Waning Intestinal Immunity After Vaccination With Oral Poliovirus Vaccines in India

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Background. The eradication of wild-type polioviruses in areas with efficient fecal-oral transmission relies on intestinal mucosal immunity induced by oral poliovirus vaccine (OPV). Mucosal immunity is thought to wane over time but the rate of loss of protection has not been examined.

Methods. We examined the degree and duration of intestinal mucosal immunity in India by measuring the prevalence of vaccine poliovirus in stool samples collected 4–28 days after a “challenge” dose of OPV among 47,574 children with acute flaccid paralysis reported during 2005–2009.

Results. Previous vaccination with OPV was protective against excretion of vaccine poliovirus after challenge, but the odds of excretion increased significantly with the time since the child was last exposed to an immunization activity (odds ratio, 1.39 [95% confidence interval .99–1.97], 2.04 [1.28–3.25], and 1.31 [1.00–1.70] comparing ≥6 months with 1 month ago for serotypes 1, 2, and 3, respectively). Vaccine administered during the high season for enterovirus infections (April–September) was significantly less likely to result in excretion, especially in northern states (odds ratio, 0.57 [95% confidence interval .50–.65], 0.58 [.41–.81], and 0.48 [.40–.57] for serotypes 1, 2, and 3).

Conclusions. Infection with OPV (vaccine “take”) is highly seasonal in India and results in intestinal mucosal immunity that appears to wane significantly within a year of vaccination.

The live-attenuated oral poliovirus vaccine (OPV) and the inactivated poliovirus vaccine both induce systemic immunity against paralytic poliomyelitis. The Global Polio Eradication Initiative has relied exclusively on the oral vaccine, however, because of its superior ability to induce mucosal immunity against infection and excretion of virus in the intestine [1–3]. Immunization with OPV has been shown to reduce the prevalence, duration, and titer of vaccine poliovirus shedding in stool samples after administration of a subsequent “challenge” dose of the live-attenuated vaccine [4, 5]. Reduction in virus shedding is associated with an increase in poliovirus-specific immunoglobulin A (IgA) secreted in the intestine [6]. Secretory IgA is not found after immunization with inactivated poliovirus vaccine except among individuals with prior exposure to live poliovirus, which explains the more limited impact of this vaccine on poliovirus shedding in the intestine after subsequent challenge [7].

Estimates of the degree of mucosal immunity induced by OPV are largely based on studies from higher-income countries [8, 9]. In lower-income countries, the immunogenicity of OPV is lower than in higher-income countries, resulting in an impaired mucosal immune response [10–15]. In India we recently found that vaccination with monovalent and trivalent OPVs induced intestinal mucosal immunity against reinfection but that the effectiveness of the vaccines varied significantly according to location and formulation [16]. Furthermore, the incomplete nature of mucosal
immunity was found to permit frequent infection with wild-type poliovirus among vaccinated children who were close contacts of children with poliomyelitis [17].

Intestinal mucosal immunity to poliovirus is likely to wane over time, contributing to the ability of the virus to reinfect the gut [18, 19]. However, the rate of decline in protection against reinfection with poliovirus after vaccination with OPV has not been established. In this article we examine factors affecting the degree of intestinal mucosal immunity induced by monovalent and trivalent OPVs and the rate of loss of protection after vaccination by measuring poliovirus excretion in stool samples collected after “challenge” with an additional dose of OPV. Stool samples were collected from children with acute flaccid paralysis (AFP) reported in India during 2005–2009, the majority of whom (98.5%) were paralyzed by causes unrelated to poliovirus. We discuss the implications of our findings for immunization strategy in India and elsewhere.

