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Factors determining anti-poliovirus type 3 antibodies among orally immunised Indian infants

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ABSTRACT

Background: Among the three poliovirus serotypes, the lowest responses after vaccination with trivalent oral polio vaccine (tOPV) are to serotype 3. Although improvements in routine immunisation and supplementary immunisation activities have greatly increased vaccine coverage, there are limited data on antibody prevalence in Indian infants.

Methods: Children aged 5–11 months with a history of not having received inactivated polio vaccine were screened for serum antibodies to poliovirus serotype 3 (PV3) by a micro-neutralisation assay according to a modified World Health Organization (WHO) protocol. Limited demographic information was collected to assess risk-factors for a lack of protective antibodies. Student's *t*-test, logistic regression and multilevel logistic regression (MLR) model were used to estimate model parameters.

Results: Of 8454 children screened at a mean age of 8.3 (standard deviation [SD]-1.8) months, 88.1% (95% confidence interval (CI): 87.4–88.8) had protective antibodies to PV3. The number of tOPV doses received was the main determinant of seroprevalence; the maximum likelihood estimate yields a 37.7% (95% CI: 36.2–38.3) increase in seroprevalence per dose of tOPV. In multivariable logistic regression analysis increasing age, male sex, and urban residence were also independently associated with seropositivity (Odds Ratios (OR): 1.17 (95% CI: 1.12–1.23) per month of age, 1.27 (1.11–1.46) and 1.24 (1.05–1.45) respectively).

Conclusion: Seroprevalence of antibodies to PV3 is associated with age, gender and place of residence, in addition to the number of tOPV doses received. Ensuring high coverage and monitoring of response are essential as long as oral vaccines are used in polio eradication.

1. Introduction

The global incidence of polio cases has declined with only two countries now considered polio endemic [1]. This remarkable reduction was achieved by the effective use of vaccines, with oral poliovirus vaccines (OPV) playing the greatest role in decreasing disease and interruption of transmission in developing countries. Although OPV has many practical advantages for mass immunisation in field settings [2], like other oral vaccines the immunogenicity and effectiveness of OPV is impaired in lower-income countries [3–5]. Potential contributing factors for low immunogenicity in these settings include a high prevalence of diarrhoea, infection of the gut with other pathogens, malnutrition, micronutrient deficiencies, and tropical enteropathy [3,6].

Abbreviations: tOPV, trivalent oral polio vaccine; PV3, poliovirus serotype 3; WHO, World Health Organization; MLR, multilevel logistic regression; SD, standard deviation; CI, confidence interval; OR, odds ratio; OPV, oral poliovirus vaccine; mOPV3, serotype-3 monovalent oral poliovirus vaccine; IPV, inactivated poliovirus vaccine; HSC, health sub-centre; PHC, primary health centre; SIA, supplemental immunisation activity; CDC, Centers for Disease Control and Prevention; $TCID_{50}$, median tissue culture infective dose; IQR, interquartile range; χ^2, Chi-square.

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Diarrhoea is independently associated with a failure to seroconvert following administration of OPV after adjusting for potential confounders like season, breast feeding, mass campaigns and maternal antibodies [7]. In northern India, reduced take of OPV was significantly associated with season [8]. Concurrent enteric infections with lower OPV response in low-income settings have been described [9,10]. Tropical enteropathy, resulting from high environmental exposure to enteric pathogens, is common among children living in poverty and may be associated with poor response to oral vaccines, both in terms of primary antibody response and its longevity [11].

Serological data are informative about vaccination coverage, immunogenicity, secondary spread of vaccine poliovirus and exposure to wild-type infections. However, there are limited published data available on antibodies to polio in Indian children in the recent past, particularly from southern India. Table 1 presents a comparison of recent data on seroprevalence from developing countries.

After vaccination with tOPV, antibody responses are greatest to poliovirus type 2 and usually lowest to serotype 3 (PV3) [3]. In 2009, the baseline seroprevalence of antibodies to PV3 among infants aged 6–9 months was just 48% in a community-based randomised clinical trial conducted in a high risk area, Moradabad in northern India [12].

