

Mucosal Immunity after Vaccination with Monovalent and Trivalent Oral Poliovirus Vaccine in India

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(See the editorial commentary by Fine, on pages 673–5.)

Background. Persistent wild-poliovirus transmission, particularly in India, has raised questions about the degree of mucosal immunity induced by oral poliovirus vaccine (OPV) in tropical countries.

Methods. Excretion of vaccine poliovirus after challenge with OPV was measured in stool samples collected from children identified by the acute flaccid paralysis surveillance program in India during 2005–2007. The effectiveness of trivalent and monovalent OPV against excretion of each poliovirus type was estimated.

Results. Vaccine poliovirus was isolated from 4994 (5.2%) of 96,641 children with 2 stool samples. The relative odds of excreting challenge poliovirus among children with ≥ 5 reported previous doses of trivalent OPV compared with 0 previous doses was 0.24 (95% confidence interval [CI], 0.12–0.45), 0.08 (95% CI, 0.04–0.14), and 0.40 (95% CI, 0.19–0.85) for serotypes 1, 2, and 3, respectively, but the relative odds increased to 0.62 (95% CI, 0.44–0.88), 0.44 (95% CI, 0.20–0.99), and 0.66 (95% CI, 0.41–1.06), respectively, in the northern states of Uttar Pradesh and Bihar. In these 2 states, the relative odds of excretion of serotype 1 was 0.32 (95% CI, 0.26–0.41) after ≥ 5 doses of type 1 monovalent OPV.

Conclusions. The mucosal immunity induced by OPV in India varies by location, serotype, and vaccine formulation. These findings have implications for global eradication and the potential role played by inactivated vaccine in this setting.

The Global Polio Eradication Initiative (GPEI) is now 9 years past the original deadline of the year 2000 to stop wild-poliovirus transmission and is under intense pressure to complete eradication, especially in the remaining 4 countries—Afghanistan, India, Nigeria, and Pakistan—with continued indigenous transmission [1, 2]. In 2007, there was a renewed commitment from the governments of these 4 countries, as well as from the GPEI's leading donors, to intensify eradication efforts

over a limited time frame [3]. This financial and political commitment has facilitated technical and tactical innovations. Monovalent oral poliovirus vaccines (mOPVs) have been licensed and extensively used by national programs along with new vaccine delivery strategies, considerably improving vaccine-induced population immunity in countries in which polio is endemic [4–6].

In India, type 1 mOPV (mOPV1) has been used to prioritize the eradication of type 1 wild virus, and reports of type 1 paralytic polio have declined markedly since 2006. However, despite reaching the highest levels of vaccine-induced immunity yet recorded in India [5], both type 1 and type 3 wild poliovirus continue to circulate in the north of the country.

The GPEI has used OPV exclusively because of its superior ability to induce gut mucosal immunity compared with inactivated polio vaccine (IPV). Mucosal immunity can limit or prevent infection and excretion of poliovirus after subsequent exposure [7, 8]. However, the persistence of polio, particularly in northern India,

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has led to questions about the degree of gut mucosal immunity induced by OPV in tropical countries and has resulted in renewed calls to supplement the use of oral vaccines with IPV [9].

Data on mucosal immunity to poliovirus in tropical countries after immunization with OPV are limited [10–13]. Furthermore, levels of mucosal immunity have not been investigated in polio-endemic countries that have a high prevalence of vaccine-induced immunity and in which the extent of participation of immunized children in the continued circulation of wild poliovirus is unclear. In India, an assessment of the level of mucosal immunity after immunization with OPV is especially important to address concerns about the ability of these vaccines to stop poliovirus transmission in a setting in which rates of seroconversion and development of systemic immunity after immunization with OPV are low [14].

Here, we use excretion of vaccine poliovirus in the stool among children given (“challenged with”) OPV as a marker for the degree of mucosal immunity to poliovirus among children in India. We examine patterns of poliovirus excretion after challenge with OPV given during supplementary and routine immunization activities and estimate the protective efficacy of mOPV and trivalent OPV (tOPV) against infection with and excretion of each poliovirus type. We discuss implications of these findings for the ongoing debate over the potential role played by IPV in interrupting wild-poliovirus transmission in northern India.

METHODS

Data collection. Since 1997, cases of acute flaccid paralysis (AFP) occurring in children <15 years old have been reported to the National Polio Surveillance Project by >10,000 health care institutions and >15,000 health care practitioners across India [15]. These cases undergo extensive 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 before the first stool collection. For each AFP case, attempts are made to collect 2 stool samples within 2 weeks of the onset of paralysis and at least 24 h apart, and these samples are tested for the presence of poliovirus and other enteroviruses. 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 [16].