METHODS

Data Collection

Children <15 years of age with AFP have been routinely reported through a network of health workers throughout India since 1997 [20]. As part of efforts to eradicate polio, approximately 50,000 children with AFP are investigated annually. Cases undergo an initial clinical and epidemiological investigation, including the collection of information on the number of doses of OPV received and the date of receipt of the most recent dose, and a follow-up investigation at 60 days to test for residual weakness [21]. Two stool samples are collected ≥24 hours apart and within 14 days of the onset of paralysis to allow laboratory testing for the presence of poliovirus and other enteroviruses [22]. Samples yielding positive results for poliovirus are investigated by intratypic differentiation tests and genetic sequencing to determine whether the isolated virus is vaccine related or wild type [21].

Biannual nationwide campaigns to vaccinate children <5 years old with OPV began in India in 1995 in an attempt to supplement the relatively low coverage achieved through routine health services [20]. Vaccination campaigns targeted at high-risk areas commenced in 2000 and have been implemented with increasing frequency since that time. Until 2005 only trivalent OPV was used during these supplementary immunization activities (SIAs). In 2005, serotype 1 and 3 monovalent OPVs began to be used during certain SIAs in response to the unrestricted circulation of these serotypes and the global eradication of serotype 2 wild-type poliovirus. The vaccination history for children reported with AFP did not include the type of vaccine used, so we inferred the number of doses of trivalent and monovalent OPV received by children with AFP before stool sample collection from the number of doses of OPV (all types) that they were reported to have received through SIAs and their exposure to SIAs based on their date of birth and district of residence, using methods published elsewhere [23]. Briefly, we multiplied the reported number of OPV doses received through SIAs by the proportion of these activities that used vaccine of a given type to obtain the expected number of doses of each vaccine type received. OPV received through routine health services was always trivalent. The type of the most recent (challenge) vaccine administered before stool sample collection could be determined from the vaccine used by the SIA that took place at the time of the reported date of receipt of the last OPV dose. For infants ≤20 weeks old who were reported to have received both supplementary and routine doses of OPV, we assumed that if the date of receipt of their last reported dose of OPV was at the time of an SIA, then this dose had been received through that SIA; otherwise it was assumed to have been received through routine services.

Institutional ethics approval for this study was not required because this was a retrospective analysis of a national surveillance database, free of personally identifiable information and recording use of standard vaccines licensed by the National Regulatory Authority of the Government of India.

Analysis of Vaccine Poliovirus Excretion After Administration of OPV

Children ≤5 years old with onset of AFP reported between 1 January 2005 and 31 December 2009 were identified for inclusion in the analysis. Children with wild-type poliovirus isolated from ≥1 stool sample, inadequate stool samples, or an incomplete vaccination history were excluded. The prevalence of excretion of each of the 3 vaccine poliovirus serotypes among children with 2 stool samples taken between 4 and 28 days after administration of either trivalent or monovalent OPV was examined in relation to variables describing demographic characteristics, vaccination history, enterovirus season, and recent history of poliomyelitis in the district of residence (excretion of virus up to 3 days after challenge was excluded, because it has been suggested that this can be the result of transient passage of vaccine in the stool rather than infection of the intestine [24]). Odds ratios for excretion of vaccine poliovirus were calculated and 95% confidence intervals (CIs) produced on the basis of the normal approximation to the log likelihood about the maximum likelihood estimate of the odds on a log scale.

Vaccine poliovirus excretion after challenge depends on the degree of poliovirus-specific intestinal mucosal immunity, the infectiousness of the vaccine virus, and other factors affecting the susceptibility of the intestine to infection. We used multivariate logistic regression to examine the impact of variables likely to affect mucosal immunity and the response to vaccination and to examine potential confounding among these variables. We included in the multivariate regression model all
variables that were significant at \( P < .05 \) in the initial univariate analysis. Nonsignificant variables were eliminated in a stepwise manner, and the final model with interaction terms chosen on the basis of maximum likelihood [25]. Time since OPV challenge was explicitly included in the multivariate model to account for the observed exponential decrease in the odds of vaccine virus excretion after infection [16]. Children with vaccine poliovirus in \( \geq 1 \) stool sample, onset of paralysis after the most recent reported OPV dose, and residual paralysis at follow-up were excluded from the multivariate regression analysis as potential cases of vaccine-associated paralysis [26]. We also excluded children who were reported to have received <2 doses of OPV containing the relevant serotype or who were not exposed to an SIA before challenge. Therefore, the association between poliovirus shedding after OPV challenge and the time since exposure to an SIA that used vaccine containing the relevant serotype was examined.

