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How polio vaccination affects poliovirus transmission

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Abstract

A fundamental complexity of polio eradication is that the elimination of wild poliovirus (WPV) alters the risk-benefit profile of using oral polio vaccine (OPV)—as WPV is eliminated, OPV produces an increasing proportion of the paralytic disease burden since, in rare instances, OPV causes paralysis in vaccine recipients and generates circulating vaccine-derived polio outbreaks (cVDPV) in under-immunized populations. Therefore, to secure the success and long-term stability of polio eradication after the elimination of WPV, OPV use should eventually cease. Type 2 OPV (OPV2) was withdrawn from routine immunization (RI) in April 2016, but detection of type 2 cVDPV has necessitated the use of OPV2 in outbreak response. Thus the world today: RI with OPV2 has stopped, but OPV2 is needed to interrupt outbreaks, and any future OPV2 use several years hence will take place in a population with an unprecedented lack of type 2 immunity. To better understand the complex risk landscape of OPV cessation, we reproducibly summarized data spanning 75 years of polio literature detailing how vaccination affects individual-level susceptibility to infection and viral shedding. We then examined individual-level immunity in the context of close-contact transmission data from the USA and India to quantify the impacts of vaccination on transmission. Our results demonstrate that in settings with inadequate sanitation: (1) OPV has been effective in all populations because it blocks transmission locally, (2) cross-immunity against type 2 produced by bivalent OPV is insufficient to block OPV2 transmission, (3) IPV boosting after

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prior OPV or WPV exposure is effective for interrupting transmission in settings where inadequate or waning immunity permits significant re-infection, and (4) OPV transmission is limited more by population immunity than attenuation and so the risk of seeding new cVDPV with OPV use will increase substantially a few years after OPV cessation. We conclude with discussion of the implications for policy decisions about IPV and OPV use and vaccine research.

Author Summary

Oral polio vaccine (OPV) has played an essential role in the elimination of wild poliovirus (WPV), which persists in only three countries. OPV contains live, transmissible viruses that can spread from person-to-person, limited by immunity in OPV recipients and their contacts, and community structure. If OPV spread is insufficiently limited, circulating vaccine-derived poliovirus (cVDPV) outbreaks can occur. After OPV is no longer used in routine immunization, as with the cessation of type 2 OPV this year, population immunity limiting transmission will decline. A key question is how this affects the potential of OPV to spread across communities. To address this, we calculated the relative strengths and roles of immunity, sanitation, and community structure in limiting OPV spread. Our results derive from a detailed review and synthesis of decades of vaccine trial data and community epidemiological studies. Shedding, dose response, and community structure are quantitatively analyzed to systematically explain and model observations of WPV and OPV circulation in low, moderate, and high-transmission settings. We show that within three years of OPV cessation, renewed OPV use will result in propagating OPV transmission and cVDPVs in high-transmission settings, and that this conclusion is compatible with the observed absence of cVDPVs in low-transmission settings.

Introduction

Through mass vaccination with the live-attenuated Sabin strains in oral polio vaccine (OPV), wild poliovirus (WPV) has been eliminated from all but three countries [1, 2]. The substitution of natural WPV infection with OPV vaccination has been responsible for a ten-thousand-fold reduction of annual paralytic polio cases [1]. Sabin OPV has been the preferred vaccine for polio eradication because it is affordable, can be reliably delivered by volunteers without medical training, and is effective against poliovirus infection [3, 4]. Unique among current human vaccines, the Sabin strains

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are readily transmissible. This transmissibility provides additional passive immunization that enhances the effectiveness of OPV for generating herd immunity. However, Sabin OPV can in rare instances cause paralytic poliomyelitis [5] and establish endemic circulation of vaccine-derived poliovirus (cVDPV) [6]. Thus, to complete the task of poliovirus eradication, Sabin OPV vaccination must eventually cease [7].

The dual role of Sabin OPV as both a vaccine and a source of transmissible poliovirus is responsible for key uncertainties surrounding the ability of the Global Polio Eradication Initiative (GPEI) to achieve and sustain eradication. To date, polio outbreaks have taken place in regions of low immunity against infection surrounded by regions of high immunity [8], OPV campaigns implemented in outbreak response have been effective for interrupting transmission [3], and cVDPV epidemics have been rare [9]. However, within a few years of global OPV cessation, a birth cohort will accumulate with an unprecedented lack of immunity against poliovirus infection. If poliovirus outbreaks occur after cessation due to accidental or deliberate re-introduction [10–12], or sustained silent transmission [2, 13–15] as has recently been observed in Nigeria following the April 2016 global type 2 OPV cessation [2], will cVDPV emergences following OPV use remain rare?

The answer to that question requires a quantitative understanding of deeper questions about how the facts of individual-level immunity, viral infectivity, and transmission dynamics fit together to explain the epidemiology of poliovirus transmission. Immunity derived from multiple vaccination with trivalent OPV (tOPV) reduces poliovirus shedding after oral exposure by a few orders of magnitude [4], but what is the quantitative relationship between shedding and transmission? How does the relationship vary among populations with different levels of fecal-oral exposure? After OPV cessation, will the effectiveness of routine immunization (RI) with inactivated polio vaccine (IPV) against transmission in high income countries [16–20] generalize to all settings to prevent cVDPV emergence from OPV use, given the limited effectiveness of IPV alone against fecal shedding [21] and the proven ability of WPV to transmit in an IPV-only country [15, 22]? Post-OPV2-cessation, how does the transmission-blocking effectiveness of the heterotypic immunity provided by types 1 and 3 bivalent OPV (bOPV) compare with that of tOPV and IPV [23, 24]? To achieve polio eradication, in what settings will the effectiveness of IPV to boost prior immunity from live poliovirus [25] be most useful for interrupting transmission? How does the relationship between immunity and transmission vary with differences in viral infectivity between the Sabin strains, cVDPV, and WPV [26–28]? Is reversion of the genetic attenuation of the Sabin strains [29] the key bottleneck preventing cVDPV emergence, or is cVDPV primarily controlled by population immunity [26]?

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The best tool to extrapolate from experience to an unprecedented situation is mathematical modeling, grounded deeply in biology and epidemiology. Building extensively from primary literature and previous reviews and models [4, 20, 21, 26–28, 30], we developed a comprehensive and transparent synthesis of the evidence for how polio vaccination affects poliovirus transmission, with the guiding principle that it is as important to communicate what our models say as why they say it.

From the totality of evidence collected over the last 75 years, we extrapolated from the epidemiology of polio before OPV cessation to set expectations for OPV use after cessation. Our analysis covers the impacts of vaccination on household and close-contact transmission of all three Sabin strains and wild poliovirus. But, because the experiment of global Sabin 2 cessation has already begun, we focus the majority of our Results and Discussion on Sabin 2 transmission. Our results show that tOPV has been effective at interrupting polio transmission wherever it has been reliably delivered because it is able to block the strongest links in the transmission chain, that IPV boosting campaigns are effective for reducing transmission in settings where re-infection is common due to high force of infection, waning immunity, and low OPV efficacy, that the cross-immunity against type 2 provided by bOPV is unlikely to provide significant transmission-blocking immunity against Sabin 2 in high transmission settings, and that the ability of Sabin 2 to transmit widely in post-OPV settings will resemble the ability of WPV to spark outbreaks in the pre-vaccine era. We conclude with discussion of the implications for OPV cessation, global IPV and OPV supply requirements and use.

Guide to the manuscript. This paper is both a review of existing literature and a novel synthesis of it, presented together so that the chain of evidence from the primary data to our conclusions about Sabin transmission is unbroken. In the Methods section, we build our mathematical model, based on a thorough review of individual-level studies of the impact of polio vaccination on poliovirus shedding and a selective review of well-reported studies of polio transmission within households and among close extra-familial contacts. Through our quantitative review of poliovirus shedding duration, fecal viral concentration, dose response, and waning immunity against intestinal infection, we developed an integrated mathematical framework unified by a statistical immune correlate—the OPV-equivalent humoral antibody titer—to model the interaction between polio vaccination and polio infection. We then reviewed detailed transmission studies to provide the basis for our model of polio transmission. Each model component provides quantatitive results that would constitute the end points of a more traditional metastudy. These

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"review results" are Methods with respect to model building, and our Results and Discussion, focused on the roles of fecal-oral exposure and immunity in Sabin 2 transmission, derive from the completed model of how polio vaccination affects poliovirus transmission.

Methods

Overview of mechanism, measurement, and modeling of poliovirus transmission

A person's eligibility to participate in poliovirus transmission depends on their ability to acquire infections given exposure (acquisition and dose response) and their propensity to shed poliovirus during infections (shedding duration and fecal viral concentration). Acquisition takes place orally, and the intestines are the primary site of infection. All infected individuals shed poliovirus in feces, and individuals with little immunity may also shed orally (for shorter durations at lower viral load relative to fecal shedding). Mucosal (intestinal) immunity limits infection. Humoral (serologic) immunity prevents viremia and thus oral shedding, central nervous system invasion, and paralytic disease. Through the effects of immunity on infection, vaccination changes the transmission dynamics in populations [4, 20, 26, 31]. Immunity against paralysis has no direct causal influence on transmission, and the effectiveness of vaccination against paralysis has been thoroughly studied [32], so paralysis is not analyzed in detail in this paper.

Through person-to-person transmission, polio infections can propagate quickly through local intimate contact networks with insufficient infection blocking immunity and also transit between local networks through weaker social ties. Community transmission is built from interactions of many intimate contact networks, more weakly connected.

OPV challenge studies provide experimental model systems for studying poliovirus transmission. With respect to transmission, successful OPV take (infection with live vaccine) creates index cases that can transmit to contacts along natural routes. Data from WPV surveillance of index cases and contacts can be analyzed similarly. From longitudinal sampling of either stool or serum, incidence can be derived, prior immunity can be inferred, and exposure rates between contacts can be estimated.

The transmission models in this paper were based on the assumption that person-to-person contact enables fecal-oral transmission, mediated by the daily exchange of small amounts of fecal

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matter. Oral shedding was ignored, and so the transmission models are most appropriate for settings with inadequate sanitation. Starting from a transmission model calibrated to a reference study of Sabin transmission in the pre-OPV era [33], and incorporating WPV surveillance data from the USA [34] and India [35], counter-factual studies were simulated to explore how changes to immunity induced by different vaccination regimens affect transmission among intimate contacts. Individuals in the transmission models represent the "average child" under five years of age expected after each vaccination regimen; individual-level variability was ignored in favor of emphasizing relative differences between vaccination regimens with all else held equal. The effects of larger family and intimate social network sizes were also explored in the context of a simple network model.

