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BRIEF REPORT

Inactivated Poliovirus Vaccine Closing the Type 2 Immunity Gap in Vietnam

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This was a cross-sectional community-based serological survey of polio antibodies assessing the immunogenicity of inactivated poliovirus vaccine (IPV) focusing on poliovirus serotype 2. IPV was administered to 5-month-old children. Type 2 antibody seroprevalence when measured 1 month after IPV administration was >95%. One IPV dose successfully closed the immunity gap.

Key words. inactivated poliovirus vaccine; polio eradication; poliomyelitis; routine immunization; Vietnam.

Afghanistan and Pakistan are the only 2 remaining endemic countries for wild poliovirus (WPV); 5 paralytic WPV cases have been reported from these 2 countries in 2021; however, in the same period, 774 paralytic cases of polio were caused by vaccine-derived poliovirus [1].

The Sabin poliovirus strains in the live oral poliovirus vaccine (OPV) may, in rare circumstances, genetically revert into a form causing paralytic disease. This circulating vaccine-derived poliovirus (cVDPV) can cause outbreaks that are clinically indistinguishable from outbreaks caused by WPV [2]. The "Polio Eradication & Endgame Strategic Plan 2013-2018" laid out the framework for interruption of WPV transmission and the phased withdrawal of OPV in order to eliminate the risk of VDPV [3]. In April 2016, there was a globally synchronized switch from trivalent OPV (tOPV) to bivalent OPV (bOPV). Since that date, no live poliovirus type 2 (PV2) vaccine has been used in routine immunization (RI) programs anywhere in the world [4].

In parallel with OPV withdrawal, the Strategic Advisory Group of Experts (SAGE) on Immunization recommended the universal introduction of at least 1 dose of inactivated poliovirus vaccine (IPV) to provide base immunity for PV2 and to mitigate the risks caused by cVDPV2 [5, 6]. This recommendation has now been modified and includes 2 IPV doses [7]. Almost 2 years after the tOPV to bOPV switch, a large number of countries have not been able to introduce IPV because of IPV supply constraints leading to country-wide IPV stock-outs [8, 9]. Vietnam was unable to introduce IPV until October 2018 leaving more than 2 birth cohorts of children unprotected from PV2. A study from 2018 in Vietnam showed a rapid decline of PV2 neutralizing antibodies in these cohorts of children [10]. As IPV became available, 1 dose of IPV was introduced in the Vietnamese RI schedule at 5 months of age, following a schedule of 3 doses of bOPV administered at 2, 3, and 4 months of age.

The objective of this study was to demonstrate the impact of IPV introduction on PV2 immunity. As the secondary objective, we compared the achieved seroprevalence through regular RI activities versus through vaccination in the controlled setting of this study. In addition, we report seroprevalence of antibodies against poliovirus types 1 and 3. The data were collected in the second half of 2020.

METHODS

This study was a cross-sectional community-based serological survey of polio antibodies in the Nga Sơn district of the Thanh Hoa province in Vietnam. The Thanh Hoa province is located ~160 km from Hanoi with a population of ~3.4 million in 27 districts.

The primary objective of the study was to quantify the level of serological protection (seroprevalence) against PV2 in children who received 1 IPV dose either as part of the study or as part of the RI schedule. The secondary objective was to quantify the seroprevalence against PV1 and PV3 in children who received 1 IPV dose and 3 bOPV doses.

Children in 2 age groups were enrolled: 5-11 months (group 1)—these children had not yet received IPV—and children aged 12-15 months (group 2), who had received IPV dose as part of RI approximately 7 months before being enrolled in this study—the receipt of IPV was documented by vaccination card and verified through the National Immunization Information System.

A sample size was calculated to estimate seroprevalence assuming 60% seroprevalence after 1 dose of IPV at 5 months. This was calculated at the 95% confidence level with 10%

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precision using assumed seroprevalence levels. The resulting sample size was 93, which was inflated to 120 to account for possible challenges with blood draws, withdrawals, and sample management.

Parents/guardians of eligible children were approached by community health workers in 10 selected health centers and provided informed consent for enrollment. In group 1, one IPV dose was administered as part of the study, and 2 mL of peripheral blood was drawn in 2 instances: at enrollment (at the same time of IPV administration) and 30 days later. In group 2, blood was only drawn once at enrollment, no vaccine was administered, and no follow-up visit was organized.