We examined patterns of vaccine virus excretion among children recorded in the AFP database after vaccination with mOPV1, type 3 mOPV (mOPV3), and tOPV. Monovalent vaccines were introduced into supplementary immunization activities (SIAs) in 2005 and have been used mainly in Uttar Pradesh (UP) and Bihar. The present study therefore examines all reported AFP cases with a date of onset of paralysis from

1 January 2005 through 31 December 2007 and for which 2 stool samples were assessed for the presence of poliovirus. Over this period, the number of doses of OPV received through routine health services and through SIAs were recorded separately. Children without complete data on age or vaccination history (reporting of the number of OPV doses received and date of last dose), with wild poliovirus isolated from either stool sample, or with inadequate stool samples (collected >14 days after the onset of paralysis or <24 h apart) and symptoms compatible with poliomyelitis were excluded from the analyses. Routine health services administer tOPV exclusively, whereas SIAs have used mOPV1, mOPV3, and tOPV at different times in different parts of the country. The district of residence and age of each child with AFP was used to infer their exposure to SIAs of different types, and the number of doses of tOPV, mOPV1, and mOPV3 received by each child through SIAs was then estimated by multiplying the reported number of SIA doses by the fraction of SIAs that used vaccine of each type. The type of the most recent (“challenge”) vaccine administered before stool sample collection could be determined from the vaccine used by the SIAs that took place at the time of the reported date of receipt of the last OPV dose. For infants <20 weeks old for whom receipt of both SIA and routine doses of OPV were reported, we assumed that if the date of receipt of their last reported dose of OPV was at the time of a SIA, then this dose had been received through that SIA; otherwise, the dose was assumed to have been received through routine services.

Institutional ethics approval was not required because this is a retrospective analysis of a national surveillance database that is free of personally identifiable information and that recorded the use of standard vaccines licensed by the National Regulatory Authority of the government of India for use in India.

Statistical analysis. The sensitivity of the laboratory test for vaccine poliovirus in the stool samples collected from children with AFP was estimated on the basis of the concordance between the first and second sample, using methods that have been described elsewhere [17]. The fraction of children with AFP who had vaccine virus isolated from at least 1 stool sample was calculated for each serotype, and the relationship with the time since the most recent challenge with OPV and the type of challenge vaccine was examined. The relationship between vaccine virus excretion among children for whom both stool samples were collected between 4 and 28 days after challenge and the age of the child and between the former and the reported number of doses of OPV previously received was also examined (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 gut [18]).

The absence of vaccine poliovirus in stool samples collected between 4 and 28 days after challenge may be the result of a protective mucosal response, cessation of excretion before stool collection, or a failure of the vaccine virus to infect the gut (“take”). To estimate the protective mucosal immunity induced by previous doses of OPV, we therefore compared excretion among children with AFP who had different reported numbers of OPV doses at different times after challenge by logistic regression. The probability of detecting vaccine virus in stool was assumed to decline exponentially with the time since the reported date of the last OPV dose, in agreement with the observed data. The log odds of excreting vaccine virus of a given type was thus related to the number of doses of OPV received before the current challenge by

$$\log(\text{odds}) = \beta_1 t + \beta_2 c + \beta_3 x_m + \beta_4 x_t,$$

where t is the time since challenge with OPV taken as the midpoint between the 2 stool samples (70% of stool samples were collected within 48 h of each other), c is the type of challenge vaccine (monovalent or trivalent), x_t is the number of doses of tOPV received before challenge, and x_m is the number of doses of mOPV of the relevant type. β_1 , β_2 , β_3 , and β_4 are the regression coefficients, with β_3 and β_4 defining the vaccine efficacy against infection and excretion of poliovirus. A total of 665 AFP cases were under review by the National Expert Review Committee for Case Classification as possible cases of vaccine-associated paralytic poliomyelitis and were therefore excluded from this analysis of vaccine efficacy against poliovirus excretion (these cases had vaccine poliovirus in at least 1 stool sample, onset of paralysis after the most recent reported OPV dose, and residual paralysis at follow-up [19]). The numbers of doses were included in analyses as both continuous and categorical variables. The potential reduction in the duration of vaccine virus excretion by immunization with OPV was examined by including an interaction term between t and x_t or x_m . The impact of location on vaccine efficacy and excretion after challenge was examined by including a location variable and its interaction with the other variables, with location defined as “UP and Bihar” or “rest of India,” reflecting the previously reported differences in OPV efficacy in these different settings [14]. The potential significance of waning mucosal immunity was assessed by including the child’s age and the interaction with the number of OPV doses in the analysis.

