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Rapid Disappearance of Poliovirus Type 2 (PV2) Immunity in Young Children Following Withdrawal of Oral PV2-Containing Vaccine in Vietnam

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Abstract

Background.—Due to global shortage of inactivated poliovirus vaccine and withdrawal of oral vaccine containing poliovirus type 2 (PV2), a PV2-containing vaccine was not used in Vietnam May 2016 to October 2018. We assessed the population immunity gap to PV2.

Methods.—A cross-sectional survey in children aged 1–18 months was carried out in January 2018. One blood sample per child was analyzed for presence of poliovirus neutralizing antibodies. In children with detectable anti-PV2 antibodies, a second sample was analyzed 4 months later to distinguish between passive (maternally derived) and active (induced by secondary transmission or vaccination) immunity.

Results.—Sera were obtained from 1106/1110 children. Seroprevalence of PV2 antibodies was 87/368 (23.6%) at age 1–7 months, 27/471 (5.7%) at 8–15 months, and 19/267 (7.1%) at 16–18 months. Seroprevalence declined with age in the 1–7 months group; in the 8–18 months group there was no significant change with age. Four months later, 11/87 (14%), 9/27 (32%), and 12/19 (37%) remained seropositive in 1–7, 8–15, and 16–18 months age groups, respectively.

Conclusions.—We found declining immunity to PV2, suggesting Vietnam is at risk for an outbreak of type 2 vaccine-derived poliovirus following virus importation or new emergence.

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Keywords

poliomyelitis; vaccination; eradication; Vietnam

The Global Polio Eradication Initiative (GPEI) has achieved interruption of wild poliovirus transmission in all but a few endemic areas of Nigeria, Pakistan, and Afghanistan [1]. However, the use of live oral poliovirus vaccine (OPV) must cease to complete eradication [2]. To accomplish this, a phased withdrawal of OPV is in progress, starting with serotype 2 (PV2), as part of the “Polio Eradication and Endgame Strategic Plan 2013–2018” [3]. The withdrawal of OPV started in April 2016 with a globally synchronized switch from trivalent OPV (tOPV) to bivalent OPV (bOPV; containing poliovirus 1 and 3 only) [4]. Since that date, no live PV2 vaccine has been used in routine immunization programs anywhere in the world.

In parallel with OPV withdrawal, the Strategic Advisory Group of Experts on Immunization of the World Health Organization recommended the universal introduction of at least 1 dose of inactivated poliovirus vaccine (IPV) in routine immunization schedules worldwide to provide base immunity for PV2 and as a risk mitigation measure (ie, to protect children from paralysis should type 2 wild or vaccine-derived poliovirus emerge or be introduced) [5]. However, starting in 2016, the GPEI has been experiencing an acute IPV supply shortage that affected almost 50 countries and caused either delays in IPV introduction or stock-outs in countries that had already introduced IPV in their routine immunization programs [6].

Vietnam was among the countries that had been unable to introduce IPV in the public health sector until October 2018 due to this global IPV shortage. Therefore, about 4 million children born between March 2016 and June 2018 had no opportunity to develop PV2 immunity through routine immunization. However, a small percentage of Vietnamese children, estimated to be <5% nationwide, were immunized with IPV purchased in private-sector healthcare facilities during this period [7].

Wild poliovirus type 2 was last detected worldwide in 1999 and the virus was declared eradicated in 2015 [8]. Despite the withdrawal of tOPV, outbreaks of type 2 circulating vaccine-derived polioviruses (cVDPV2) have been detected. From the time of the tOPV to bOPV switch until February 2019, 12 separate cVDPV2 outbreaks were reported from 7 countries in Asia and Africa [1]. Many additional VDPV2s, classified as ambiguous or immunodeficiency related, were detected from paralyzed persons, from immunodeficient children, or in environmental samples around the world. In this epidemiological context, an importation of a VDPV2 into Vietnam could result in a large-scale outbreak of paralysis if a large proportion of the population remains immunologically naive to PV2.