Sera were analyzed at the Centers for Disease Control and Prevention (CDC) in Atlanta for the presence of neutralizing antibodies against all 3 polio serotypes using standard microneutralization assays [11]. Antibody titers were reported on a $\log_2$ scale. Seropositivity was defined as reciprocal titers of poliovirus neutralizing antibodies ≥1:8 (≥3 on $\log_2$ scale). The proportion of seropositive children and median antibody titers was calculated for each group. Highest reported antibody titer was 1:1448 (10.5 on $\log_2$ scale). In group 1, seroconversion for each serotype was defined as a change from seronegative at enrollment to seropositive post-IPV administration among children who were seronegative at enrollment. The seroprevalence and seroconversion, expressed as percentages, were presented along with Clopper-Pearson adjusted 95% confidence intervals (CIs) for proportions. The comparison of seroprevalence was performed using Fisher's exact test. The median titers across the groups were compared using the Wilcoxon rank-sum test. *P*-value < .05 was considered as statistically significant. STATA 17.0 was used for the statistical analysis of data.

RESULTS

A total of 128 children between the age of 5 and 11 months (group 1) and 130 children between the age of 12 and15 months (group 2) were enrolled. The analyzable number of children was 119/128 (93.0%) in group 1 and 130/130 (100%) in group 2; the sera from the remaining children were insufficient to complete the analysis or the children were lost to follow-up between the first and second study visits in group 1. The baseline study characteristics are presented in Table 1. All children had a vaccination card available with a date of IPV vaccine administration. The median age at IPV administration in group 1 was 6 months (95% CI, 6-7 months) compared with 5 months (95% CI, 5-6 months) in group 2 ($P = .043$).

Seroprevalence of PV2 antibodies in group 1 was 18 out of 119 (15.1%) before IPV (corresponding with the expected prevalence of maternal antibodies at 6 months of age) and 118/119 (99.2%) one month after verified administration of 1 IPV dose. In group 2, the type 2 seroprevalence was 77 out of 130 (59.2%) measured approximately 7 months after the IPV dose was administered as part of RI (Figure 1).

Seroprevalence of type 1 polio antibodies was 117/119 (98.3%) before and after IPV administration in group 1 and 129/130 (99.2%) in group 2. Type 3 seroprevalence was 60/119 (50.4%) before IPV; and 88/119 (73.9%) after IPV in group 1; and 77/130 (59.2%) in group 2 (Figure 1).

We assessed seroconversion in group 1 for all 3 serotypes. For serotype 2, it was 99% (100/101, 95% CI, 94.6-100); while for type 1 and type 3 it was 50% (1/2; 95% CI, 1.2-98.7) and 47.5% (28/59; 95% CI, 35.3-60.0), respectively.

Median type 2 antibody titers were significantly higher in group 1 compared with group 2 (6.50 vs 3.17; $P < 0.001$). Median antibody titers and reverse cumulative distribution curves for PV2 antibodies can be found in the Supplementary Material. In bivariate analysis, we did not find any risk factors for type 2 seronegativity.

DISCUSSION

Our study demonstrated that 1 dose of IPV administered at 5 months of age or later efficiently closed the immunity gap

Table 1. Distribution of Baseline Characteristics in the 2 Groups

	Group 1 N = 128 (5-11 mo)		Group 2 N = 130 (12-15 mo)		
	n/N	% or IQR	n/N	% or IQR	*P*-value
Female child	65/128	50.8	71/130	54.6	.541
Median age at enrollment (months, IQR)	6	5-7	13	12-14	**<.001**
Child received 3 doses of pentavalent vaccine	84/128	65.6	130/130	100.0	**<.001**
Child did not receive any pentavalent vaccine	1/128	0.8	0/130	0	.307
Child received IPV	0/128	0	130/130	100.0	**<.001**
Age at IPV administration (median months, 95% CI)		6 (6-7)		5 (5-6)	**.043**
Child received 3 doses of bOPV	80/128	62.5	129/130	99.2	**<.001**
Child did not receive any bOPV	1/128	0.8	0/130	0	.307

All children had a vaccination card available with a date of IPV vaccine administration. Abbreviations: IQR, interquartile range; IPV, inactivated poliovirus vaccine; bOPV, bivalent oral poliovirus vaccine. Bold indicates statistical significance at $P<0.05$.