In our modeling of Sabin transmission among close contacts shortly after OPV vaccination, we ignored the possibility that genetic evolution may alter the infectiousness of the Sabin strains in the few weeks after OPV exposure. From the known timescales of genetic reversion, it is likely that the typical polioviruses shed in the first few weeks after monovalent OPV (mOPV) challenge have reverted the attenuating nucleotide substitutions in the 5' non-coding region but maintain attenuating substitutions in the coding region [36]; this interpretation is compatible with the evidence for partial attenuating marker reversion after the first week in the reference transmission study [33]. We then approached understanding the role of complete reversion to wild-phenotype and cVDPV emergence through quantified differences between the Sabin strains and wild polioviruses.

The data and biological inferences that informed each aspect of the immunity and transmission models are described below. The quantitative details of the models follow the relevant data, and data tables, analysis code, modeling code and parameters (Table S1) are provided in the supplement. Interactive tools to explore the digitized primary data are available at `famulare.github.io/howPolioVaccinationAffectsPoliovirusTransmission/`.

OPV-equivalent humoral immunity model

Previous reviews have demonstrated that homotypic OPV-induced humoral neutralizing antibody titers (denoted N_{Ab}, measured as the geometric mean reciprocal dilution of serum that is able to neutralize 100 TCID50 of the relevant poliovirus serotype) are predictive of infection acquisition probability, shedding duration, and excreted viral load after OPV challenge [30, 37]. IPV-induced humoral antibody titers are not predictive of shedding and acquisition [30], but the impacts of vaccine schedules containing IPV on fecal shedding can be described in terms of modeled

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OPV-equivalent humoral antibody titers (first introduced by Behrend *et al* [30] and called "mucosal immunity" therein).

The concept of OPV-equivalent humoral antibody titer unifies shedding and acquisition data for different vaccine schedules. Following the results of Behrend *et al* [30], we assumed that the typical immunologically-naive individual with no history of poliovirus exposure ("unvaccinated") and no measurable humoral immunity ("seronegative") is defined to have an OPV-equivalent humoral antibody titer equal to one: $N_{\mathrm{Ab}} = 1$, that the maximum median homotypic OPV-equivalent titer is $N_{\mathrm{Ab}} = 2048\,(= 2^{11})$, and that homotypic antibody titers for each serotype are independent.

Sources of data on individual-level shedding and acquisition

Almost all relevant studies on OPV shedding, acquisition, and transmission published prior to 2012 were reviewed by Duintjer Tebbens *et al* [9]. Digitized data on shedding duration and fecal viral load were taken from the supplementary material in Behrend *et al* [30], corrected where discrepancies were noticed, and studies missing or involving bOPV were added [23–25]. Dose response data were first digitized and made publically-available here. The analyses are broadly inclusive of published data, but this paper does not represent a systematic review with pre-specified exclusion criteria. Whole studies and trial arms were excluded if they reported evidence of substantial uncontrolled or unmeasured natural exposure to either wild poliovirus or vaccines strains by contact prior to OPV challenge or WPV infection [38–44] or when data across vaccination regimens or serotypes could not be disaggregated [45]. We included OPV challenge studies in which low levels of natural exposure were possible but not common. A summary of all included data describing vaccination regimens, OPV challenge formulation or WPV exposure, ages, and available shedding and dose reponse data, and possible natural exposure is provided in Table S2 [23–25, 33, 46–62]. For a deeper discussion of data quality from the included studies, see Duintjer Tebbens *et al* [9].

Statistical comparisons and model fitting

Shedding duration and dose response can be quantified with respect to prevalence of poliovirus in stool after OPV challenge or WPV exposure. For each dataset considered, infection prevalence was estimated as the number of subjects shedding in stool at each time point over the number tested. In many cases, the data were digitized from published figures and the sample sizes at each time point are approximate. For binary comparisons directly from prevalence data, all p-values reported in line

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with the text correspond to two-tailed Fisher's exact tests. All model parameters describing prevalences were fit by maximum likelihood assuming binomial sampling (at each time point when relevant), and 95% confidence intervals were estimated by parametric bootstrap with 1000 replicates. Models for positive-definite quantities (concentration of poliovirus in stool, antibody titer) were estimated by ordinary least squares on log(quantity), and 95% confidence intervals assume log-normality. To estimate bootstrap confidence intervals of parameters that are conditionally-dependent on previously estimated parameters, we propagated uncertainty by independently resampling parameters from the 95% confidence intervals assuming normality (log-normality where appropriate) prior to resampling the data and re-estimating the parameters currently under investigation. Differences in comparable quantities are considered statistically significant at $\alpha = 0.05$.

Shedding duration

Shedding duration after OPV challenge is an important correlate of an individual's capacity to transmit to others, and longitudinal studies of shedding duration after OPV challenge provided the most informative starting point for comparing the impact of different routine immunization regimens on transmission. 94 trial arms from 18 published studies provided adequate measurements of the probability of fecal shedding over time given successful vaccine take after OPV challenge. The data quantify shedding duration for each serotype for unvaccinated and known seronegative children, as well as children who experienced one of 14 distinct RI regimens combining OPV and IPV. Most subjects were 5 years old or younger at OPV challenge, although two cohorts of adults with natural immunity were also included [46, 59]. As described in detail below, RI regimen is predictive of shedding duration. Conditional on RI regimen, data exploration revealed no associations of shedding duration with age at OPV challenge or the precise RI schedule. Three studies of shedding duration after WPV exposure contained adequate longitudinal data to estimate the duration of shedding after wild poliovirus exposure in previously unimmunized individuals (either paralytic cases or individuals with known serology) [34, 63, 64]; no data are available to test for serotype differences in WPV shedding duration.

Immunologically-naive and maximally-immune individuals. With respect to shedding after OPV challenge, there were no significant differences in shedding duration between unvaccinated and confirmed seronegative children, and thus both subject types constitute the class of

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immunologically-naive individuals. There were also no significant differences in Sabin shedding duration by serotype. Conditional on vaccine take, the maximum likelihood estimate of the median shedding duration in an immunologically-naive individual shedding any Sabin strain is $30.3\,(23.6, 38.6)$ days, shorter than the median shedding duration of WPV, $43.0\,(35.7, 51.7)$ days (Fig. 1). The Sabin shedding duration given vaccine take associated with maximum antibody titer ($N_{\mathrm{Ab}} = 2048$) is $6\,(4, 10)$ days, as defined by the data from the tOPVx3 arm of Asturias *et al* [24]. That trial arm was chosen to define maximal immunity because its subjects had the shortest interval between the RI and OPV challenge (4 weeks), shortest median shedding duration and lowest probability of vaccine take after mOPV challenge of all trial arms in all studies. Shedding duration distributions for all represented RI regimens are shown in Fig. S1 and an online interactive exploration of the digitized shedding duration data is available online.

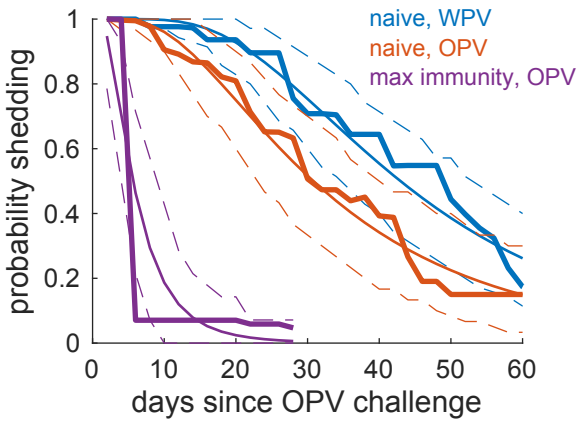

Figure 1. Shedding duration probability for immunologically-naive and maximally-immune individuals. Empirical shedding duration reverse-cumulative distributions, model maximum likelihood estimate, and 95% CI range shown.

Shedding duration after OPV challenge is correlated with $\log(N_{\mathrm{Ab}})$ [30], and so the probability an individual is still shedding given an infection, as a function of OPV-equivalent humoral antibody titer based on the data in Fig. 1, is plausibly distributed as:

$$P\big(\text{shedding at } t \big| N_{\mathrm{Ab}}; \text{infected at } t = 0\big) = \frac{1}{2}\left(1 - \mathrm{erf}\left(\frac{\log(t) - (\log(\mu) - \log(\delta)\log(N_{\mathrm{Ab}}))}{\sqrt{2}\log(\sigma)}\right)\right), \quad (1)$$

with Sabin parameters $\mu_S = 30.3\,(23.6, 38.6)$ days and $\sigma_S = 1.86\,(1.57, 2.27)$ days, WPV parameters $\mu_{WPV} = 43.0\,(35.7, 51.7)$ days and $\sigma_{WPV} = 1.69\,(1.21, 1.94)$ days, and $\delta = 1.16\,(1.13, 1.21)$ days. This model for Sabin shedding with insignificantly different parameters was derived through alternate means in the supplemental software of Behrend *et al* [30] but was not described, and it was

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used without derivation in references [36, 65].

Effects of routine immunization on shedding duration and pre-challenge immunity. To enable quantitative comparisons between different RI regimens of the effect of pre-challenge immunity on shedding after OPV challenge, we estimated the median shedding durations and inferred pre-challenge OPV-equivalent antibody titers for all represented RI regimens and serotypes using the maximum likelihood model for shedding duration after OPV challenge in Eq. (1) and aggregated data for each RI regimen. Results across all RI regimens are shown in Fig. S2 and online. For ease of comparison in the figures below, uncertainty in the median shedding duration for the unvaccinated groups is recast as uncertainty in the median antibody titer rather than uncertainty in the maximum likelihood parameters of Eq. (1).

Routine immunization with OPV. Median shedding duration and inferred pre-challenge antibody titers for RI regimens based on OPV are shown in Fig. 2. Immunity generally increases with the number of pre-challenge OPV doses. As is well known, repeated vaccination with tOPV provokes stronger immunity against type 2 than type 1 or especially type 3. A single dose of tOPV or mOPV are roughly equivalent for types 1 and 2. IPV prior to and concurrent with tOPV provided no additional reduction in shedding duration over tOPV alone [21]. The lower overall level of immunity in the IPV & tOPV data relative to the tOPV-only data may reflect setting-dependent differences in vaccine effectiveness (Israel vs. majority of data from Latin America) or fast waning (challenge 90 days after last RI dose for IPV & tOPV vs. 28 days after last RI dose for the majority of tOPVx3 data; waning is discussed in detail later). As a rule of thumb, an additional dose of OPV increases the modeled OPV-equivalent antibody titer by roughly a factor of 10.

Routine immunization with IPV only. There is no cumulative reduction of shedding duration with the number of pre-challenge IPV doses (Fig. 3). All IPV-only RI regimens with significant inferred pre-challenge immunity are supported by data from IPV trials conducted in otherwise tOPV-using or pre-WPV-eradication settings [51, 55, 56, 60], whereas the studies showing no impact from IPV examined shedding in the youngest cohort studied in an OPV-using setting [23] or an established IPV-only setting [58]. These data are consistent with the hypothesis that IPV-only vaccination has no impact on shedding duration [21], in agreement with molecular evidence that IPV produces no mucosal immunity in the absence of prior exposure to live poliovirus [66]. We discussed IPV boosting in the dose response section.