Previous studies have suggested that in countries with high OPV coverage, the transmission of vaccine viruses continues for about 3 months after the cessation of OPV use and the emergence of VDPVs in a well immunized population is unlikely [9–11].

We assessed the population immunity gap to PV2 in children born in Vietnam after the withdrawal of PV2-containing vaccine. Specifically, we aimed to quantify the level of

serological protection (seroprevalence) against PV2 in different age groups in Vietnam and to evaluate whether continued circulation of PV2 might have persisted after removal of tOPV by assessing anti-PV2 antibodies in age groups not immunized by PV2-containing vaccine.

METHODS

We performed a cross-sectional survey with serial measurements at baseline and 4 months, in 2 provinces of Vietnam, Binh Phuoc and Phu Tho. Binh Phuoc province in the south of Vietnam is about 120 km from Ho Chi Minh City, with a population of 930 000 in 11 districts and is in an area with tropical climate. Phu Tho province in the north of Vietnam is about 100 km from Hanoi, with a population of approximately 1.5 million in 13 districts and has a temperate climate. The rationale for selecting 1 province in the north and 1 in the south was to provide representation of populations living in the temperate climate as well as those living in tropical climate, where poliovirus transmission is favored [12].

This study was approved by the Ethics Review Committee of the National Institute of Hygiene and Epidemiology, Ministry of Health, Vietnam, and by the World Health Organization's Ethics Review Committee in Geneva.

In stage 1, children 1 and <19 months of age were selected to participate in the study. This age group was selected to represent children with and without residual maternal antibodies, as well as those born around the time of the tOPV to bOPV switch.

Within each province, 1 district was selected on the basis of convenience and all children in the study age groups residing in that district were identified by community health workers and invited to participate in the study until the targeted sample size was achieved. Eligibility criteria included healthy child (child without chronic or acute disease at the time of interview), residence in the selected area, and no known history of IPV immunization in the private sector. Parents of eligible children were approached and, if consent was provided, enrolled. The subjects were then invited to the nearest health center where a 2-mL blood sample was collected by venipuncture and a short questionnaire completed.

The blood specimens were allowed to clot. Sera were separated and transported to national laboratories in Hanoi or Ho Chi Minh City, where they were stored at -20°C until shipment to the Centers for Disease Control and Prevention in Atlanta. The sera were tested for the presence of poliovirus neutralizing antibodies using standard neutralization assays. Seropositivity was defined as reciprocal titers of poliovirus neutralizing antibodies ≥ 8 . The maximum reciprocal titer reported was 1:1448; therefore, the value of 1:1448 indicated reciprocal titer $\geq 1:1448$ and the minimum titer reported was $<1:5.7$ [13].

Vaccination history of the enrolled children was recorded from vaccination cards and an electronic national immunization information system when available; otherwise, the history was obtained through parental recall.

Stage 2 of the survey included children whose neutralization test from stage 1 confirmed presence of antibodies against PV2. These children were again invited to the nearest health

center and 1 additional blood draw was carried out. The handling of blood samples, shipping, and analysis of sera from stage 2 was the same as in stage 1. Stage 1 was performed in January 2018 and Stage 2 in May 2018.

The required sample size for stage 1, assuming overall PV2 seroprevalence of at least 15% with a precision of $\pm 2.5\%$, 95% confidence interval (CI), and comprising 20% refusals, was found to be 1050 children.

For analysis of PV2 serology, we categorized children into 3 age groups: (1) children aged 1–7 months who likely had maternal antibodies (in our sample these children were born between June 2017 and Dec 2017); (2) children without known exposure to PV2 aged 8–15 months (in our sample these children were born between October 2016 and May 2017); and (3) children born 2–5 months after the tOPV to bOPV switch with potential secondary exposure to PV2 through their close contacts who had been vaccinated with tOPV prior to the switch. This last group were the oldest children in our sample, aged between 16 and 19 months and born between June and September 2016.