### RESULTS

A total of 266,095 children were reported in India with AFP during 2005–2009. Of these 47,574 met the inclusion criteria for the univariate analysis; 11,407 had stool samples collected 4–28 days after trivalent OPV, 31,157 after serotype 1 monovalent OPV, and 50,107 after serotype 3 monovalent OPV. In the univariate analysis a number of variables including the age, vaccination history, location, enterovirus season, time since the last reported case of poliomyelitis in the district, and enterovirus season were significantly associated with excretion of vaccine poliovirus 4–28 days after administration of OPV for some or all serotypes (Table 1).

In the final multivariate regression model, past vaccination with serotype 1 and 3 monovalent OPVs was strongly protective against excretion of vaccine poliovirus on subsequent challenge with OPVs containing these serotypes (Table 2). The impact of trivalent OPV on vaccine virus excretion was less marked with the exception of serotype 2. The greater effectiveness of monovalent vaccines is confirmed by the significantly higher probability of infection and excretion that was observed after administration of these vaccines (Table 2).

Vaccine virus excretion after OPV administration was significantly lower in the high season for enterovirus transmission compared with the low season, indicating poorer vaccine “take” at this time of year (isolation of nonpolio enteroviruses among children with AFP is higher April through September) (Table 2, Figure 1). In addition, even after adjustment for seasonal effects, vaccine virus excretion after OPV administration was less likely in the northern states of Uttar Pradesh and Bihar, the traditional strongholds for wild-type poliovirus transmission in India, compared with other parts of India (serotypes 1 and 3 only) (Table 2).

The prevalence of vaccine virus excretion after administration of OPV increased significantly with the time since a child was last exposed to an SIA that used OPV containing the relevant serotype (Table 2, Figure 1). The odds of excreting vaccine poliovirus among children exposed to an SIA \( \geq 6 \) months before challenge (mean, 9–15 months previously, depending on serotype) was 1.4–2.0 times that observed among children exposed in the month before challenge (defined as in the past 40 days because monthly SIAs typically occur 28–35 days apart). Furthermore, in the case of serotype 1, excretion of vaccine poliovirus was significantly higher in children exposed to an SIA just 2–5 months before challenge (compared with in the past 40 days). There was no significant difference in the increased odds of vaccine virus excretion with time since exposure to an SIA in Uttar Pradesh and Bihar compared with other states (likelihood ratio test; \( P = .57, .36, \) and .61 for serotypes 1, 2, and 3, respectively).

The time since the last reported case of poliomyelitis in a district was not associated with the prevalence of vaccine poliovirus excretion of the corresponding serotype in the final multivariate model. Alternative measures of past exposure to wild-type poliovirus based on the number of children with poliomyelitis reported in the same district or within 100 km of the center of the district also showed no significant association with excretion of vaccine poliovirus after challenge (data not shown).

### DISCUSSION

Vaccination with monovalent OPV was strongly protective against excretion of vaccine poliovirus after a subsequent dose of OPV and significantly more effective than trivalent OPV, in agreement with findings of previous studies [16, 27]. Here we show for the first time, however, that protection decreases significantly with time since exposure to an SIA. Given the high coverage achieved during SIAs (generally >90% according to independent monitoring data), for the majority of children the time since exposure to an SIA is equivalent to the time since vaccination. Consequently, these data suggest mucosal immunity wanes quite rapidly after OPV vaccination. We cannot establish the exact time scale for the loss of protection because we do not know whether an immunological response occurred at the time of vaccination (owing to the absence of data on serum antibody titers). However, the increased prevalence of excretion of challenge poliovirus several months after an SIA, even among children <2 years old (Supplementary Table 1), suggests that significant waning of intestinal mucosal immunity occurs within a year. This attenuation of protection occurs despite the possibility of secondary exposure to vaccine poliovirus excreted by other children who have received OPV and did not show any significant variation by location.