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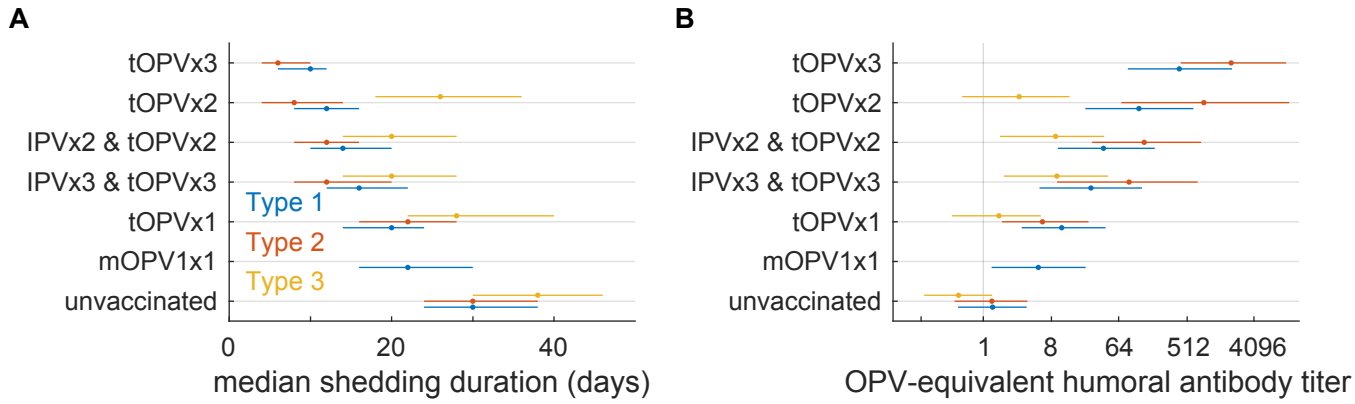

Figure 2. Effects of pre-challenge OPV vaccination on shedding duration and inferred pre-challenge antibody titers. Median shedding durations derived from trial data (A) decrease and modeled pre-challenge homotypic OPV-equivalent humoral antibody titers (B) increase with the number of OPV doses. Results for OPV challenge with each serotype are represented by the same color code throughout the paper (type 1, blue; type 2, red; type 3, orange).

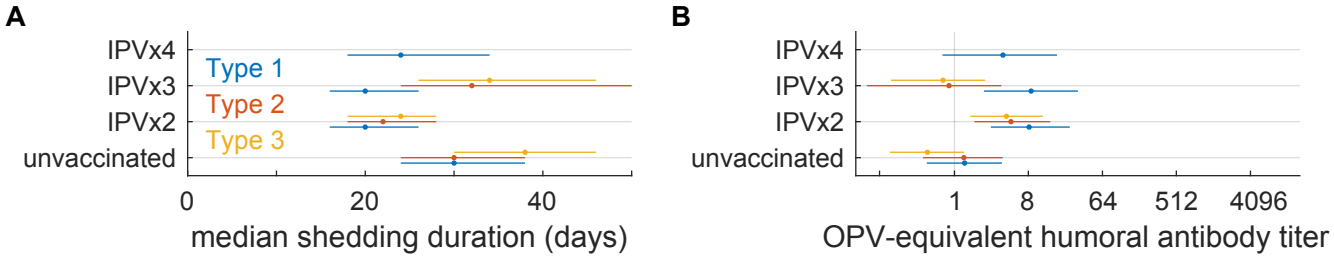

Figure 3. Effects of pre-challenge IPV vaccination on shedding duration and inferred pre-challenge antibody titers. Median shedding durations derived from trial data (A) and modeled pre-challenge homotypic OPV-equivalent humoral antibody titers (B) are uncorrelated with the number of IPV doses.

Heterotypic immunity provided by bOPV against mOPV2 challenge. In preparation for the recent global switch from tOPV to bOPV in routine immunization and the need to understand how the switch could impact type 2 immunity, recent studies have examined the heterotypic immunity against mOPV2 challenge provoked by RI schedules containing bOPV and possibly one or two doses of IPV [23, 24]. In settings where primary risks associated with OPV vaccination outweigh transmission risks, current RI regimens use at least one dose of IPV followed by at least one dose of bOPV, and in settings where type 1 transmission risk is of high concern, three doses of bOPV are recommended with at least one dose of IPV concurrent with later doses of bOPV.

With respect to shedding duration, bOPVx3 & IPVx2 is the most effective vaccination regimen for producing immunity against type 2 infection [24]. However, all bOPV-based regimens are roughly equivalent to each other: the largest difference in median shedding duration after mOPV2 challenge among the bOPV schedules (from bOPVx3 to bOPVx3 & IPVx2) is 4 (3,5) days, only 28% of the 14

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(13,15) day difference in going from tOPVx1 to tOPVx2. The similarity of schedules containing one dose of bOPV to those containing three doses of bOPV suggest that most of the oberved immunity is coming from the first successful bOPV take. As a reference, bOPVx3 in RI produces immunity against type 2 equivalent to one dose of tOPV.

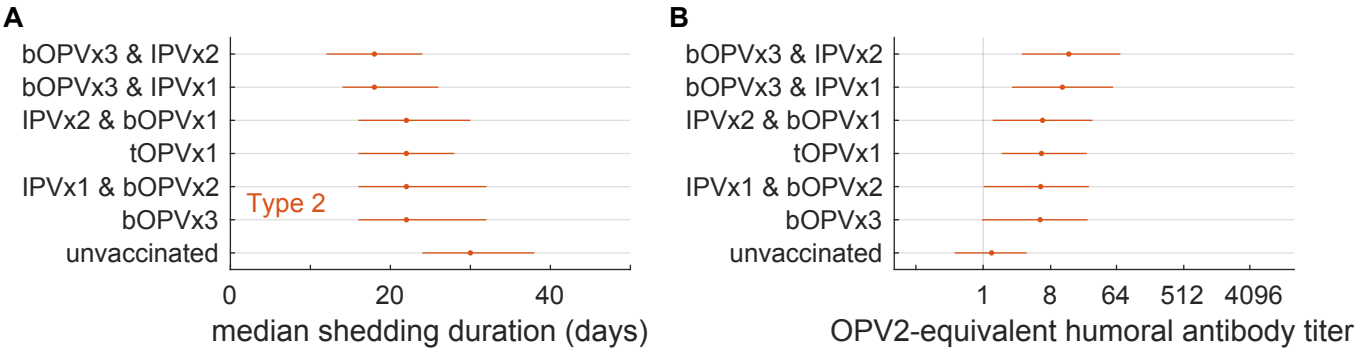

Figure 4. Effects of pre-challenge bOPV vaccination on shedding duration and inferred homotypic OPV-equivalent pre-challenge antibody titers against type 2 poliovirus. Median shedding durations derived from trial data (A) decrease and modeled pre-challenge homotypic OPV-equivalent humoral antibody titers (B) are shown for RI regimens containing bOPV. All bOPV schedules provide statistically significant increases in immunity to type 2 relative to unvaccinated individuals, and the inferred immunity against type 2 shedding after recieving bOPV is roughly equivalent to receiving one dose of tOPV.

It is also interesting to note that while our immune correlate, OPV-equivalent humoral antibody titer, is a statistical construct that is not intended to be directly measurable for vaccination regimens in which IPV provides primary homotypic serologic immunity, our inferred median values for the OPV-equivalent humoral antibody titer against Sabin 2 for bOPVx3 and bOPVx3 & IPVx1 agree with the measured stool neutralization titers recently reported for the same trial subjects by Wright *et al* [67].

Concentration of poliovirus in stool

The concentration of poliovirus in stool is an important component of an individual's ability to transmit to others because it affects the dose delivered via fecal-oral exposure. Quantitative data describing the concentration of poliovirus in stool after OPV challenge was available for 21 trial arms from seven of the longitudinal shedding duration studies [23, 24, 46–48, 58, 59]. The included studies reported viral load as the geometric mean infectious dose per gram of stool (TCID50/g) averaged across all subjects positive for poliovirus at each time point, and individual-level variation data was generally not available. Ages at challenge ranged from 7 months to 65 years or more. The majority of trial arms challenged subjects with mOPV2 (mOPV1, $n = 5$; mOPV2, $n = 11$; mOPV3, $n = 5$).

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Data exploration revealed no systematic differences in viral load by serotype (Fig. S3 and online). We are not aware of similar data for WPV shedding.

Immunologically-naive individuals. In individuals lacking immunity against poliovirus infection (unvaccinated, seronegative, or IPV-only RI), peak concentration depends on the age at infection (Fig. 5), falling roughly two orders of magnitude over the first three years of life. To model the age-dependence, we fit an exponential model to the peak shedding concentration:

$$\log_{10}\big(\text{peak TCID50/g}\big|\text{age}; N_{\text{Ab}} = 1\big) = \begin{cases} S_{\max} & \text{age} < 7 \text{ months} \\ (S_{\max} - S_{\min})\exp\big(\frac{7-\text{age}}{\tau}\big) + S_{\min} & \text{age} \geq 7 \text{ months} \end{cases} \quad (2)$$

with maximum likelihood parameters $S_{\max} = 6.7\,(5.9, 7.5)$, $S_{\min} = 4.3\,(3.5, 5.0)$ TCID50 per gram, and $\tau = 10\,(1, 33)$ months (Fig. 5B). The time constant of roughly one year is consistent with major developmental milestones including the transition to solid food and immune system maturation [68, 69], after which the limited data indicate stability of peak shedding in immunologically-naive individuals for life.

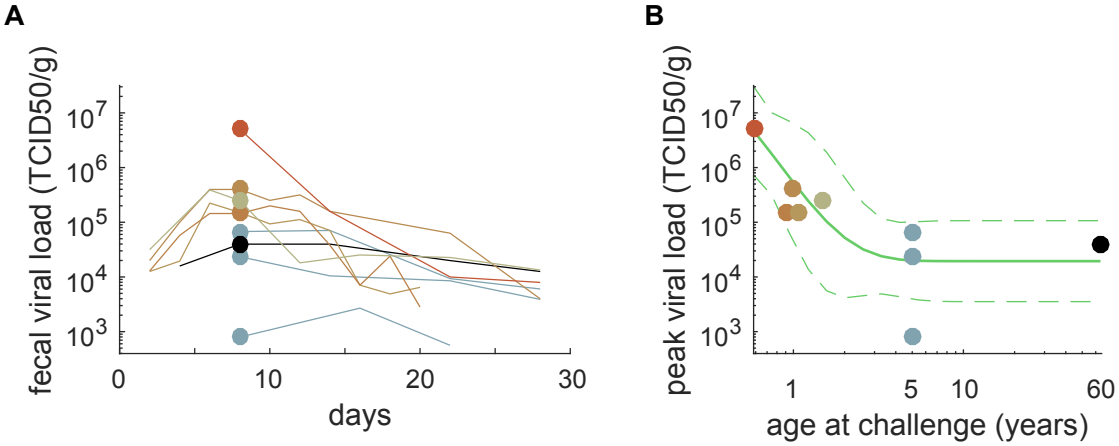

Figure 5. Peak poliovirus concentration in stool depends on age. Geometric mean concentrations over time (TCID50 per gram) (A) and peak concentration vs. age (B) are shown for individuals with no prior immunity to poliovirus infection (unvaccinated, seronegative, or IPV-only RI). Data for trial arms are colored by age at OPV challenge. Age-dependence model shown in green (mean, solid line; 95% confidence interval, dashed). Peak concentration declines with age in the first three years of life and then stabilizes. (Interactive visualization online.)