The seroprevalence for all 3 PV types were expressed as percentages with exact binomial confidence intervals in each age group. Median reciprocal titers were reported for each of the 3 serotypes. The 95th percentile bootstrap confidence intervals were presented for median titers, obtained from 10 000 bootstrap samples [14]. The median titers by age groups were compared using Kruskal-Wallis test. Seroprevalences for the 3 types were compared using χ^2 test with Bonferroni correction across the 3 age groups. Wilcoxon signed rank test was applied to compare the stage 1 and stage 2 median PV2 titers within each age group.

We estimated half-life of PV2 antibodies by calculating decline in reciprocal titers between stage 1 and stage 2 in children ≥ 7 months of age who had measurable PV2 antibodies at both stage 1 and stage 2. In these children, we averaged the decline in antibodies and expressed the decline as fold-decline per month, and then calculated the average time needed to reach half of the initial antibody titer [15].

RESULTS

In stage 1, the community health workers identified 4170 children in the 2 targeted provinces and approached 1255 eligible children for potential enrolment. We enrolled 1110/1255 (88.4%) children; the other children's parents did not provide consent. For stage 1, we present results from 1106/1110 (99.6%) enrolled children who provided analyzable blood samples. There were 133 children eligible to be enrolled in stage 2, with 118 (88.7%) of these children providing acceptable specimens for analysis. The remaining children were either lost to follow-up or received IPV from the private sector between stage 1 and stage 2 (Supplementary Figure 1).

Baseline demographic characteristics are presented in Table 1. Of note, the number of doses of bOPV received by children according to vaccination history was significantly higher in Phu Tho than in Binh Phuoc in all age groups ($P < .05$).

Seroprevalence of PV2 antibodies was 87/368 (23.6%) in the 1–7 months age group, 27/471 (5.7%) in the 8–15 months age group, and 19/267 (7.1%) in the 16–18 months age group (Figure 1). The seroprevalence in the youngest age group was significantly higher than in the other 2 age groups ($P < .05$), but there was no significant difference in seroprevalence between the 2 older age groups ($P = .082$). There were no significant differences in PV2 seroprevalence between provinces ($P = .051$). The seroprevalence declined with age between the first and seventh month of age. In children 8–18 months old, it remained without significant change, ranging between 0% and 15% (Figure 2).

Stage 2 was carried out 4 months after stage 1 with children who had been seropositive for PV2 in stage 1. Between stage 1 and stage 2, 76/87 (86%), 18/27 (68%), and 7/19 (37%) previously seropositive children became seronegative for PV2 in the 1–7, 8–15, and 16–18 months age groups, respectively (Figure 3). The difference was significant for comparison between the 1–7 months age group with either the 16–18 months age group ($P < .001$) or the 8–15 months age group ($P = .03$). However, the difference between the 8–15 months and 16–18 months age groups was not significant ($P = .055$).

Median reciprocal titers of anti-PV2 antibodies were not significantly different between stage 1 and stage 2 for all age groups (Table 2). Five children were included in the estimation of half-life of PV2 antibodies (those who were 7 months of age at stage 1 and had measurable PV2 antibodies at both stage 1 and stage 2). In these children, we estimated the half-life of maternal antibodies for PV2 to be 40 days (95% CI, 29–47 days).

Seroprevalence of anti-PV1 and anti-PV3 antibodies was very high in the 2 older age groups (Figure 4) with no significant differences between provinces despite previously documented lower vaccine immunogenicity in tropical areas [16]. There were 54/118 (45.7%) children who received bOPV between stage 1 and stage 2. We assessed seroconversion among those who had been seronegative at stage 1. There were 15/54 and 24/54 seronegative children for anti-PV1 and anti-PV3 antibodies, respectively, at stage 1; of these, 14/15 (93.3%; 95% CI, 61.7%–98.4%) and 23/24 (95.8%; 95% CI, 78.9%–99.9%) seroconverted for PV1 and PV3, respectively.