RESULTS

Patterns of vaccine virus excretion. During 2005–2007, a total of 100,754 cases of AFP were reported in India. Two stool samples were available for 96,641 (95.9%) of the children with AFP. Of these, 4994 (5.2%) had vaccine virus and 1512 (1.6%) had wild poliovirus isolated from at least 1 stool sample. The

vast majority of AFP cases for which wild poliovirus was not isolated from stool are the result of a variety of conditions, including Guillain-Barré syndrome, trauma, and other infectious diseases [20]. Vaccine poliovirus was isolated from at least 1 stool sample for 2994 (3.1%), 957 (1.0%), and 1959 (2.0%) of the children with AFP who had 2 stool samples for serotypes 1, 2, and 3, respectively. Of these children, 123 excreted serotypes 1 and 2, 298 excreted serotypes 1 and 3, 183 excreted serotypes 2 and 3, and 156 excreted all 3 serotypes. The estimated sensitivity of the laboratory test for excretion of vaccine poliovirus among children with AFP who had 2 stool samples was 80%, 91%, and 89% for serotypes 1, 2, and 3, respectively.

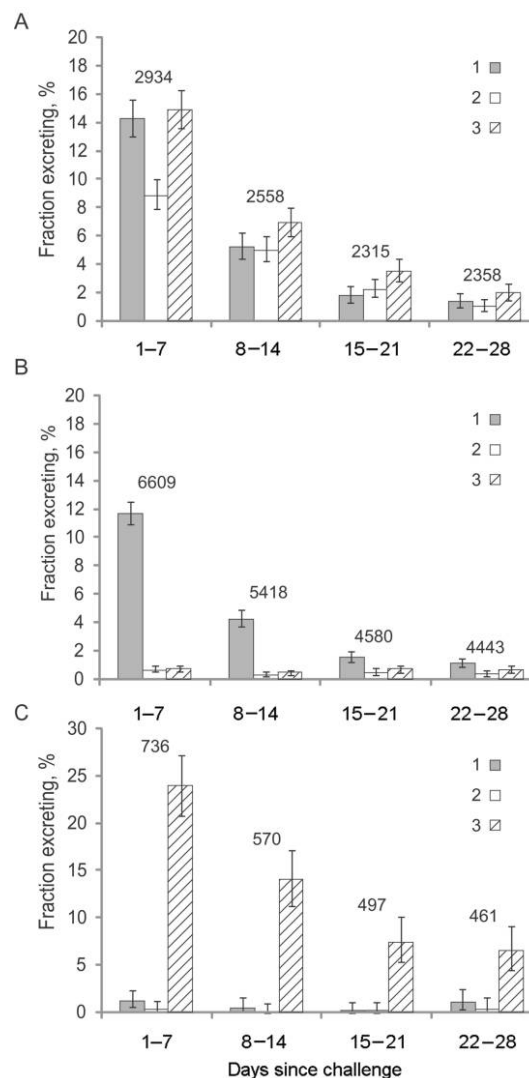


Figure 1. Fraction of children excreting each type of vaccine poliovirus, by the time in days after challenge with trivalent oral poliovirus vaccine (OPV) (A), monovalent type 1 OPV (B), or monovalent type 3 OPV (C). Excretion of vaccine virus not related to the challenge dose is likely to be the result of exposure to secondary transmitted OPV. Error bars indicate 95% confidence intervals, and values above the bars indicate the number of children tested.

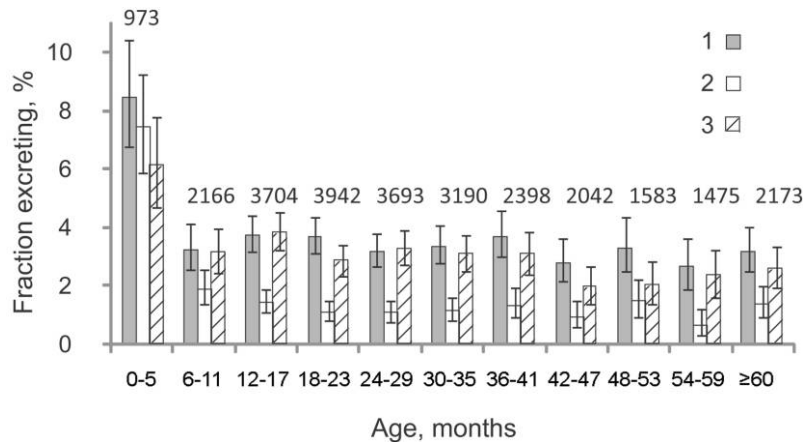


Figure 2. Fraction of children excreting each type of vaccine poliovirus, by 6-month age groups, where both stool samples were collected between 4 and 28 days after challenge with oral poliovirus vaccine (irrespective of type). Error bars indicate 95% confidence intervals, and values above the bars indicate the number of children tested.

The estimated probability of misclassifying a child from the AFP database as not excreting vaccine virus was, therefore, 0.0062, 0.00091, and 0.0022, respectively, on the basis of the prevalence of vaccine poliovirus excretion among children with AFP.