Effects of OPV-equivalent prior immunity on concentration after mOPV2 challenge. Pre-challenge immunity has a strong effect on concentration in stool. Age-adjusted stool

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concentrations for individuals positive after mOPV2 challenge are shown in Fig. 6. Individuals with maximal immunity, challenged one month after three doses of tOPV (tOPVx3), excrete poliovirus in one-thousand times lower concentrations than immunologically-naive individuals. Concentration declines with increasing OPV-equivalent antibody titer as:

$$\log_{10}\big(\text{peak TCID50/g}\big|N_{\text{Ab}};\text{age}\big) = (1 - k\log_2(N_{\text{Ab}}))\log_{10}\big(\text{peak TCID50/g}\big|N_{\text{Ab}} = 1;\text{age}\big) \quad (3)$$

with $k = 0.056\,(0.01, 0.079)$.

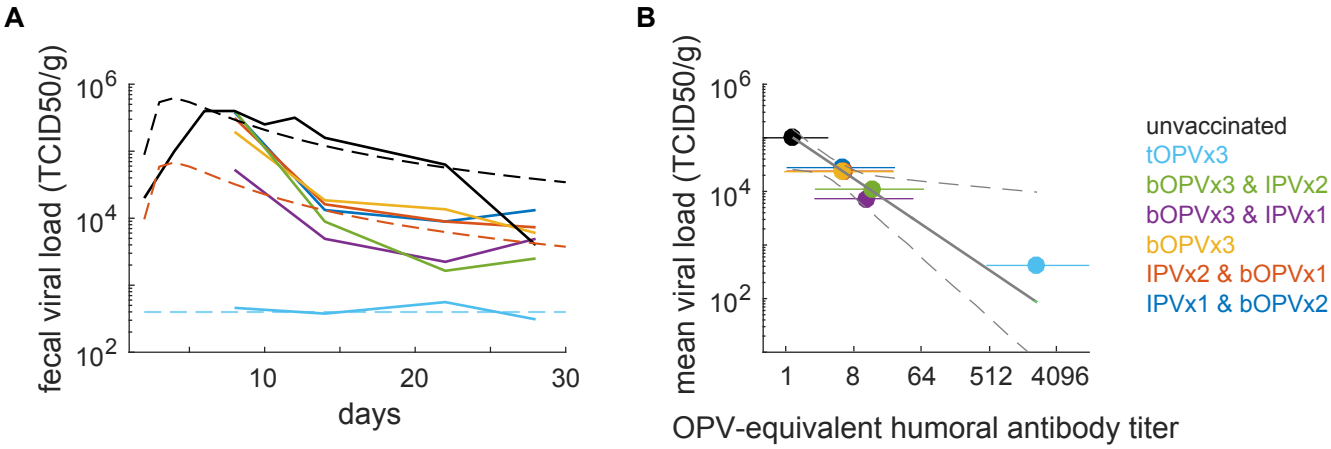

Figure 6. Effects of pre-challenge vaccination on concentration in stool. (A) Geometric mean concentrations (TCID50/g; age-adjusted to 12 months using Eq. (2)). Dashed lines show model timecourses from Eq. (4) for OPV-equivalent antibody titers $(1, 8, 2048)$. Data curves are colored by RI regimen. (B) Time-averaged age-adjusted viral load vs. OPV-equivalent humoral antibody titer are shown for subjects who shed after mOPV2 challenge; gray lines show maximum likelihood model and 95% CI. Prior immunity against type 2 challenge induced by bOPV in RI reduces peak shedding by roughly one order of magnitude, and immunity from three doses of tOPV reduces shedding by three orders of magnitude. (Interactive visualization online.)

Model of concentration in stool given detectable poliovirus infection. Poliovirus concentrations peak shortly after acquiring infection and decline slowly thereafter. To model viral load over time, following refs. [30, 65], we fit a quasi-log-normal shedding profile to the age-adjusted aggregated data for immunologically-naive individuals (Fig. S4). Viral loads for all immunity levels were well-fit by the product of the immunologically-naive temporal profile and the peak concentration described in Eq. (3):

$$\big(\text{concentration }(t)\big|N_{\text{Ab}};\text{age}\big) = \max\left(10^{2.6}, \big(\text{peak TCID50/g}\big|N_{\text{Ab}};\text{age}\big)\left(\frac{\exp\left(\eta - \frac{\nu^2}{2} - \frac{(\log(t)-\eta)^2}{2(\nu+\xi\log(t))^2}\right)}{t}\right)\right) \quad (4)$$

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with $\eta = 1.65\,(1.26, 2.09)$, $\nu = 0.17\,(0.01, 0.78)$, $\xi = 0.32\,(0.08, 0.71)$, and lower bound $10^{2.6}$ TCID50/g to reflect the minimum reported detectable shedding (Fig. 6A).

Heterotypic immunity provided by bOPV against type 2 shedding. With respect to concentration in stool after mOPV2 challenge, all bOPV-based regimens are roughly equivalent to each other and to one dose of tOPV. The largest difference in peak concentration after mOPV2 challenge among the bOPV schedules is a factor of three, whereas the average of all bOPV-containing schedules reduced concentration from immunologically-naive by a factor of ten, equivalent to the prediction from Eq. (3) for the reduction in shedding from one dose of tOPV.

Routine immunization with IPV only. We found no significant differences in fecal concentration between seronegative children and IPV-only children when looking across trials. However, one study in Cuba that did not meet our inclusion criteria because only one sample was collected per subject reported that IPV in RI reduced fecal concentration by a factor of 3 one week after OPV challenge [70]. That difference is small relative to the factor of 10 difference following bOPV (& one or more doses of IPV). From all the evidence known to us, the effect of IPV on fecal shedding in the absence of live poliovirus exposure is negligible in comparison to effect of OPV.

Dose response to OPV challenge

Dose response is important for quantifying the ability of fecal-oral exposure to infect contacts of individuals infected with poliovirus, and for modeling the relationship between individual-level shedding and acquisition data derived from the large doses in OPV to smaller doses acquired naturally. Primary sources of dose response data were reviewed in refs. [27, 28]. To better understand dose response over a range of exposures, we analyzed nine trial arms from four studies [48, 51, 53, 55] that measured the probability of shedding after exposure from doses delivered in oral droplets ranging from 10 to 10^6 TCID50 and clearly described the pre-challenge immune histories of their subjects. Three studies challenged with Sabin 1, none used Sabin 3, and one unusual human-passage study challenged with Sabin 2 and type 2 poliovirus derived from Sabin 2 after five days of replication in children [48]. We also included data from studies that only tested vaccine doses (10^{5-6} TCID50) to place the effects of bOPV RI regimens [23, 24] and IPV boosting on prior OPV exposure in context [25]. There were no significant differences between Sabin 1 and Sabin 2, but statistical power at low doses is poor since typical samples sizes are of order ten

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samples per dose; we examined further evidence for differences in infectivity by serotype and vaccine or wild-type in later sections on transmission-informed dose response models.

Effects of pre-challenge immunity on dose response. Healthy individuals with no immunity against infection are susceptible to oral OPV doses of roughly 10 TCID50 or greater (Fig. 7A-B). Pre-challenge OPV-equivalent immunity estimated from shedding duration is associated with a reduction in the probability of infection at all doses (Fig. 7C). At vaccine doses, RI regimens involving bOPV reduce acquistion by 25%, again roughly one third of the reduction provided by three doses of tOPV.

Dose response model. We fit a beta-Poisson dose response model to summarize data for all doses and OPV-equivalent immunity levels estimated from shedding duration (Fig. 7C-E). The beta-Poisson model is based on the assumptions that a single infectious unit is sufficient to start a detectible infection, that multiple infectious units contribute independently to the total probability of infection, and that the probability an infectious unit survives the host gauntlet from initial exposure to the site of infection is beta-distributed [71]. After finding that the model in Behrend *et al* [30] fit poorly at low doses, we explored various parameterizations of the model and found that a parsimonious description of all the OPV challenge data was provided by:

$$P\big(\text{infection}\big|\text{dose}, N_{\text{Ab}}\big) = 1 - \left(1 + \frac{\text{dose}}{\beta}\right)^{-\alpha(N_{\text{Ab}})^{-\gamma}}, \tag{5}$$

with scale parameter $\beta = 14\,(3, 59)$ TCID50, shape parameter $\alpha = 0.44\,(0.29, 0.83)$, and immunity-dependent shape parameter $\gamma = 0.55\,(0.51, 0.57)$.

The dose response model assumes all naive subjects are capable of being infected at standard OPV doses as is observed in healthy subjects. However, in settings in which diarrhea, non-polio enterovirus infection, and malnutrition are common, enteropathy prevent OPV take [30, 72, 73]. To account for these host factors that prevent poliovirus infection, the dose response model in Eq. (5) should be multiplied by a setting-specific vaccine take probability ranging from zero to one (as included in our analysis of Sabin transmission below).