DISCUSSION

In the 2 selected provinces, the seroprevalence of anti-PV2 antibodies was low in children born after the tOPV to bOPV switch except in the youngest age group protected by maternal antibodies. More children in the youngest age group became seronegative in stage 2 than in the other age groups, indicating that the younger children had maternal antibodies that waned between stage 1 and stage 2. The origin of antibodies in the older children is less clear; there was little waning observed between stage 1 and stage 2, indicating that the antibodies were induced either by undeclared vaccination with IPV prior to stage 1 or through secondary contact with live PV2 emanating from tOPV recipients. There was an increase, albeit statistically not significant ($P = x .08$), in PV2 antibody prevalence in children born shortly after the switch, which may represent more intense secondary transmission of PV2 in the period immediately after the switch. Previous studies estimated that PV2 remains in the populations for about 3 months after the last use of PV2-containing

vaccine [9, 11]; our data indicated that it is unlikely that PV2 transmission persisted for longer than that in the studied provinces of Vietnam. Further supporting this finding, laboratory analysis of stool samples from children with acute flaccid paralysis, carried out as part of regular surveillance, did not detect any PV2 virus in the postswitch period [1].

In our study, we did not observe a significant difference in seroprevalence of any serotype between the northern and the southern provinces and we were therefore unable to confirm differential immunogenicity of bOPV in tropical and temperate climates.

The half-life of polio maternal antibodies was previously estimated to be between 28 and 30 days [17]. In our sample, we observed the half-life to be 40 days; however, because only 5 children were included in this analysis, our confidence interval is wide and includes the estimates from previous studies [15].

The seroprevalence of anti-PV1 and anti-PV3 antibodies achieved with 3 doses of bOPV was very high and provided an unbiased confirmation that the Expanded Program on Immunization in Vietnam is of high quality and able to reach children even in more remote areas such as the Binh Phuoc province.

Our study had some limitations. Due to delay in study initiation, no children born prior to the switch were included, which would have better demonstrated the influence of tOPV on PV2 antibodies prior to the switch from tOPV to bOPV. In addition, as IPV was available in the private market in Vietnam, it may have been administered to some of the study subjects despite the fact that history of IPV was among exclusion criteria. We selected the study districts in each province on the basis of convenience. We do not consider that this selection of districts introduced bias because there are only minor socioeconomic or other within-province differences.

Catch-up campaigns with IPV are planned to protect the missed children from paralysis in case of a cVDPV2 outbreak; however, the timing of such campaigns is still uncertain. The ongoing shortage of IPV and prioritization of IPV for endemic and other high-risk areas puts Vietnam and other similar countries at risk of cVDPV2 outbreak, with potentially serious consequences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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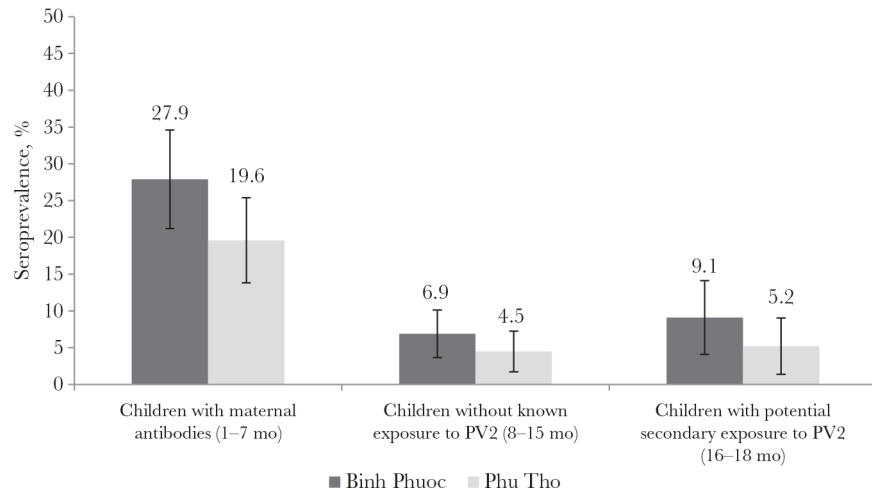


Figure 1. Seroprevalence of poliovirus type 2 (PV2) antibodies per province and age group. Error bars are 95% confidence intervals.