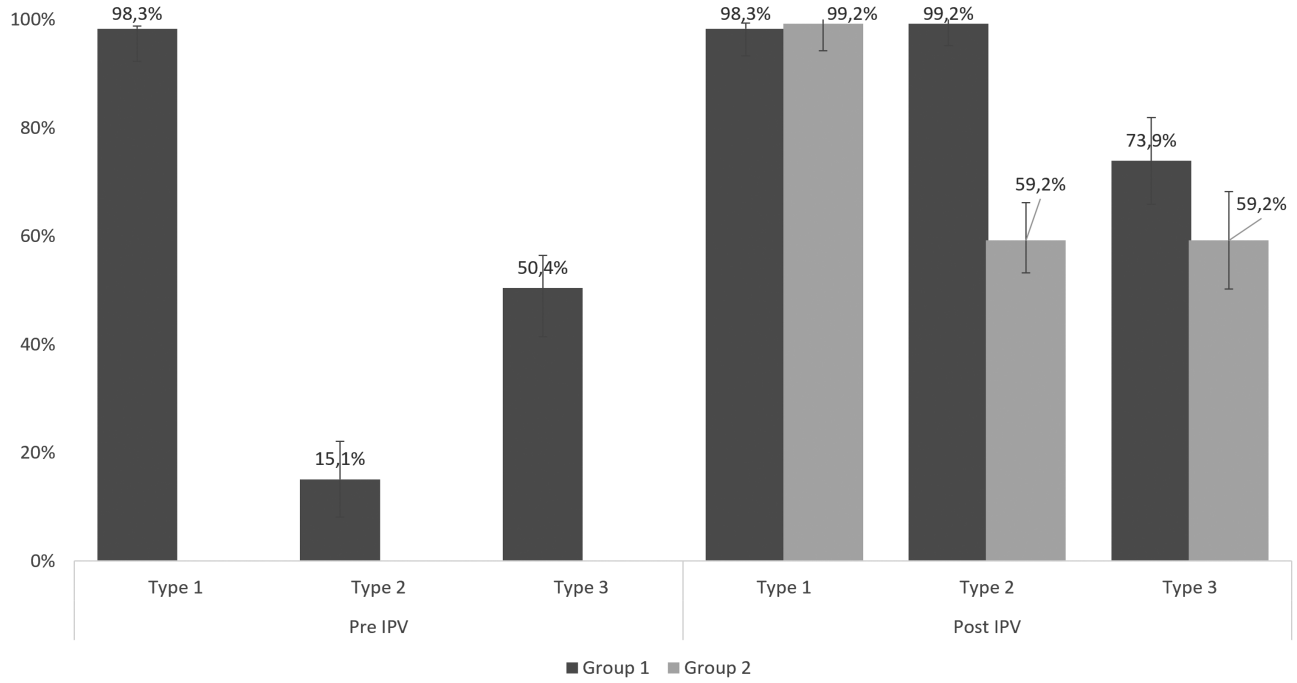

Figure 1. Seroprevalences of types 1, 2, and 3 by age groups (group 1: 5-11 months; group 2: 12-15 months). Samples were collected 1 month after IPV administration in group 1, and 7-10 months after IPV administration in group 2. IPV, inactivated poliovirus vaccine.

for poliovirus type 2. We were surprised at the finding that type 2 seroprevalence and antibody titers were significantly different when measured approximately 7 months after IPV compared with measurement 1 month after IPV administration (59.2% vs 99.2%, respectively), although this difference is in 2 separate cohorts of children. We were unable to distinguish whether this difference was due to waning of humoral immunity during the 7-month period between IPV administration and blood draw in group 2, or due to children in group 1 having received IPV on average 1 month later in life than in group 2, or because the history of IPV administration in RI is not certain—vaccination records may not be precise. Previous studies in Pakistan and elsewhere described antibody waning after IPV but not at such scale nor speed [10, 12, 13]. IPV improper storage or low batch efficacy must also be considered as potential causes of this difference, albeit quite unlikely in the case of Vietnam where the immunization program is well supervised.

Recently, SAGE recommended that 2 doses of IPV are included in all RI schedules worldwide to provide better immunogenicity [14]; however, our findings suggest that 1 IPV dose administered at a later age (≥5 months) is sufficiently immunogenic.

A limitation of the study was the acquisition of the vaccination history record of the children. The history was provided by the parents/guardian through immunization cards (100% children with card) and verified against the Vietnamese information system. It is possible that the vaccination cards were not a correct reflection of vaccination history. The fact that children in group 1 were sampled 1 month after IPV and children in group 2 were sampled approximately 7-10 months after IPV administration introduced bias due to possible waning of antibodies and comparison of possibly disparate groups of children.

Our study provides evidence regarding the importance of IPV in closing the type 2 immunity gap. Furthermore, the study findings underline the imperative to catch up cohorts of Vietnamese children that had been missed by IPV because of stock-outs and provided evidence that 1 dose of IPV, when administered at 5 months of age or later, is sufficient to provide close to 100% serological protection in case of VDPV2 emergence or importation.

Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

Notes

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