IPV boosting on prior OPV experience. The dose response data clarify the distinction between IPV boosting on previous experience with live poliovirus and IPV-only immunization. As shown in molecular immunology studies [66] and clearly demonstrated in OPV challenge studies in

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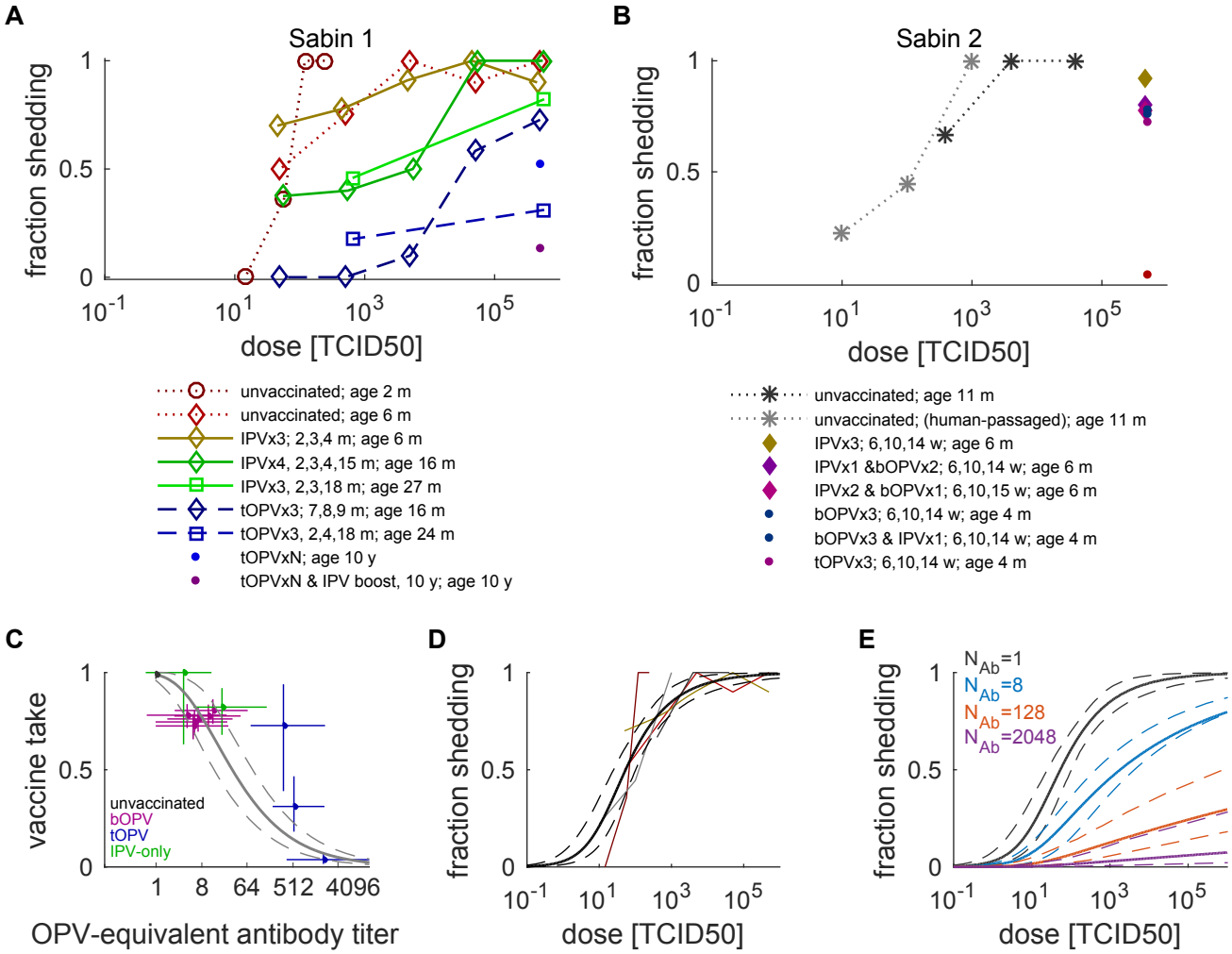

Figure 7. Fraction shedding after mOPV challenge. (A) Dose response study data for all trial arms that challenged with Sabin 1; (B) for Sabin 2 or material closely related to Sabin 2 derived from human stool. Line style indicates pre-challenge immunity: naive (dotted), IPV-only (solid), tOPV (dashed). Legend: immune status; RI schedule if relevant; age at challenge. (C) Susceptibility to infection reduces with increasing OPV-equivalent immunity, due either to natural exposure or direct vaccination. Maximum likelihood model and 95% CI (Eq. (5)) shown for a dose of $10^{5.7}$ TCID50. (D) Dose response model fit to subjects with no immunity against infection ("unvaccinated" or "IPVx3" with no history of live poliovirus exposure). These individual-level data reveal no significant differences by serotype, but household transmission data provide additional evidence to resolve serotype differences (Table 1). (E) Model dose response curves for various immunity levels.

India [25], IPV is a highly effective booster of immunity against infection induced by OPV. We used the dose response model in Eq. (5) to estimate the OPV-equivalent antibody titer after IPV boosting on children with many prior doses of tOPV in India [25], and the maximum likelihood estimate of the OPV-equivalent antibody titer is $N_{\mathrm{Ab}} = 950\,(512, 1800)$, insignificantly different from the maximal immunity produced by tOPVx3 prior to any waning of infection-blocking immunity.

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In contrast, the data for dose response studies repeat the pattern from shedding duration that IPV-only vaccination produces no immunity against infection. As mentioned in our analysis of shedding duration, the distinction between having no prior experience with live poliovirus and IPV boosting likely explains the studies that show some impact of IPV on intestinal infection. In the dose response data, the two trial arms we reviewed with IPV booster doses after one year of age show reduced susceptibility [51, 55] (Fig. 7A). Both studies took place in tOPV-using communities, one reported direct evidence of transmission-acquired infection in the cohort prior to the booster [51], and shedding durations for these trial arms were also reduced, consistent with the influence of live poliovirus exposure (Fig. 3).

Waning immunity against infection

By examining the OPV-equivalent antibody titers inferred from shedding duration or from dose response in studies with subjects of many ages, we built a composite picture of waning immunity against infection. To estimate waning rates, we considered data for individuals that were likely maximally immune after their last poliovirus exposure prior to OPV challenge, either due to immunization with 3 or more doses of tOPV [24, 25, 55] or natural immunity [46, 59], and for which the interval between the last immunization and OPV challenge was known or could be reasonably estimated (Fig. 8; see Supplement for additional details).

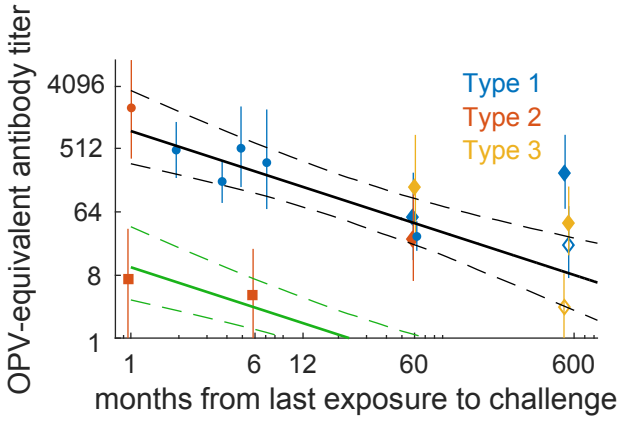

Figure 8. Waning immunity against infection. OPV-equivalent antibody titer vs. time between last exposure and mOPV challenge. Symbols indicate source of pre-challenge immunity: tOPVx3+, •; seroposve and naturally-immunized, ♦; seronegative but likely naturally-immunized, ◊; bOPVx3, ■. Bar and dot color indicate challenge serotype. Lines: black, homotypic immunity; green, heterotypic immunity against type 2 from bOPV.

A clear pattern describing waning immunity exists over the 50+ year range of intervals between

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last immunization and mOPV challenge. We fit a power law to the OPV-equivalent antibody titers,

$$N_{\mathrm{Ab}}(t) = \max\big(1, N_{\mathrm{Ab}}(1)\ \big(t^{-\lambda}\big)\big)\,, \tag{6}$$

where t is measured in months between last immunization and mOPV challenge, $N_{\mathrm{Ab}}(1)$ is the baseline immunity one month post-immunization, and we found the exponent to be $\lambda = 0.75\,(0.59, 0.89)$. The power law captures fast and slow waning with a single parameter: it takes $22\,(12, 42)$ months for immunity to drop by one order of magnitude and $40\,(16, 100)$ years to drop by a second.

The limited available evidence indicates that homotypic immunity against infection persists for life in well-immunized people at levels greater than or equivalent to one dose of tOPV in children, regardless of serostatus. This interpretation of significant persistent immunity in seronegative elderly people differs from the interpretation given in Abbink *et al* [59] in which the lack of correlation between the speed of serologic immune response and shedding were used to argue that memory immunity provides no protection from shedding. Their data support the hypothesis that post-challenge memory response does not discriminate differences in shedding, but they did not have a control group of never-exposed subjects to compare deeply waned immunity with true naive immunity. As seen through metastudy, the observed shedding durations in the seronegative elderly are reduced relative to the shedding durations in unvaccinated and seronegative children, and are compatible with the hypothesis that previously-exposed elderly people retain waned but persistent immunity against infection, as has been suspected previously [28, 74].

Waning of heterotypic immunity against type 2 in bOPV recipients. The two bOPVx3 control arms in Asturias *et al* [24] provide data on shedding from mOPV2 challenge one month and six months after bOPV vaccination. The data are consistent with the hypothesis that heterotypic immunity against type 2 infection wanes at the same rate as homotypic immunity (Fig. 8). Under that hypothesis, the cross-protective effect from bOPV likely wanes to negligible levels $2\,(1, 6)$ years after the last bOPV exposure. No data exist to examine if IPV boosting would return heterotypic immunity to peak levels as it does for homotypic immunity. Regardless of the specific details of heterotypic waning, the immunity against infection induced by a bOPVx3 & any IPV is likely inferior at all ages that induced by multiple doses of tOPV, even decades after immunization.

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Sources of data on household and close-contact transmission of poliovirus

To make the connection between the individual-level data on how polio vaccination affects polio shedding to the epidemiology of polio transmission, individual shedding and acquistion must be interpreted in the context of transmission study data. The data on individual-level aspects of polio infection show remarkable coherence across studies, but the same is not true of literature on community transmission of poliovirus. Much of this is due to the setting-specific nature of intimate contact transmission between subjects and the inherent increase in complexity of monitoring a population as a whole and not just uncorrelated individuals as in a clinical trial setting. In lieu of a comprehensive review of the primary literature describing poliovirus transmission (see refs. [26, 28]), we chose to model the three studies we found most informative—studies with large sample sizes in which the population under surveillance is clearly described and information about pre-exposure immunity was reported (either directly through vaccination histories or serostatus, or indirectly via shedding duration).

Sabin transmission among close contacts of OPV recipients

Houston 1960. The most comprehensive and best reported study on Sabin transmission to date took place in a community with low socioeconomic status (low-SES) in Houston during the winter of 1960 [33]. Young children aged 2 to 18 months were enrolled to receive a dose of OPV (mOPV1, mOPV2, mOPV3, or tOPV), and weekly stool samples were collected from the vaccine-recipient index children, their siblings (under age 15 years; average age 4 years), and primary extrafamilial social contacts of siblings to observe poliovirus shedding due to direct vaccination and subsequent transmission. Typical enrolled families contained three children under 18 years of age. Groups receiving each type of OPV were segregated geographically to minimize contact between trial arms. The relevant results of the study are summarized here.