The reduction in intestinal mucosal protection may relate to decreases in the amount of poliovirus-specific IgA reaching...
the mucosa and secreted into the gut lumen, or potentially to declines in effectors of the innate immune response. A limited number of studies have examined secretory IgA titers in small numbers of children after administration of OPV and typically found more rapid decreases in fecal and nasopharyngeal IgA levels over a period of several months compared with the gradual decreases observed over several years for serum neutralizing immunoglobulin G. The relatively rapid decline in protection against reinfection with poliovirus that we observed may therefore be expected if protection against infection is mediated by high titers of poliovirus that we observed may therefore be expected if

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serotype 1 (Proportion)</th>
<th>Serotype 2 (Proportion)</th>
<th>Serotype 3 (Proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uttarakhand and Bihar</td>
<td>4.92 (395/6025)</td>
<td>4.17 (235/5637)</td>
<td>6.4 (390/6098)</td>
</tr>
<tr>
<td>Other states</td>
<td>3.27 (1128/34539)</td>
<td>4.82 (278/5770)</td>
<td>7.17 (740/10319)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4.9 (253/5165)</td>
<td>8.35 (131/1568)</td>
<td>9.3 (203/2182)</td>
</tr>
<tr>
<td>1</td>
<td>3.66 (483/13202)</td>
<td>4.13 (146/3537)</td>
<td>6.54 (330/5046)</td>
</tr>
<tr>
<td>2</td>
<td>3.33 (385/11549)</td>
<td>4.21 (124/2948)</td>
<td>7.11 (306/4304)</td>
</tr>
<tr>
<td>3</td>
<td>3.36 (251/7470)</td>
<td>3.37 (65/1926)</td>
<td>6.25 (176/2816)</td>
</tr>
<tr>
<td>4</td>
<td>2.92 (151/5178)</td>
<td>3.29 (47/1428)</td>
<td>5.56 (115/2069)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3.53 (634/17964)</td>
<td>4.17 (205/4913)</td>
<td>6.48 (456/7038)</td>
</tr>
<tr>
<td>Male</td>
<td>3.61 (889/24597)</td>
<td>4.74 (308/6492)</td>
<td>7.19 (674/9377)</td>
</tr>
<tr>
<td>Vaccine type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trivalent</td>
<td>4.2 (479/11407)</td>
<td>4.5 (513/11407)</td>
<td>5.62 (641/11407)</td>
</tr>
<tr>
<td>Monovalent</td>
<td>3.35 (1044/31157)</td>
<td>0.791 (0.178–0.883)</td>
<td>9.76 (489/5010)</td>
</tr>
<tr>
<td>Previous doses of OPV containing relevant serotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>16.1 (103/638)</td>
<td>17.7 (139/787)</td>
<td>13.5 (149/1103)</td>
</tr>
<tr>
<td>2–4</td>
<td>4.44 (116/2614)</td>
<td>0.241 (0.182–0.32)</td>
<td>8.32 (299/3595)</td>
</tr>
<tr>
<td>5–7</td>
<td>4.11 (229/573)</td>
<td>0.223 (0.174–0.285)</td>
<td>6.57 (274/4169)</td>
</tr>
<tr>
<td>8–11</td>
<td>3.48 (362/10393)</td>
<td>0.187 (0.148–0.237)</td>
<td>5.33 (209/3923)</td>
</tr>
<tr>
<td>≥12</td>
<td>3.05 (713/23346)</td>
<td>0.164 (0.131–0.205)</td>
<td>5.49 (199/3627)</td>
</tr>
<tr>
<td>Time since last reported case of poliomyelitis of relevant serotype in district</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>3.82 (450/11773)</td>
<td>1.02 (0.923–1.14)</td>
<td>8.66 (344/3973)</td>
</tr>
<tr>
<td>≥6 months</td>
<td>3.48 (1073/30791)</td>
<td>0.909 (0.812–1.02)</td>
<td>6.32 (786/12444)</td>
</tr>
<tr>
<td>Time since previous SIA containing vaccine virus of same serotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 days</td>
<td>2.91 (468/16074)</td>
<td>3.01 (32/1064)</td>
<td>6.2 (116/1872)</td>
</tr>
<tr>
<td>2–5 months</td>
<td>3.7 (843/22803)</td>
<td>1.28 (1.14–1.44)</td>
<td>6.45 (625/9686)</td>
</tr>
<tr>
<td>≥6 months</td>
<td>6.43 (58/902)</td>
<td>2.29 (1.73–3.04)</td>
<td>8.57 (231/2697)</td>
</tr>
<tr>
<td>Not alive at last SIA</td>
<td>5.53 (154/2785)</td>
<td>1.95 (1.62–2.35)</td>
<td>7.31 (158/2162)</td>
</tr>
<tr>
<td>Enterovirus season</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (October–March)</td>
<td>4.31 (834/19331)</td>
<td>5 (293/5855)</td>
<td>8.48 (684/8062)</td>
</tr>
<tr>
<td>High (April–September)</td>
<td>2.97 (689/23233)</td>
<td>0.678 (0.612–0.751)</td>
<td>5.34 (446/8355)</td>
</tr>
<tr>
<td>Total</td>
<td>3.58 (1523/42564)</td>
<td>4.60 (513/11407)</td>
<td>6.88 (1130/16417)</td>
</tr>
</tbody>
</table>