Of the children with AFP reported during the study period, 74,576 (74.0%) met the inclusion criteria for the analyses—45,444 from UP and Bihar and 29,132 from the rest of India. Of these children, 27,339 had both stool samples collected between 4 and 28 days after the administration of OPV—8499 after receipt of tOPV, 17,031 after receipt of mOPV1, and 1809 after receipt of mOPV3. The probability of detecting vaccine virus after administration of OPV declined exponentially with time since the reported date of challenge (figure 1). Vaccine virus excretion between 4 and 28 days after challenge was more frequent among infants <6 months old than among older children (figure 2).

Mucosal immunity after immunization with OPV. The probability of detecting vaccine virus in either stool sample collected between 4 and 28 days after challenge declined as the number of doses of OPV received before challenge increased (table 1). Logistic regression to analyze the independent impact of doses of tOPV and mOPV on excretion after subsequent challenge with OPV demonstrated that tOPV has a significant protective effect against all 3 poliovirus types and that mOPV1 has a significant protective effect against type 1 poliovirus (table 2 and figure 3). There were insufficient SIAs with mOPV3 to allow the protective efficacy of this vaccine to be determined (table 2). The protective efficacy of tOPV against excretion of poliovirus type 2 was significantly greater than that against types 1 and 2 (figure 3).

Among children in UP and Bihar, the relative odds of excreting type 1 challenge virus was 0.32 (95% confidence interval [CI], 0.26–0.41) for those with ≥ 5 reported previous doses of

Table 1. Percentage of Children Excreting Vaccine Virus in Stool Samples Collected between 4 and 28 Days after Challenge with Monovalent Oral Poliovirus Vaccine (mOPV) or Trivalent OPV (tOPV), by the Reported Number of OPV Doses Previously Received That Contained Vaccine Virus of the Relevant Serotype

No. of doses of tOPV and mOPV received before the last (challenge) dose ^a	tOPV			mOPV	
	Type 1	Type 2	Type 3	mOPV1, type 1	mOPV3, type 3
0	18 (23/128)	20 (41/206)	8 (15/181)	31 (19/62)	23 (17/75)
1	8 (11/132)	14 (24/173)	13 (24/181)	14 (15/108)	16 (25/156)
2–4	5 (37/745)	4 (42/1003)	8 (77/1002)	4 (37/842)	14 (75/547)
5–7	5 (72/1354)	3 (47/1501)	6 (97/1509)	4 (74/1895)	13 (48/364)
8–11	4 (87/2237)	3 (66/2258)	5 (119/2258)	3 (130/3855)	7 (23/348)
≥ 12	3 (135/3903)	3 (103/3358)	5 (172/3368)	3 (325/10,269)	9 (28/319)
All	4 (365/8499)	4 (323/8499)	6 (504/8499)	4 (600/17,031)	12 (216/1809)

NOTE. Data are percentage (proportion) of children who were given the indicated vaccine and excreted the indicated serotype. mOPV1, type 1 mOPV; mOPV3, type 3 mOPV.

^a Excludes doses of mOPV of a type different from the poliovirus excreted.

Table 2. Results of Logistic Regression of Vaccine Virus Excretion among Children with Acute Flaccid Paralysis from Whom 2 Stool Samples Were Collected between 4 and 28 Days after Challenge with Oral Poliovirus Vaccine (OPV)

Category	UP and Bihar			Rest of India		
	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
No. of doses of OPV received before the last (challenge) dose						
mOPV ^{a,b}						
0	1.00 (reference)	...	1.00 (reference)	1.00 (reference)	...	1.00 (reference)
1	0.65 (0.49–0.85)	...	1.17 (0.83–1.63)	1.29 (0.76–2.17)	...	2.57 (0.13–49.37)
2–4	0.49 (0.39–0.62)	...	0.84 (0.51–1.40)	1.02 (0.66–1.58)
5–7	0.35 (0.27–0.46)	...	8.67 (0.31–241)	1.82 (0.98–3.38)
8–11	0.34 (0.25–0.45)	0.35 (0.05–2.62)
≥12	0.23 (0.15–0.36)
≥5	0.32 (0.26–0.41)	...	1.20 (0.12–11.71)	1.40 (0.77–2.53)
tOPV ^b						
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	0.83 (0.52–1.34)	1.73 (0.62–4.87)	1.31 (0.74–2.30)	0.44 (0.17–1.17)	0.44 (0.19–1.01)	0.82 (0.29–2.31)
2–4	0.60 (0.41–0.89)	0.60 (0.24–1.51)	0.91 (0.55–1.49)	0.20 (0.10–0.43)	0.09 (0.04–0.19)	0.66 (0.30–1.46)
5–7	0.58 (0.39–0.87)	0.35 (0.14–0.89)	0.74 (0.44–1.24)	0.33 (0.17–0.65)	0.08 (0.04–0.16)	0.52 (0.24–1.12)
8–11	0.67 (0.46–0.97)	0.51 (0.22–1.20)	0.60 (0.36–1.00)	0.20 (0.10–0.40)	0.06 (0.03–0.11)	0.36 (0.17–0.79)
≥12	0.61 (0.42–0.87)	0.44 (0.19–1.00)	0.66 (0.40–1.08)	0.21 (0.11–0.42)	0.09 (0.05–0.17)	0.37 (0.17–0.80)
≥5	0.62 (0.44–0.88)	0.44 (0.20–0.99)	0.66 (0.41–1.06)	0.24 (0.12–0.45)	0.08 (0.04–0.14)	0.40 (0.19–0.85)
Challenge vaccine, mOPV vs tOPV ^{a,b}						
	1.31 (1.06–1.62)	...	1.86 (1.47–2.37)	1.00 (0.68–1.46)	...	0.57 (0.08–4.28)
Mean duration of excretion (1/β ₁), days						
	6.6 (6.0–7.4)	7.3 (5.9–9.6)	8.1 (7.0–9.5)	7.6 (6.0–9.3)	7.4 (5.9–9.8)	8.7 (7.2–11.2)