The majority of index children had prior serological immunity either due to maternal antibodies or prior IPV vaccination, but none had any evidence for prior exposure to live poliovirus. The authors reported that they found no statistically significant differences in poliovirus fecal shedding between IPV recipients and unvaccinated children. This paper follows their lead and treats all index subjects as a single cohort, although a small reduction in shedding in older children may be apparent on re-analysis (see Supplement and Fig. S5). No information about prior immunity or live poliovirus exposure was presented for siblings or contacts.

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The proportions of subjects shedding poliovirus after receiving monovalent OPV are shown in Fig. 9. Due to differences in vaccine take in this population, index children who recieved mOPV2 shed significantly more than those who received either mOPV1 or mOPV3, and shedding was similar for mOPV1 and mOPV3 (mean prevalence over 5 weeks: type 1 vs. type 2 $p < 0.001$; type 1 vs. type 3 $p = 0.75$).

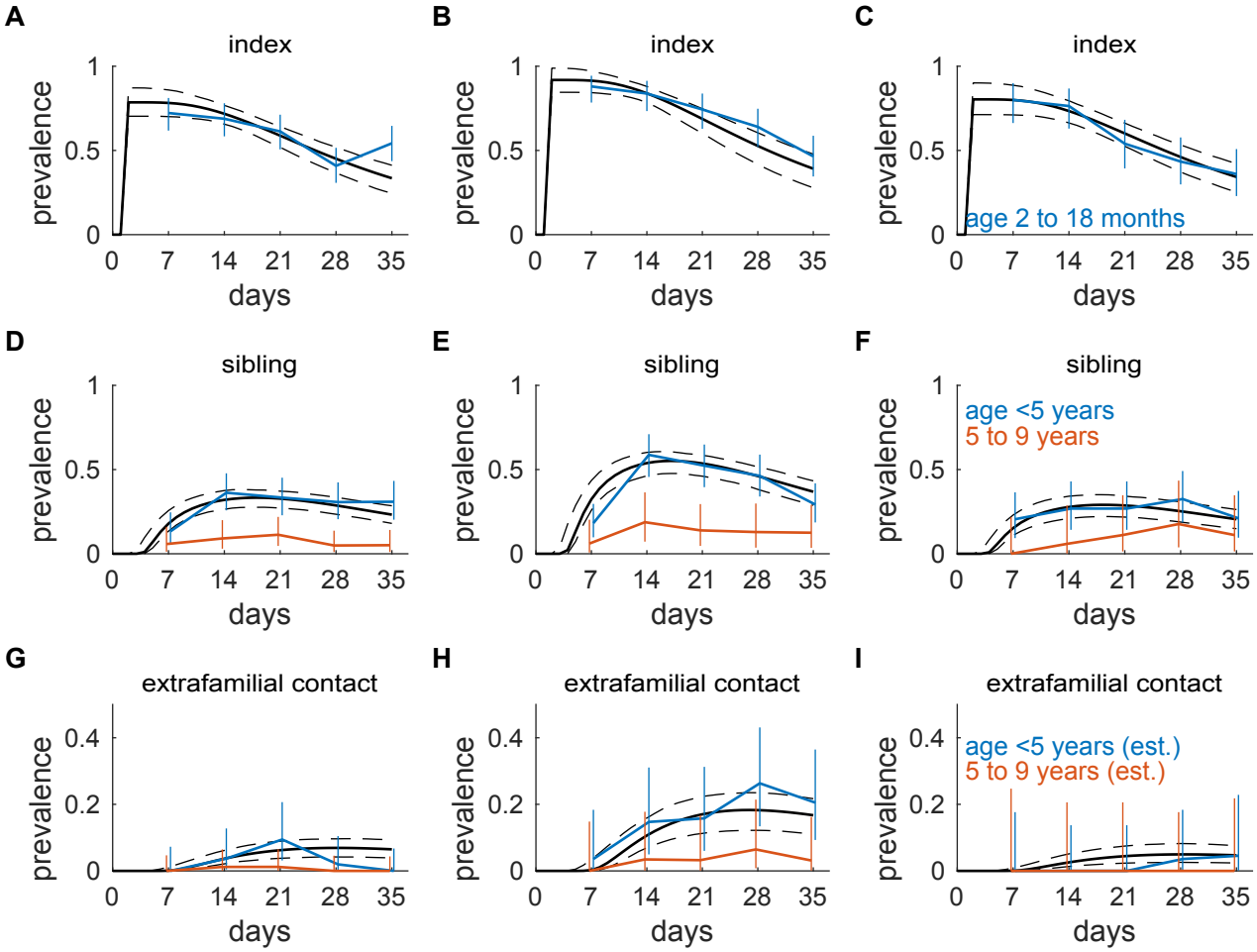

Figure 9. Fraction shedding after mOPV challenge by cohort and age range. Observed fraction shedding after mOPV challenge and 95% binomial confidence interval for each serotype, subject type, and age cohort (children under age five years, blue; age five to nine, red; model fit to prevalence under age five, black). (A-C) index children given Sabin 1 ($n = 94$), Sabin 2 ($n = 75$), or Sabin 3 ($n = 55$). Modeled prevalence in index children is given by the shedding duration distribution for "naive, OPV" in Fig. 1. (D-F) Fraction of siblings shedding types 1 ($n = 190$), 2 ($n = 122$), or 3 ($n = 69$). (G-I) Fraction of extra-familial contacts of siblings shedding types 1 ($n = 138$), 2 ($n = 71$), or 3 ($n = 47$). Type 2 transmitted at highest intensity, both because of elevated shedding in infants relative to types 1 and 3, and due to the higher infectivity of type 2 (Table 1).

Siblings of index children were not directly vaccinated, but became infected with Sabin strains

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via transmission. Shedding due to transmission is significantly higher in siblings under 5 years of age than in children ages 5 to 9 for all serotypes (mean prevalence by age: type 1 $p < 0.001$; type 2 $p < 0.001$; type 3 $p = 0.002$). All model results and statistical comparisons in this paper for siblings and contacts are based on the age under 5 years cohort (see Supplement for discussion of the more-detailed age breakdown presented in the original paper). Shedding rates were very low in parents and children age 10 years and older ($< 2\%$) [33], and so it is likely the transmission was direct from index child to sibling and was not mediated by infected caretakers. Shedding due to transmission-acquired type 2 was significantly more common than for types 1 and 3, and shedding due to transmission was similar for types 1 and 3 (mean prevalence: type 1 vs type 2 $p = 0.002$; type 1 vs type 3 $p = 0.33$).

Primary extrafamilial contacts of siblings exhibited a similar pattern of increased type 2 shedding and comparable type 1 and 3 shedding (type 1 vs type 2 $p < 0.001$; type 1 vs type 3 $p = 0.73$). Although the authors did not describe the relationships between siblings and extrafamilial contacts in detail, it is likely that the contacts were close friends of the siblings and were directly infected by the siblings, as the authors also describe a smaller set of more socially-distant "secondary extrafamilial contacts" who "were drawn from the neighborhoods or schools attended by the siblings" and who were infected at lower rates than the primary contacts [33]. No detailed demographic decomposition by trial arm was reported for the contacts, and so we assumed the contact and sibling demographics were the same, and estimated shedding fractions by age cohort for the contacts were derived as described in the supplement.

Index–sibling–extrafamilial contact transmission model

To develop a quantitative understanding of the impact of pre-exposure immunity on transmission, the individual-level effects of vaccination on shedding and acquisition need to be understood in the context of transmission data. To do so, we built a model of the index child to older sibling to extrafamilial contact transmission chain (Fig. 10A) described above in which each subject has appropriate immunity, dose response, and poliovirus exposure to explain the transmission study data.

The data describing prevalence over time for each subject type provided estimates of each subject's probability of shedding after direct mOPV challenge or exposure to shedding contacts. In the model, transmission starts when the infant is challenged with mOPV. The probability of shedding after mOPV2 challenge is determined by the dose response model, Eq. (5) and a per-dose

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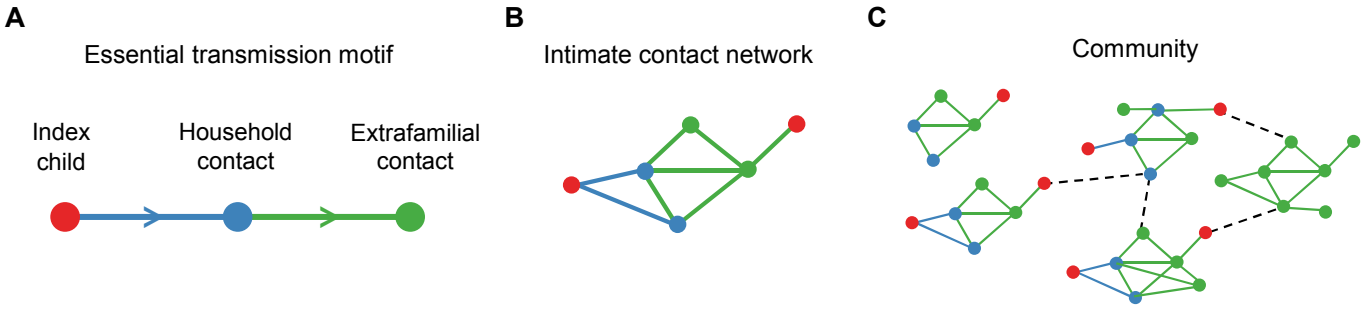

Figure 10. Network motifs of poliovirus transmission. (A) The essential motif of poliovirus transmission is index child to within-household contact to between-household contact. Under typical circumstances in the pre-OPV-cessation era, young children are most likely to be index cases within a household as they are least likely to be immunized. The age mixing patterns of young children make it likely that extrafamilial transmission is most often mediated by older siblings of index children and not direct contact to infants between houses. (B) Intimate contact networks among children involve their siblings and close friends in other households. These friend groups form the central network motif of community transmission, passing virus between households. (C) Communities are built of many intimate contact networks, loosely connected. To predict qualitative changes in the dynamics of transmission at the community level after OPV cessation, we modeled quantitative changes among intimate contact networks.

efficacy to represent study-specific variation in mOPV take. Given infection, the infant sheds poliovirus at fecal concentrations described by Eq. (4) with declining probability over time, Eq. (1). Siblings are exposed to a daily oral dose of fecal matter from the infants that contains poliovirus in proportion to the amount shed, and siblings are infected with the probability determined by the dose response model. Assuming all transmission to extrafamilial contacts occurs only from the siblings, an extrafamilial contact is similarly exposed to sibling fecal matter, which in turn doses them with poliovirus in proportion to the probability the sibling is shedding at its viral concentration. The free parameters specific to the transmission study were the pre-challenge immunity of each subject type, the daily fecal dose (micrograms of stool) between infants and siblings, the daily dose between siblings and contacts, and the mOPV take rates for each serotype. Transmission equations and simulation code are provided in the supplement.

