performance of Rotavirus and Oral Poliovirus Vaccines in Developing Countries (PROVIDE) study in Dhaka, Bangladesh, as participants in two separate concomitant randomized open-label clinical trials to study infant poliovirus and rotavirus vaccine interventions, structured in a 2×2 factorial design. The four study groups were: (1) dose 4 IPV + No Rotavirus; (2) dose 4 IPV + Rotavirus; (3) dose 4 tOPV + No Rotavirus; (4) dose 4 tOPV + Rotavirus. The study was funded by the Bill and Melinda Gates Foundation. The study design and baseline clinical characteristics of the PROVIDE study cohort have been reported [6]. The poliovirus outcomes were assumed to be independent of co-administered rotavirus vaccine in the second concurrent trial [7]. Pregnant mothers from the Mirpur slum area of Dhaka were screened for eligibility and upon live birth, enrolled by field research assistants into the cohort. Eligibility for enrollment required delivery of a live infant of maximum age 7 days, absent frank congenital abnormalities, birth defects, or irregular stool frequency or consistency. Oral tOPV (GlaxoSmithKline) doses were given at infant age 6, 10, and 14 weeks, and either oral tOPV or injected IPV (IMOVAX®, Sanofi Pasteur) at 39 weeks. The government EPI schedule for poliovirus vaccination at the time of the trial design in 2010 was 6, 10, 14, and 38 weeks. The fourth tOPV dose was administered at 39 weeks in this trial but was within the preferred vaccination window and was chosen to balance participant and clinic burden, safety, and science in the context of a larger program to study the impact of environmental enteropathy on vaccine under-performance. The rationale for this choice is described in more detail in the Supplementary Appendix. Participants received free primary care during the study.

The study protocol was reviewed and approved by the icddr,b Research Review and Ethical Review Committees, and by Institutional Review Boards at the Universities of Virginia and Vermont. All mothers signed an informed consent on behalf of their infant child before enrollment into the study and were free to withdraw at will. The study was conducted in compliance with the Declaration of Helsinki and the Belmont Report [8]. Good Clinical Practice standards were applied throughout with monitoring of study progress and adverse events by an independent medical monitor. Severe adverse events were recorded for the full protocol period until the final day 25 fecal excretion sample at 52 weeks of age; adverse events linked to vaccine administration were recorded for 48 h post-vaccination. Adverse events were reported to ethics boards or committees per local requirements.

2.2. Randomization and masking

Before enrollment, sequential study subject identification numbers (SIDs) were randomized to one of four 2×2 treatment groups using permuted block randomization with random block size (4 or 8). Sealed envelopes with treatment group assignment for each SID were produced by the Data Coordinating Center and sent to the Dhaka clinic. SIDs were assigned sequentially to each infant/mother pair at the enrollment visit. The envelope was opened at the infant's week six visit. Neither mothers nor clinic staff were masked. The laboratories that performed the outcomes assays to detect poliovirus in stool by cell culture (National Polio Laboratory) and serum neutralizing antibody (Centers for Disease Control and Prevention) were masked to specimen trial arm assignment.

2.3. Procedures

The poliovirus vaccine cell culture-based fecal excretion assays were performed at the National Polio Reference Laboratory, Institute of Public Health, Government of Bangladesh as per the WHO Polio Laboratory Manual [9,10]. Extraction of viral RNA from stool and fecal multiplex RT-qPCR detection has been previously described for the PROVIDE study [11,12]. Samples were tested for serum neutralizing antibodies (SNAb) at the Centers for Disease Control and Protection (Atlanta, Georgia, USA) using a standard microneutralization assay for antibodies to poliovirus types 1, 2, and 3 according to established protocols [13,14]. Each specimen was run in triplicate in the same assay run; neutralization titers were estimated by the Spearman-Kärber method[15] and reported as the reciprocal of the calculated 50% endpoint. A serum sample was considered seropositive if antibodies were present at $\geq$1:8 dilution, antibody titers <1:8 were seronegative.

2.4. Outcomes

The primary outcome was the presence of any of three Sabin poliovirus vaccine types determined by cell culture, in any of five fecal samples collected after tOPV challenge dose at week 52, sampled at day 0 (immediately pre-vaccination), and days 4, 11, 18, and 25 days post-vaccination. Secondary poliovirus shedding outcomes were similar but stratified to each Sabin poliovirus type. These outcomes were also assayed by direct fecal RT-qPCR detection as confirmation. A secondary RT-qPCR-based quantitative index of total viral shedding was tested by poliovirus type. Secondary measures of humoral immunity were seropositivity for neutralizing antibody by serotype one week post-intervention dose at 39 weeks, and seroconversion from 18 to 40 weeks. Week 18 SNAb titer was adjusted for residual maternal antibody, assuming 28 days half-life for maternally transmitted antibody measured at 6 weeks. Failure to seroconvert was defined as less than +2 change in $\log_2$ titer at week 40 if adjusted SNAb (week 18) $\leq$8.5 and >2.83; SNAb (week 40) <10.5 if adjusted SNAb (week 18) >8.5 and <10.5; and SNAb (week 40) $\leq$2.83 if adjusted SNAb (week 18) $\leq$2.83 (seronegative) [16]. Infants with $\log_2$ titer 10.5 at week 18 were excluded from seroconversion analyses.