This analysis includes children from whom both stool samples were collected 4–28 days after administration of trivalent vaccine or monovalent vaccine containing the relevant serotype during 2005–2009.

Abbreviations: CI, confidence interval; NA, not applicable because serotype 2 wild poliovirus was last recorded in 1999 and monovalent vaccine containing this serotype has not been used; OPV, oral poliovirus vaccine; OR, odds ratio; SIA, supplementary immunization activity.

* Sex was not recorded for 2 children given trivalent OPV and 1 child given serotype 1 monovalent OPV.
Vaccine poliovirus excretion after administration of OPV was significantly less likely in Uttar Pradesh and Bihar than in other states, as well as during the high season for enteroviruses and other enteric infections (April–September) compared with the low season. This remained the case after accounting for any differences in vaccination status of children in the multivariate regression. The lower probability of vaccine poliovirus excretion (vaccine "take") after administration of OPV in Uttar Pradesh and Bihar is consistent with the lower efficacy of the vaccine against poliomyelitis previously estimated for these states [12].

The observation of a seasonal response to vaccination is consistent with studies in The Gambia demonstrating poorer immunogenicity and effectiveness of OPV during the rainy season [32, 33]. However, the seasonal effect is more marked in India and significantly larger in northern Indian states compared with other states (likelihood ratio test; \( P < .001 \)).

The mechanisms responsible for the reduced effectiveness of OPV in lower-income settings are not well understood, although potential explanations include interference by enteroviruses or other enteric pathogens, a high prevalence of diarrhea, malnutrition, micronutrient deficiencies, virus neutralization by breast milk antibodies, and tropical enteropathy [11, 34]. The approximately 2-fold variation in the response to OPV that we observed in Uttar Pradesh and Bihar suggests a very significant role for seasonal infections and diarrhea in the reduced effectiveness of this oral vaccine. Seasonal variation in vaccine potency that might contribute to this pattern is not supported by data on vaccine vial monitors or potency testing of vaccine retrieved from the field.