NOTE. Data are the relative odds of excretion of the indicated serotype, unless otherwise indicated. Values in parentheses are 95% confidence intervals, and ellipses indicate that data were not available.

^a mOPV1 for type 1 excretion and mOPV3 for type 3 excretion.

^b Controlling for doses of tOPV or mOPV.

mOPV1 compared with 0 doses and was 0.62 (95% CI, 0.44–0.88) for those with ≥5 reported previous doses of tOPV compared with 0 doses (odds ratio for mOPV1 vs tOPV, 0.52 [95% CI, 0.34–0.80]) (table 2). There were insufficient SIAs with mOPV1 to obtain an estimate of mOPV1 efficacy outside of UP and Bihar. After correcting for the protective effect of vaccination, the odds of vaccine virus excretion after challenge was lower in UP and Bihar than in the rest of India, indicating lower take of the challenge vaccine (relative odds for serotypes 1, 2, and 3, 0.51 [95% CI, 0.23–1.12]), 0.17 [95% CI, 0.06–0.50], and 0.69 [95% CI, 0.28–1.71], respectively). The protective effect of immunization was also more limited, such that doses of tOPV had a significantly lower efficacy in UP and Bihar than in the rest of India ($P = .013$, $P = .002$, and $P = .81$ for serotypes 1, 2, and 3, respectively) (figure 3). The age of the child was not found to be significantly associated with the probability of excreting vaccine virus after correction for the number of OPV doses received and did not show any significant interaction with the estimated efficacy of the vaccine.

Inclusion of the number of doses of mOPV or tOPV as a

continuous rather than categorical variable, such that the odds of excretion declined exponentially with increasing number of doses, resulted in a significantly worse fit to the data for poliovirus types 1 and 2 ($P < .001$ for both, likelihood ratio test) but not for type 3 ($P = .14$). The first 4 doses of mOPV or tOPV were associated with a significantly greater protective immune response against excretion of type 1 and 2 challenge poliovirus compared with subsequent doses ($P = .004$ and $P = .025$ for tOPV and mOPV1 against serotype 1; $P = .037$ for tOPV against serotype 2).

Children in UP and Bihar were more likely to excrete types 1 and 3 vaccine virus after challenge with mOPV than after challenge with tOPV (odds ratios for types 1 and 3, 1.31 [95% CI, 1.06–1.62] and 1.86 [95% CI, 1.47–2.37], respectively) (table 2). There was no significant interaction between the type of challenge vaccine (monovalent or trivalent) and the number of doses, indicating that vaccine efficacy was not significantly affected by the type of challenge vaccine. The duration of vaccine virus excretion showed a significant decline with increasing number of doses of tOPV before challenge in the case of sero-

type 1 outside UP and Bihar only (the mean duration of excretion among children with 0 doses of tOPV was ~7 weeks, compared with 7 days among children with ≥ 5 doses [$P = .010$]).

DISCUSSION

The present study demonstrates that significant protective gut mucosal immunity develops after vaccination with OPV in India. Excretion of poliovirus types 1 and 2 in stool samples obtained between 4 and 28 days after challenge with mOPV or tOPV dropped from 18%–31% among previously unvaccinated children to 3% among children who received multiple doses of OPV (table 1). mOPV was significantly more likely to induce good mucosal immunity against type 1 poliovirus than tOPV (figure 3). The greater efficacy of mOPV and the high levels of coverage recently achieved in western UP likely explain the elimination of indigenous type 1 wild poliovirus from this traditional poliovirus stronghold in August 2007, before the re-introduction of virus from Bihar in May 2008.