We now report a community-based seroprevalence study of anti-poliovirus type 3 antibodies among infants of age 5–11 months who had not previously received inactivated poliovirus vaccination (IPV) residing in rural and urban areas of Vellore district of Tamil Nadu, southern India. This study was done to screen for a clinical trial on the effect of azithromycin on the immunogenicity of serotype-3 monovalent oral poliovirus vaccine (mOPV3) given to healthy infants without antibodies to serotype-3 poliovirus [10], which found that removal of bacterial pathogens by azithromycin treatment did not increase the proportion of children who responded to mOPV3.

2. Methods

2.1. Study design and setting

The cross sectional survey was carried out in 210 health subcentres (HSC, each serves a population of 5000) of 42 primary health centres (PHC, each serving approximately 20,000–30,000) in 14 health blocks (serving 80,000–120,000 and as referral facility for 3–4 PHCs) of the rural and urban parts of Vellore district of Tamil Nadu between July 2014 and January 2015.

Infants in the study area receive routine immunisation either from government or private health care facilities, tOPV is given with BCG at birth and at 6, 10 and 14 weeks along with DPT in the study area. IPV was not available in the government sector during the study period. The last supplemental immunisation activity (SIA) was in February 2014 and no SIAs were carried out during the study period.

The Christian Medical College Institutional Review Board and the Imperial College Research Ethics Committee approved the study and appropriate central and state governmental permissions were obtained prior to conducting the screening. Investigators and study coordinators met with local community leaders, private and government health providers and informed them about the study and requested their cooperation.

2.2. Study population

We did a door to door survey to identify infants and written informed consent was obtained from all willing parents of eligible healthy infants aged between 5 and 11 months. The Village Health Nurses (VHNs) of the concerned Health sub-centres discussed the study with potential participants and motivated the families to participate. A screening camp was organised in each village, and parents brought the child to the camp. Each infant was assigned a unique screening identification number and basic demographic details were collected. A study physician examined the infant for eligibility for screening and recorded the infant's age and polio vaccination history from the immunisation cards. Additional doses received during National Immunization Days were obtained from verbal history as these doses are not recorded on immunisation cards and if immunisation cards were not available, the mother's statement was recorded. Exclusion criteria included children who had received IPV-through private healthcare providers, had any congenital or chronic illness or had high grade fever or any other illness that prevented participation as decided by the study physician. Infants temporarily excluded because of minor illnesses were asked to visit the camp held in a neighbouring village.

2.3. Laboratory methods

Blood specimens were collected by trained phlebotomists and study nurses. Samples were stored on ice and delivered to the laboratory on the same day. Assessment of poliovirus-specific neutralising antibodies to serotype 3 was done using a microneutralisation assay according to the World Health Organization (WHO) protocol with modifications [13]. Briefly, a 2-fold dilution of each serum sample (50 μl) ranging from 1/4 to 1/8 was mixed with 50 μl of approximately 100 median tissue culture infective dose ($TCID_{50}$) of Sabin 3 poliovirus in replicate wells at each dilution and the mixture was incubated at 37 °C (5% CO_2) for 1 h. 100 μl of Vero cell suspension (5000 cells/well) was then added to all the wells and the plates were incubated for 3 days at 37 °C (5% CO_2). As part of quality control, standard polio antisera from the U.S. Centers for Disease Control and Prevention were included in each run. For each assay, a back-titration titre of 30–300 $TCID_{50}$ was considered acceptable. Cell controls were included in each assay. A reciprocal titre of <8 was considered non-protective.

Table 1
Type specific seroprevalence of anti-poliovirus antibodies among infants in lower and upper middle income countries.

Place	World Bank Income classification	Year of study	Age group	Sample size	Sero prevalence			References
					Type 1 (%)	Type 2 (%)	Type 3 (%)	
Egypt	Lower middle income	2004	6–11 months	973	99.0	99.0	91.0	[36]
Moradabad, India	Lower middle income	2007	6–12 months	467	88.0	70.0	75.0	[19]
Islamic republic of Iran	Upper middle income	2010	7 months	72	84.7	95.8	70.8	[37]
Kano, Northern Nigeria	Lower middle income	2011	6–9 months	161	81.0	75.0	73.0	[22]
Northern India	Lower middle income	2010	6–7 months	1280	98.0	66.0	77.0	[38]
Pakistan	Lower middle income	Published in 2013	6–11 months	554	96.0	87.9	86.7	[39]
Sri Lanka	Lower middle income	2014	9–11 months	100	96.0	98.0	85.0	[15]