It might be expected that intestinal mucosal immunity among the children included in this study is also affected by exposure to circulating wild-type poliovirus [35]. However, measures of exposure to wild-type poliovirus based on the location and timing of reported cases of poliomyelitis were not found to be significantly associated with the odds of excreting challenge poliovirus. In such a heavily vaccinated population where the number of reported cases of poliomyelitis is small and the birth cohort very large this is perhaps unsurprising (even if asymptomatic infections among vaccinated individuals can result in the number of infections associated

| Table 2. Multivariate Logistic Regression Model of Vaccine Virus Excretion 4–28 Days After Administration of Monovalent or Trivalent Oral Poliovirus Vaccine (OPV) |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Variable | Serotype 1 | Serotype 2 | Serotype 3 |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| OR (95% CI) | \( P \) | OR (95% CI) | \( P \) | OR (95% CI) | \( P \) |
| Child in Uttar Pradesh or Bihar rather than other states | 0.61 (.48–.77) | .001 | 0.85 (.57–1.26) | .410 | 0.72 (.55–.94) | .017 |
| Enterovirus high season compared with low season | | | | | |
| Uttar Pradesh and Bihar | 0.57 (.50–.65) | .001 | 0.58 (.41–.81) | .002 | 0.48 (.40–.57) | <.001 |
| Other states | 0.82 (.63–1.05) | .118 | 0.84 (.58–1.22) | .352 | 0.80 (.61–1.05) | .104 |
| Monovalent OPV challenge compared with trivalent challenge | 1.24 (1.05–1.47) | .010 | NA | NA | 1.81 (1.52–2.15) | <.001 |
| Time since previous SIA | | | | |
| \(<40 \text{ days}\) | 1 | 1 | 1 | | |
| 2–5 months | 1.18 (1.04–1.34) | .012 | 1.00 (1.64–1.59) | .985 | 1.06 (.84–1.35) | .616 |
| \(\geq 6 \text{ months}\) | 1.39 (1.99–1.97) | .058 | 2.04 (1.28–3.25) | .003 | 1.31 (1.00–1.70) | .048 |
| Doses of trivalent OPV | | | | |
| 0–1 | 1 | 1 | 1 | | |
| 2–4 | 0.80 (.66–.97) | .022 | 0.36 (1.9–.67) | .001 | 1.06 (.80–1.40) | .697 |
| \(\geq 5\) | 0.91 (.76–1.09) | .327 | 0.26 (1.15–.47) | <.001 | 0.92 (.70–1.22) | .581 |
| Doses of monovalent OPV | | | | |
| 0–1 | 1 | NA | 1 | | |
| 2–4 | 0.73 (.61–.88) | .001 | NA | 0.67 (1.54–.83) | <.001 |
| \(\geq 5\) | 0.58 (.49–.70) | .001 | NA | 0.17 (.04–.72) | .016 |
| Duration of excretion, mean (95% CI), days | 6.9 (6.4–7.4) | | 6.1 (5.3–7.1) | | 8.0 (7.3–8.9) | |

Children reported in the acute flaccid paralysis database during 2005–2009 were included.

Abbreviations: CI, confidence interval; NA, not applicable (because serotype 2 monovalent OPV had not been used); OR, odds ratio; SIA, supplementary immunization activity.
with each case significantly exceeding the 100–1000 infections estimated from unvaccinated populations [36, 37]).

This study has a number of limitations related to its retrospective nature and the reliance on verbal recall and SIA records to describe each child’s vaccination history. These limitations could result in inaccurate estimates of the effectiveness of OPV in protecting against reinfection with vaccine poliovirus. It is also possible that the time since a child was last exposed to an SIA was confounded with unmeasured determinants of vaccine poliovirus excretion after challenge with OPV. For example, the frequency of SIAs may be higher in districts with a poor response to OPV and therefore reduced excretion of poliovirus after challenge. However, the frequency of SIAs experienced by a child before challenge was not associated with vaccine poliovirus excretion in the multivariate analysis, suggesting that any such confounding was not significant (data not shown). Furthermore, patterns of excretion of different vaccine poliovirus serotypes were consistent with that expected based on the inferred vaccination history for each child (see also [16]). This study is based on testing of stool samples collected from children reported with AFP. Failure to exclude children with vaccine-associated paralytic poliomyelitis from the multivariate analysis would result in estimates of vaccine-induced immunity that include the protective effect of OPV against poliomyelitis in addition to asymptomatic shedding. We therefore excluded children who had symptoms compatible with vaccine-associated paralytic poliomyelitis [26]. The imperfect, waning protection offered against paralytic poliomyelitis and suggests that the sample of children with AFP that we examined is reasonably equivalent to a sample from the healthy population.