The highest level of mucosal immunity provided by tOPV was against type 2 poliovirus, consistent with the results of studies of systemic immunity in developing countries that demonstrate a greater probability of seroconversion to type 2 after administration of tOPV [21]. Preferential seroconversion to type 2 is the result of interference between the (Sabin) vaccine viruses in the gut and the greater fitness of type 2 compared with the other 2 vaccine types [18]. Use of the monovalent product avoids this interference, resulting in a significantly greater probability of seroconversion [22].

The efficacy of tOPV against excretion of serotypes 1 and 2 was significantly lower in UP and Bihar than in the rest of India, consistent with the results of studies demonstrating that tOPV has a lower efficacy against paralytic disease in these states [14]. This reduced efficacy is likely to be the result of the high prevalence of diarrhea and of other infections that can interfere with induction of immunity by the live attenuated vaccine virus [21, 23]. Use of mOPV rather than tOPV compensates for this interference, and levels of mucosal immunity against serotype 1 after multiple doses of mOPV1 in UP and Bihar are comparable to those achieved with tOPV in those parts of India where wild-poliovirus transmission has been stopped (table 2).

Detection of type 3 vaccine virus after challenge with tOPV or mOPV remained at a slightly higher level than detection of serotypes 1 and 2, even after multiple doses of OPV (table 1). This is presumably the result of lower levels of immunity to type 3 in this population, reflecting both the markedly greater use of mOPV1 than mOPV3 and the limited efficacy of tOPV against type 3 polio in this setting [14].

Overall, levels of excretion of vaccine virus during the first week after challenge with tOPV in this highly immunized population (figure 1) are comparable to those in published studies

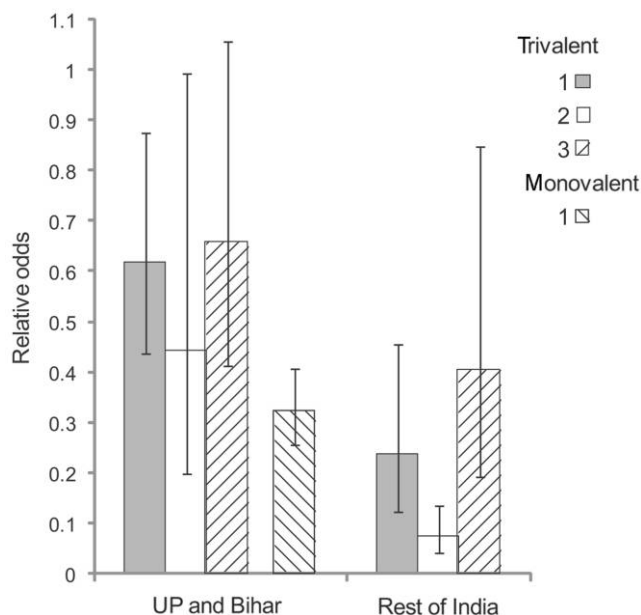


Figure 3. Relative odds of excreting each type of vaccine poliovirus after challenge with oral poliovirus vaccine (OPV) among children in Uttar Pradesh (UP) and Bihar who had previously received ≥ 5 doses of trivalent OPV or monovalent type 1 OPV, compared with children who had received 0 doses. Estimates are based on logistic regression and account for receipt of doses of each vaccine type. Error bars indicate 95% confidence intervals.

from other settings, which have typically found excretion 7 days after challenge in 10%–20% of children who had previously received 2–5 doses of tOPV [7, 8, 10, 11, 13, 24–26]. Although mOPV is more effective than tOPV at preventing infection with poliovirus, the imperfect nature of mucosal immunity limits the ability of OPV to induce protection against challenge virus in all immunized children. We found that the first few doses of mOPV or tOPV gave significantly greater protection than did subsequent doses, and indeed some degree of excretion of type 1 challenge virus continued among children with ≥ 12 reported doses of mOPV1 (table 2). This is in contrast to findings of studies of the protective efficacy of OPV against paralytic poliomyelitis in the same setting, which have found a constant probability of seroconversion per dose and complete systemic immunity to disease after seroconversion [4, 14].

There are several factors that could affect the precision of our estimate of the efficacy of oral vaccines against excretion of challenge poliovirus. We were not able to control for exposure to secondary transmitted OPV, which could reduce the estimated efficacy of the vaccine. However, excretion of vaccine virus after the reported date of the most recent OPV dose declined exponentially with time, in agreement with our model of primary exposure during supplementary and routine immunization. Our estimates could also be affected by misre-

porting of the number of doses or the date of most recent dose received by children with AFP. However, a more detailed follow-up investigation of a subset of children during 2005 revealed limited misreporting [4]. Differences in exposure to wild poliovirus resulting in naturally acquired immunity among some children could confound our analysis. However, repeating the analysis with a 1:1 matched design using control children (who had no vaccine virus in stool) chosen from the same district and from whom stool samples were collected around the same time (within 6 months) as the children with AFP gave similar estimates for vaccine efficacy (albeit with broader CIs), suggesting that exposure to wild poliovirus is not a significant confounder (data not presented).