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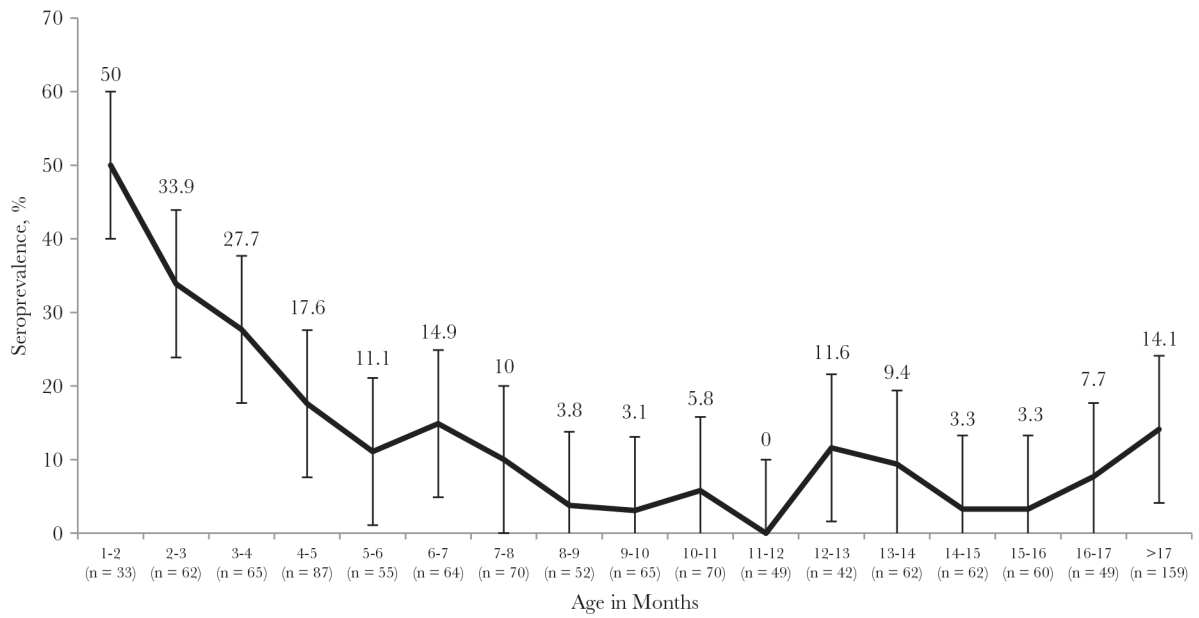


Figure 2. Seroprevalence of poliovirus type 2 antibodies, from Binh Phuoc and Phu Tho provinces combined, per age in months. Error bars are 95% confidence intervals.

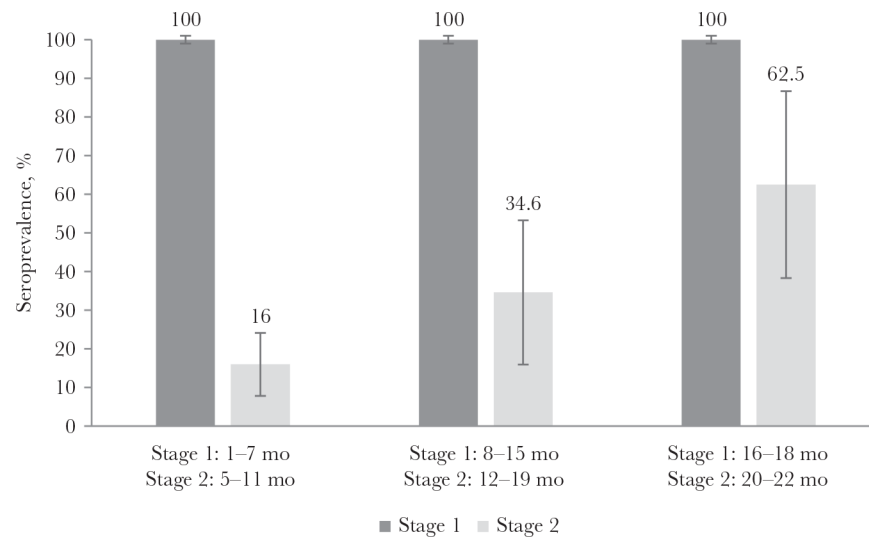


Figure 3. Seroprevalence of poliovirus type 2 antibodies at stage 2 among children who had been seropositive for PV2 in stage 1. Age groups in stage 1 and stage 2 are given on x-axis; stage 2 was 4 months after stage 1.