An additional limitation is that we did not measure the quantity of vaccine poliovirus shed in stool samples. This is likely to be lower among children with OPV-induced immunity compared with naive children [4, 5]. A reduction in shedding will in part be manifest by a lower probability of detecting virus in stool samples and therefore captured by our study. However, in the future it would also be interesting to estimate the impact of waning mucosal immunity on protection against infection based on the quantity of vaccine poliovirus shed. Studies that measure vaccine poliovirus excretion among children vaccinated several years before challenge compared with more recently vaccinated children are also required to estimate the extent of waning of mucosal immunity over a longer period than that described in our study.

The strongly seasonal response to vaccination observed in this study implicates enteric infections in the reduced immunogenicity and effectiveness of OPV in India. However, the relative importance of different infections and the immunological mechanisms underlying reduced immunogenicity are unknown. Infection with other enteroviruses at the time of vaccination and diarrhea, with or without identification of associated bacterial pathogens, have been found to be associated with reduced immunogenicity of OPV [32, 38–42]. However, these studies have often enrolled small numbers of individuals, raising the possibility of publication bias.
particularly because several other studies have failed to find a similar effect [10, 43]. Larger studies to identify enteric pathogens associated with the reduced immunogenicity of OPV in India are required and could lead to interventions to improve the response to OPV and other oral vaccines in lower-income countries.

Waning intestinal mucosal immunity after vaccination with OPV is likely to make the interruption of wild-type poliovirus transmission more challenging. We have previously found frequent infection with wild-type polioviruses among healthy, OPV-vaccinated children in contact with children with poliomyelitis [17]. However, the contribution of these children and of vaccinated adults to the transmission of wild-type polioviruses in India and elsewhere is unknown. In theory, incomplete immunity against reinfection can lead to a reinfection threshold for the basic reproduction number (transmissibility) of an infection, above which herd immunity is insufficient to stop transmission [44]. However, failure to find wild-type polioviruses in stool or sewage samples collected in India during most of 2011 suggests a herd-immunity effect associated with the use of OPV sufficient to interrupt transmission. It should be noted that even among children exposed to an SIA >6 months ago and with waning mucosal immunity, significant protection against vaccine poliovirus shedding after challenge is retained, compared with poorly vaccinated children. For example, among children vaccinated with ≥5 doses of serotype 1 monovalent OPV who were last exposed to an SIA ≥6 months ago, the relative odds of shedding serotype 1 vaccine poliovirus after challenge, compared with children vaccinated with only a single dose of monovalent or trivalent OPV, were 0.58 × 1.39 = 0.81 (95% CI, .55–1.21), based on Table 2; the odds for children vaccinated with trivalent OPV against serotype 2 poliovirus or monovalent OPV against serotype 3 were 0.53 (95% CI, .25–1.13) and 0.22 (95% CI, .05–.96), respectively. Moreover, it is possible that frequent, almost monthly SIAs in areas with persistent reporting of children with poliomyelitis have continually boosted mucosal immunity, permitting the interruption of fecal-oral transmission of wild-type polioviruses in these areas. Although this may have succeeded in India, our findings suggest that strategies to more effectively induce and boost mucosal immunity will considerably facilitate the interruption of wild-type poliovirus transmission in remaining infected areas.

**Supplementary Data**

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/our_journal/jid). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**References**