The continued reporting of type 1 wild poliovirus in India despite the use of mOPV1 since 2005 and the recent reintroduction of this serotype into western UP from Bihar has renewed interest in the use of IPV to stop wild-poliovirus transmission [9]. Studies in industrialized and developing countries suggest that IPV has a limited impact on gut mucosal immunity in seronegative children who have not previously received or responded to OPV [27–29]. However, there is some evidence that IPV could boost mucosal immunity among children who have previously responded to OPV by stimulating the memory immune response [30, 31]. Although this does not appear to significantly reduce the probability of infection and excretion of vaccine or wild poliovirus in the feces after challenge or natural exposure, it could reduce the titer and duration of shedding after infection [11, 13, 24, 27–29, 32, 33]. In addition, IPV would provide protection against paralysis in those children who had not responded to OPV [13, 34].

Because the effect that immunization with OPV has on mucosal immunity in India was previously unknown, there was limited capacity to gauge whether IPV would have a meaningful impact and the levels of coverage that would be required. The present study finds that immunization with OPV, particularly the monovalent product, has a significant effect on mucosal immunity in India but also demonstrates that additional doses of OPV have a limited ability to further boost mucosal immunity in children with multiple reported doses of mOPV. Although IPV is likely to achieve high levels of seroconversion in India [13, 29, 33–37], the effect that this vaccine has on mucosal immunity among OPV-immunized children in India is unknown. This, in addition to the levels of coverage that can be achieved with this injectable vaccine, should be rapidly assessed, either in studies specifically designed for that purpose or as part of the eradication program by supplementing the current OPV immunization activities with IPV.

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References

1. Chumakov K, Ehrenfeld E, Wimmer E, Agol VI. Vaccination against polio should not be stopped. *Nat Rev Microbiol* **2007**; 5:952–8.
2. Arita I, Nakane M, Fenner F. Is polio eradication realistic? *Science* **2006**; 312:852–4.
3. World Health Organization. The case for completing polio eradication. Geneva: World Health Organization, **2007**.
4. Grassly NC, Wenger J, Durrani S, et al. Protective efficacy of a monovalent oral type 1 poliovirus vaccine: a case-control study. *Lancet* **2007**; 369:1356–62.
5. World Health Organization. End-2007 report on milestones from the case for completing polio eradication. Geneva: World Health Organization, **2008**.
6. Jenkins HE, Aylward RB, Gasasira A, et al. The effectiveness of immunization against polio in Nigeria. *New Engl J Med* **2008**; 359:1666–74.
7. Henry JL, Jaikaran ES, Davies JR, et al. A study of poliovaccination in infancy: excretion following challenge with live virus by children given killed or living poliovaccine. *J Hyg (Lond)* **1966**; 64:105–20.
8. Onorato IM, Modlin JE, McBean AM, Thoms ML, Losonsky GA, Bernier RH. Mucosal immunity induced by enhanced-potency inactivated and oral polio vaccines. *J Infect Dis* **1991**; 163:1–6.
9. Ehrenfeld E, Glass RI, Agol VI, et al. Immunisation against poliomyelitis: moving forward. *Lancet* **2008**; 371:1385–7.
10. WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines. Combined immunization of infants with oral and inactivated poliovirus vaccines: results of a randomized trial in The Gambia, Oman, and Thailand. *J Infect Dis* **1997**; 175(Suppl 1):S215–27.
11. du Chatelet IP, Merchant AT, Fisher-Hoch S, et al. Serological response and poliovirus excretion following different combined oral and inactivated poliovirus vaccines immunization schedules. *Vaccine* **2003**; 21: 1710–8.
12. John TJ. Oral polio vaccination of children in the tropics. II. Antibody response in relation to vaccine virus infection. *Am J Epidemiol* **1975**; 102:414–21.
13. Sutter RW, Suleiman AJM, Malankar P, et al. Trial of a supplemental dose of four poliovirus vaccines. *New Engl J Med* **2000**; 343:767–73.
14. Grassly NC, Fraser C, Wenger J, et al. New strategies for the elimination of polio from India. *Science* **2006**; 314:1150–3.
15. Banerjee K, Hlady WG, Andrus JK, Sarkar S, Fitzsimmons J, Abeykoon P. Poliomyelitis surveillance: the model used in India for polio eradication. *Bull WHO* **2000**; 78:321–9.
16. Indian Ministry of Health and Family Welfare. Field guide: surveillance of acute flaccid paralysis. New Delhi: Child Health Division, Department of Family Welfare, Ministry of Health and Family Welfare, **2005**.
17. Gary HE Jr, Sanders R, Pallansch MA. A theoretical framework for evaluating the sensitivity of surveillance for detecting wild poliovirus. I. Factors affecting detection sensitivity in a person with acute flaccid paralysis. *J Infect Dis* **1997**; 175(Suppl 1):S135–40.
18. Krugman S, Warren J, Eiger MS, Berman PH, Michaels RM, Sabin AB. Immunization with live attenuated poliovirus vaccine. *Am J Dis Child* **1961**; 101:23–9.
19. Kohler KA, Banerjee K, Hlady WG, Andrus JK, Sutter RW. Vaccine-associated paralytic poliomyelitis in India during 1999: decreased risk despite massive use of oral polio vaccine. *Bull WHO* **2002**; 80:210–6.
20. Marx A, Glass JD, Sutter RW. Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance. *Epidemiol Rev* **2000**; 22:298–316.
21. Patriarca PA, Wright PF, John TJ. Factors affecting the immunogenicity of oral poliovirus vaccine in developing countries: review. *Rev Infect Dis* **1991**; 13:926–39.
22. El-Sayed N, El-Gamal Y, Abbassy AA, et al. Double-blind randomized controlled clinical trial of monovalent type 1 oral poliovirus vaccine. *N Engl J Med* **2008**; 359:1655–65.
23. Posey DL, Linkins RW, Oliveria MJC, Monteiro D, Patriarca PA. The effect of diarrhea on oral poliovirus vaccine failure in Brazil. *J Infect Dis* **1997**; 175:S258–63.