For all three serotypes and all subject types, the maximum likelihood estimate of the OPV-equivalent pre-challenge immunity was negligible (consistent with $N_{\mathrm{Ab}} = 1$). In this study, mOPV take in the infants was highest for type 2, $0.92\,(0.85, 1.0)$, and similar for type 1, $0.79\,(0.70, 0.88)$ and type 3, $0.81\,(0.71, 0.91)$. The estimated effective daily fecal-oral exposure in siblings from infants was $5\,(1, 45)\,\mu$g per day, and between siblings and their extrafamilial contacts was roughly ten times higher, $46\,(2, 92)\,\mu$g per day.

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Transmission-informed dose response model parameters for OPV. When we assumed that there were no serotype-specific differences in dose response (Eq. (5)), we found that the estimated fecal exposure was highest for type 2, followed by type 1 and then type 3. Rather than attributing serotype differences in the daily probability of transmission to differences in stool exposure, it is more reasonable to assume that fecal exposure did not vary by serotype but dose response does. Given equivalent fecal exposure across arms and assuming that our previous results are most appropriate for Sabin 1 (Fig. 7), we found that the maximum likelihood estimates of the β parameters in the dose response model in Eq. (5) are $\beta_{S1} = 14\,(3, 59)$ TCID50 for Sabin 1 (as dereived from dose-response literature reviewed above), $\beta_{S2} = 8\,(2, 30)$ TCID50 for Sabin 2 and $\beta_{S3} = 18\,(5, 63)$ TCID50 for Sabin 3. The transmision study added information to the dose response parameter estimates, but the adjustments were not large—the updated point estimates for types 2 and 3 are covered by the 95% confidence intervals of the aggregate estimate from the dose response studies.

WPV transmission among close contacts

To better understand the implications of household and close-contact Sabin transmission with respect to the risk of transmission in large populations, we looked to transmission studies of wild poliovirus to estimate how Sabin transmissibility compares to WPV transmissibility.

Louisiana 1953–1955. The most appropriate comparator to the Houston study on Sabin transmission was the Gelfand Louisiana study on community surveillance of WPV incidence [34]. Briefly, from 1953 to 1955, Gelfand *et al* enrolled families with newborn children to undergo regular surveillance for naturally-acquired polio infections. Whenever a newly-infected index child was identified, household contacts were assessed for evidence of subsequent polio infection, either through increases in humoral antibody titers or positive detection of poliovirus in stool. Over the duration of the study, 92% (136 of 148) of all seronegative household contacts showed serologic evidence of recent polio infection, and as did 20% (61 of 304) of seropositive household contacts (with median pre-exposure antibody titers of $N_{\mathrm{Ab}} = 93$).

Transmission-informed dose response model parameters for WPV. To estimate WPV infectiousness from the Louisiana surveillance data, we assumed that the daily fecal exposure between index cases of WPV and household contacts in Louisiana was the same as that between

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Table 1. Maximum likelihood estimate and 95% CI of the infectious dose which would infect 50% of immunologically-naive subjects upon oral challenge.

strain	HID50
Sabin 1	$54\,(9, 155)$ TCID50
Sabin 2	$30\,(5, 83)$ TCID50
Sabin 3	$67\,(12, 182)$ TCID50
WPV	$7\,(1, 55)$ TCID50

infants and siblings in Houston, and then determined WPV infectivity from the total incidence in contacts given infection in the index child. Under this assumption, we estimate that the infectivity of WPV in the dose response model is $\beta_{WPV} = 1.8\,(0.2, 29)$. Data were aggregated across serotypes, and all WPV serotypes were present in roughly equal amounts, and so we cannot examine differences in WPV infectivity by serotype.

With all the dose response and transmission data examined, we summarized the differences in infectivity between the Sabin strains and wild poliovirus by the estimated oral dose that would infect 50% of people with no pre-challenge immunity (HID50). We found that it is likely that WPV is between three and twelve times more infectious than Sabin 2, which is in turn roughly twice as infectious as Sabin 1 and Sabin 3 (Table 1).

Uttar Pradesh and Bihar 2003–2008. From the above analyses, we have calibrated a model of individual shedding and dose response for the three Sabin strains and wild poliovirus. We have estimated the daily fecal-oral exposure in low-SES populations in the Southern USA during the endemic era, measured in tens of micrograms per day. Those studies represent places of moderate transmission intensity in which WPV can remain endemic indefinitely in the absence of vaccination [75] but also in which multi-year quiescent periods are possible (such as those that supported the accumulation of an immunologically-naive birth cohort in Houston).

To estimate a reasonable upper-bound for daily fecal-oral exposure in regions of extremely high polio transmission intensity, we examined WPV surveillance data from India described by Grassly *et al* [35]. In that study, the authors describe measurements of the prevalence of poliovirus in stool from close contacts of children with acute flaccid paralysis (AFP) from WPV infection, most of which occurred in Uttar Pradesh and Bihar. In a case-control analysis of WPV prevalence in contacts of polio AFP cases versus contacts of children with non-polio AFP, the authors inferred from stools collected one to ten weeks after AFP onset that $51\%\,(16, 84)\%$ of contacts who reported only 0-2 pre-exposure doses of tOPV and $12\,(8, 16)\%$ of contacts reported 6 or more doses or tOPV

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were positive for wild poliovirus.

Immunity after 6+ doses of tOPV and estimated daily fecal exposure in Uttar Pradesh and Bihar. Grassly *et al* observed that the majority of contacts reported 6+ doses of tOPV and the authors estimated that contacts shed for an average of 11 days. From our model of shedding duration, we inferred that the median OPV-equivalent antibody titer of contacts with 6+ doses is $N_{\mathrm{Ab}} = 512$, similar to what would be expected after two or three doses in clinical trial settings (Fig. 2). Under our model for shedding duration after WPV infection, the observation that 50% of contacts reporting zero to two doses of prior OPV were positive for WPV in stool in the 10 weeks after the onset of paralyis in the index cases (which occurs two to five weeks after initial infection [76]) implies that essentially 100% must have been infected and shed for the maximal duration (Fig. 1). This inference follows from the structure of the model: most of the incidence in contacts occurs before the onset of paralysis, and the median WPV shedding duration of 43 days in naive individuals indicates that many contacts clear their infections before stool collection. Thus, we inferred that the contacts with 0-2 reported tOPV doses had no functional immunity ($N_{\mathrm{Ab}} = 1$), reflecting the poor efficacy of OPV in northern India during the time of the study [77]. To explain the 12% rate of positivity averaged over the fifteen weeks after index case infection in well-immunized contacts of polio AFP cases, assuming that the index cases directly infected their contacts, our model infers that daily fecal exposure in Uttar Pradesh and Bihar was $630\,(30, 7500)$ times greater than it was in Houston. These macroscopic exposure estimates range from milligrams to grams per day, almost certainly represent the accumulated dose of multiple daily exposures, and provide a likely upper bound on the force of infection in a human population.

Intimate contacts network model

The three reviewed transmission studies reveal the essential network motif of poliovirus transmission: infected young children transmit to household contacts who may in turn transmit to their intimate social contacts outside the home (Fig. 10A). Our model of close-contact transmission within households and between close extrafamilial contacts allowed us to estimate parameters that are closely tied to detailed transmission study data, but its description of transmission intensity in terms of fecal-oral exposure does not easily compare to more common models of disease transmission.

To introduce a concept of the reproduction number—the average number of secondary infections caused by an index infection—we considered intimate contact networks built from friendships among

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young children (Fig. 10B). We defined the local reproduction number as

$$R_{\text{eff}} = p_{hh} N_h, \tag{7}$$

where p_{hh} is the total probability that an index child transmits in one household transmits through an older sibling contact to an extrafamilial contact in another household, and N_h is the number of intimate extra-familial contacts (and is thus a measure of the number of contact households exposed). The dependence on immunity and daily fecal-oral exposure levels in p_{hh} is calculated from the detailed model of household to extrafamilial contact transmission described above (see supplement for details).

The local reproduction number in a given setting (daily fecal-oral exposure and typical number of close extrafamilial contacts) defines the potential for poliovirus to transmit within intimate contact networks. Local R_{eff} describes the expected number of transmission events from an infected household to other households. For Houston, we assumed the typical number of intimate extrafamilial contacts of an older child is $N_h = 4$, reflecting the typical number of close friends in America childhood social networks [78]. For an upper bound in Uttar Pradesh and Bihar, we assumed $N_h = 10$ based on scaling the typical USA social network size in proportion to the two-fold larger typical classroom sizes in northern India [79, 80].

Local transmission is important for community transmission (Fig. 10C) because interventions that shut down local transmission are guaranteed to shut down community transmission (local $R_{\text{eff}} < 1$ and local R_{eff} is greater than community R_{eff} for a person-to-person disease almost always [81]). And conversely, in any settings where local transmission of Sabin virus after OPV cessation will have R_{eff} similar to WPV before eradication, then we can conclude that the only thing stopping Sabin (and cVDPV) outbreaks is the weakness of more distant social ties, just as is the case for transmission after WPV importation.

Results

Vaccine impacts on individual-level immunity against infection

The shedding index—defined as the total amount of virus shed during an infection (measured in TCID50/g of stool) multiplied by the probability of infection after mOPV challenge—provides a composite statistic to describe the acquisition and shedding factors that determine an individual's

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role in poliovirus transmission. Fig. 11A shows our model of shedding index as a function of OPV-equivalent humoral antibody titer based on Eqs. (1), (4), and (5), assuming 18 months of age at mOPV2 challenge.