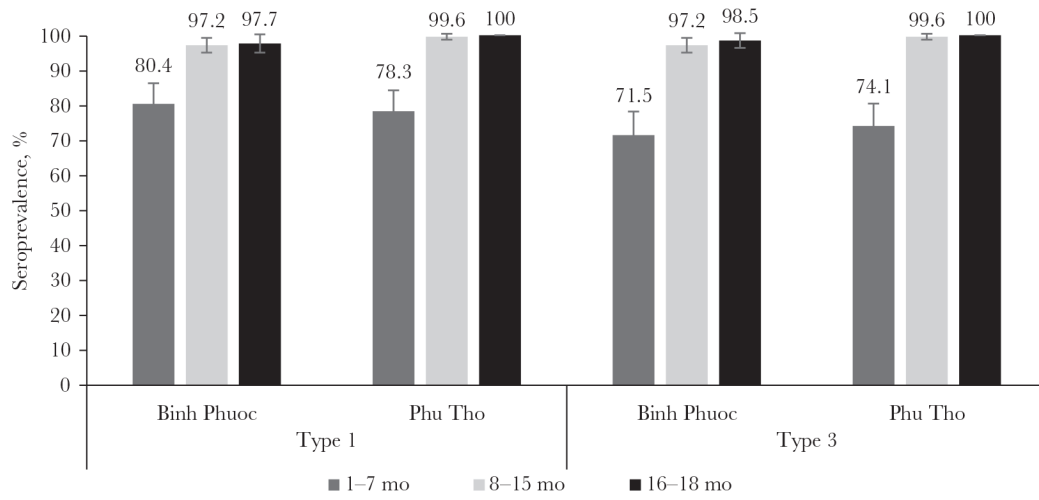


Figure 4. Seroprevalence of antipoliovirus type 1 (PV1) and anti-PV3 antibodies at stage 1, per age in months. Error bars are 95% confidence intervals. Age group, poliovirus type, and province are given on the x-axis.

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Table 1.
Baseline Demographics and Vaccination History of Children in the 3 Age Groups

	No. of Children/ Total No. Enrolled (%)		
	1–7 mo	8–15 mo	16–18 mo
Gender female			
Binh Phuoc	88/179 (49.2)	123/247 (49.8)	65/132 (49.2)
Phu Tho	86/189 (45.5)	98/224 (43.8)	66/135 (48.9)
Mother illiterate			
Binh Phuoc	4/179 (2.2)	6/247 (2.4)	5/132 (3.8)
Phu Tho	2/189 (1.1)	1/224 (0.4)	1/135 (0.7)
3 Doses of bOPV history ^a			
Binh Phuoc	35/179 (22.4)	211/247 (879)	121/132 (93.8)
Phu Tho	76/189 (49.4)	211/224 (96.8)	130/135 (99.2)

Abbreviation: bOPV, bivalent oral poliovirus vaccine.

^aThere was a significantly higher proportion of children with 3OPV doses in Phu Tho than Binh Phuoc in all age groups ($P < .05$).

Table 2.

Median Reciprocal Titer of Anti-PV2 Antibodies in Stage 1 and Stage 2 Among Children Positive for PV2 in Both Stages

Age Group	n	Median Reciprocal Titer (CI)		P Value
		Stage 1	Stage 2	
1–7 mo	12	11 (9–57)	11 (10–23)	.859
8–15 mo	8	39 (11–724)	171 (9–362)	.674
16 mo	10	142 (23–1152)	379 (16 to 1448)	.208

Abbreviations: CI, 95% confidence interval; PV2, poliovirus type 2.

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