24. Laassri M, Lottenbach K, Belshe R, et al. Effect of different vaccination schedules on excretion of oral poliovirus vaccine strains. *J Infect Dis* **2005**; 192:2092–8.
25. Modlin JF, Halsey NA, Thoms ML, Meschievitz CK, Patriarca PA. Humoral and mucosal immunity in infants induced by three sequential inactivated poliovirus vaccine- Live attenuated oral poliovirus vaccine immunization schedules. *J Infect Dis* **1997**; 175(Suppl 1):S228–34.
26. Swartz TA, Green MS, Handscher R, et al. Intestinal immunity following a combined enhanced inactivated polio vaccine/oral polio vaccine programme in Israel. *Vaccine* **2008**; 26:1083–90.
27. Ghendon YZ, Sanakoyeva II. Comparison of the resistance of the intestinal tract to poliomyelitis virus (Sabin's strains) in persons after naturally and experimentally acquired immunity. *Acta Virol* **1961**; 5:265–73.
28. Marine WM, Chin TDY, Gravelle CR. Limitation of fecal and pharyngeal poliovirus excretion in Salk-vaccinated children: a family study during a type 1 poliomyelitis epidemic. *Am J Hyg* **1962**; 76:173–95.
29. Galindo M, Lago PM, Caceres V, et al. Randomized, placebo-controlled trial of inactivated poliovirus vaccine in Cuba. *N Engl J Med* **2007**; 356:1536–44.
30. Herremans TM, Reimerink JH, Buisman AM, Kimman TG, Koopmans MP. Induction of mucosal immunity by inactivated poliovirus vaccine is dependent on previous mucosal contact with live virus. *J Immunol* **1999**; 162:5011–8.
31. Krieg C, Maier R, Meyerhans A. Gut-homing ($\alpha_4\beta_7^+$) Th1 memory responses after inactivated poliovirus immunization in poliovirus orally pre-immunized donors. *J Gen Virol* **2004**; 85:1571–9.
32. Gelfand HM, Leblanc DR, Potash L, Fox JP. Studies on the development of natural immunity to poliomyelitis in Louisiana. IV. Natural infections with polioviruses following immunization with a formalin-inactivated vaccine. *Am J Hyg* **1959**; 70:312–27.
33. Asturias EJ, Dueger EL, Omer SB, et al. Randomized trial of inactivated and live polio vaccine schedules in Guatemalan infants. *J Infect Dis* **2007**; 196:692–8.
34. Moriniere BJ, van Loon FP, Rhodes PH, et al. Immunogenicity of a supplemental dose of oral versus inactivated poliovirus vaccine. *Lancet* **1993**; 341:1545–50.
35. Nirmal S, Cherian T, Samuel BU, Rajasingh J, Raghupathy P, John TJ. Immune response of infants to fractional doses of intradermally administered inactivated poliovirus vaccine. *Vaccine* **1998**; 16:928–31.
36. Krishnan R, Jadhav M, John TJ. Efficacy of inactivated poliovirus vaccine in India. *Bull WHO* **1983**; 61:689–92.
37. Dayan GH, Thorley M, Yamamura Y, et al. Serologic response to inactivated poliovirus vaccine: a randomized clinical trial comparing 2 vaccination schedules in Puerto Rico. *J Infect Dis* **2007**; 195:12–20.