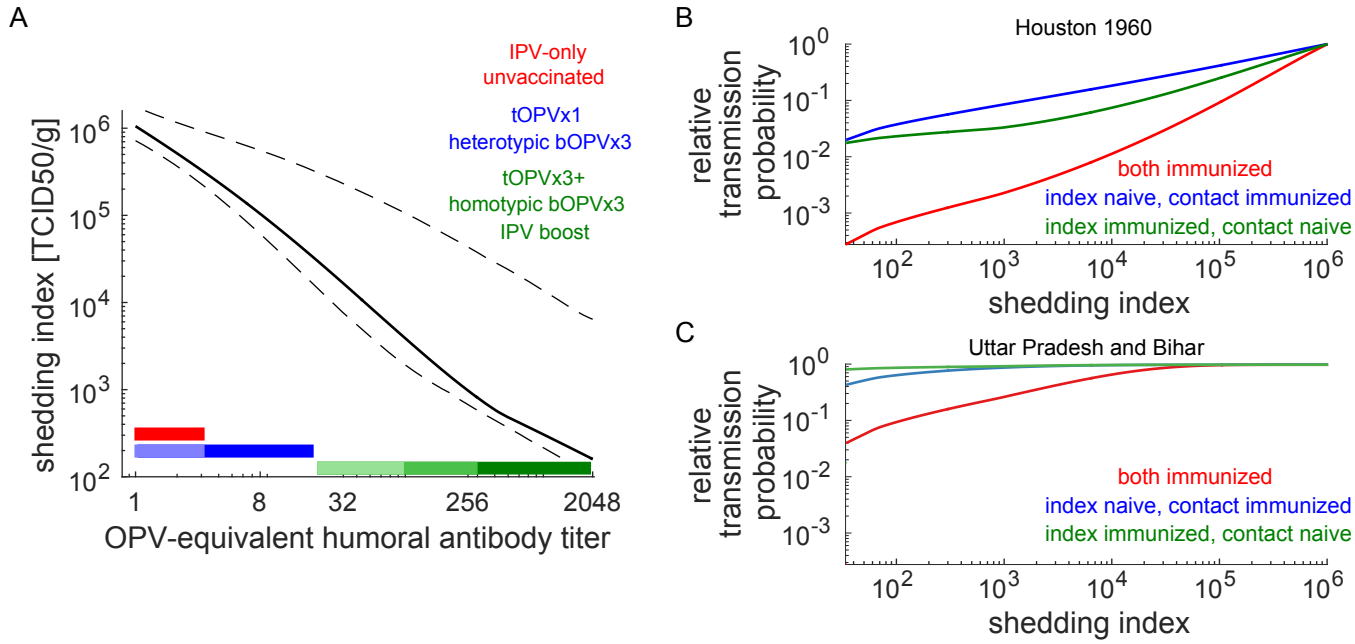

Figure 11. The effect of pre-exposure immunity on individual shedding and person-to-person transmission. (A) Shedding index vs. OPV-equivalent antibody titer. Colored bars indicate range of immunity provided by IPV-only immunization (red), one dose of tOPV or heterotypic type 2 immunity from bOPVx3 and zero or more doses of IPV (blue), and homotypic immunity from three or more doses of OPV or IPV boosting on previous OPV (green). Gradient indicates approximate waning one, two through five, and more than five years since last immunization. (B) Relative transmission probability from an index case to an intimate contact vs. shedding index for immunized members of the pair in a setting with moderate fecal-oral transmission (daily fecal-oral exposure 46 μg per day). Red, both members have same OPV-equivalent immunity; green, index immunized and contact naive; blue, index naive and contact immunized. (C) Relative transmission probability from an index case to an intimate contact vs. shedding index for immunized members of the pair in a setting with very high fecal-oral transmission (daily fecal-oral exposure 340 mg per day). In all cases, the transmission probability is sub-linear with declining shedding index. In very high transmission settings, substantial immunity in both index and contact is required to appreciably reduce transmission.

Protection from shedding. Our results consolidate data and discussions collected over decades into one figure (Fig. 11A). Relative to unvaccinated individuals, homotypic immunity in children who have been fully immunized with OPV reduces shedding by roughly three orders of magnitude. Heterotypic immunity from bOPVx3 provides a roughly one order of magnitude reduction in shedding when challenged with Sabin 2, and this is roughly equivalent to the protection provided by single dose of tOPV. Simultaneous administration of IPV and OPV does not substantially increase

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the effectiveness against infection of routine immunization in comparison to an additional OPV dose, whether for homotypic immunity from tOPV & IPV or heterotypic immunity against type 2 from bOPV & IPV. IPV boosting on previous immunization with OPV restores immunity against infection and, due to high vaccine take rates [25], is the most efficacious intervention available to improve immunity in previously OPV-vaccinated individuals. In the absence of exposure to live poliovirus, IPV alone produces no immunity against intestinal infection, and the studies that have indicated otherwise were likely affected by some degree of IPV boosting on unobserved prior live virus experience.

Waning immunity. Waning immunity against infection increases shedding index by roughly one order of magnitude during the first few years after immunization, but further waning takes decades. The fast waning removes homotypic protection equivalent to roughly one dose of OPV, and so the multi-dose schedules in routine immunization ensure that adults who were fully immunized in childhood remain well-protected throughout their child-bearing years, as is compatible the observations in detailed above from Houston [33] and elsewhere [62]. The limited data on heterotypic type 2 waning after bOPV vaccination is consistent with similar waning dynamics, and so it is reasonable to expect that the protection against type 2 shedding provided by bOPV wanes to neglible levels within a few years of vaccination.

Variations in OPV efficacy. Throughout this paper, we have assumed that three doses of tOPV is sufficient to provide maximal immunity. However, OPV take [30, 72, 73] and immunogenicity [77] is reduced in impoverished settings with poor sanitation. Because all the individual-level clinical trial data is derived from healthy individuals, we do not have direct data on dose response and shedding in low-effectiveness settings. However, in our analysis of WPV transmission among contacts of polio AFP cases in Uttar Pradesh and Bihar, building off the work of Grassly *et al* [35], we found that the OPV-equivalent immunity in individuals who report receiving six or more doses of tOPV had immunity equivalent to two to three doses of tOPV in healthy trial subjects. Low efficacy can manifest itself as failures of OPV take or reduced antibody titer responses [82]. Because our model captures the average effect of vaccination on individual immunity, it does not distinguish between these two failure modes. Thus, while we are not able to draw conclusions about variation in individual immunity in low efficacy settings, it is reasonable to assume from our results that cohorts of children who receive three doses of tOPV in settings with poor efficacy are behave similarly to

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cohorts who receive one dose of tOPV in the studies reviewed here.

The impacts of pre-exposure immunity on person-to-person transmission

In Fig. 11B&C, we show how pre-exposure immunity against infection, manifested as reductions in shedding index, reduce the probability of person-to-person transmission between pairs of intimate contacts. In settings like Houston 1960 with moderate fecal-oral transmission (estimated daily fecal-oral exposures less than one milligram per day), small changes in pre-exposure immunity significantly reduce transmission. When both the index shedder and the exposed contact have similar immunity, the transmission probability declines linearly with shedding index over the first two orders of magnitude. When the pair has heterogeneous immunity in which one is immunized while the other is not, transmission is more common when the shedder is naive rather than the recipient. In these settings, transmission is driven by immunologically-naive individuals, and while re-infection of previously immunized people may be common, the re-infected individuals play a smaller role in transmission to unimmunized contacts (and to each other) than would be expected from prevalence alone.

In contrast, in settings like Uttar Pradesh and Bihar in the 2000s with very high fecal-oral transmission (where estimated fecal-oral exposures are hundreds of milligrams per day), the probability of transmission between close contacts is unaffected until substantial pre-exposure immunity is present in both members of the pair. When one member has been immunized while the other has not, very little reduction in transmission occurs, and re-infected individuals are capable of essentially unhindered transmission to immunologically-naive contacts. In these settings, re-infected individuals likely contribute substantially to the overall transmission chain.

IPV boosting to interrupt transmission before OPV cessation. At the individual-level, IPV is a highly effective booster of immunity against infection derived from live virus exposure. In high transmission settings where re-infection plays a significant role in transmission, IPV vaccination campaigns to boost immunity will have a substantial impact on between-household transmission. In Fig. 12, we consider a scenario that may have been common in Bihar when WPV was still endemic [35, 83]. The chain of transmission starts with a child who received 6+ low-efficacy doses of tOPV prior to being re-infected with WPV. That index child transmits to an unvaccinated contact in another household, who in turn transmits to a sibling with a history of 6+ doses of tOPV, thus propagating infection from one household through the next. Based on our model calibrated to WPV

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surveillance data in Uttar Pradesh and Bihar, there is a 65% chance that a WPV infection in a re-infected child in one household will propagate to re-infect a child in another household. Thus, if the original child has unvaccinated intimate contacts in two or more households, then local $R_{\text{Eff}} > 1$ (Eq. (7)) and WPV transmission is likely to sustain itself (as was observed during the period of the 2003–2008 study our model is calibrated to). If the same WPV exposure occurs shortly after an mOPV campaign in this low efficacy setting, the probability of transmission along this contact chain would be reduced to 33% due to the combined effects of mOPV vaccination on shedding and acquisition in all children. However, if the WPV exposure occurs shortly after an IPV campaign, transmission along this contact chain would be reduced to 19% solely due to the substantially higher effectiveness of IPV to boost immunity against re-infection in the previously immunized children.

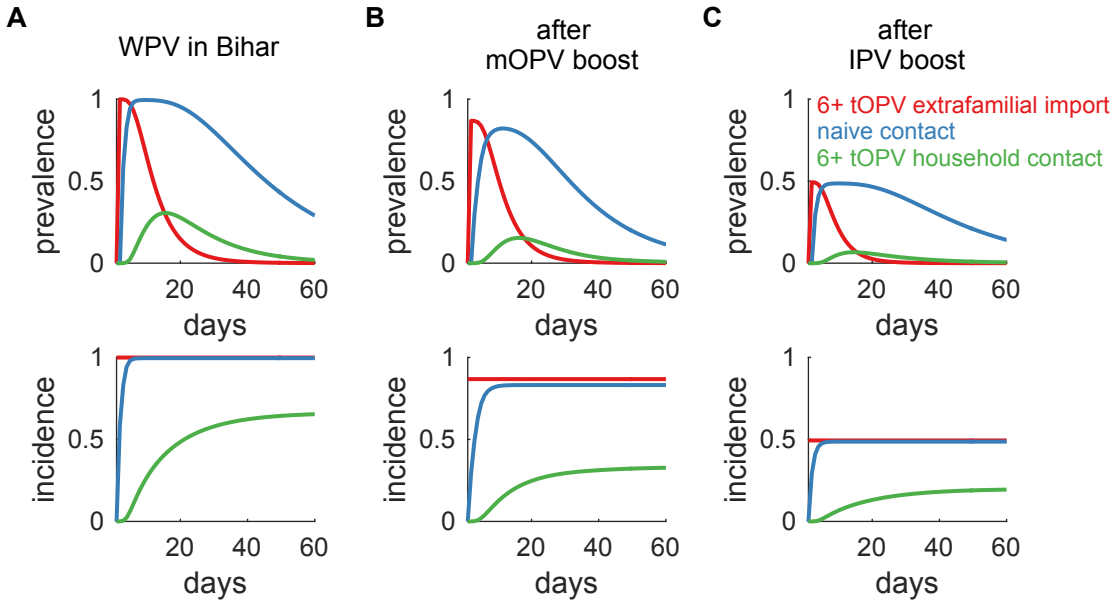

Figure 12. Impact of IPV boosting on WPV transmission in high transmission settings. (A) Prevalence and incidence of a scenario in which WPV passes from a previously immunized extrafamilial contact ($N_{\text{Ab}} = 512$) to an unvaccinated child ($N_{\text{Ab}} = 1$) and then from the unvaccinated child to a previously immunized household contact ($N_{\text{Ab}} = 512$). In 65% of households exposed to the index case, infection propagates through both children. (B) Same transmission chain if WPV exposure follows shortly after an mOPV campaign with low vaccine efficacy. The mOPV campaign increases the immunity of a typical recipient by the equivalent of a third of a dose in high efficacy settings (6+ tOPV goes to $N_{\text{Ab}} = 680$ and unvaccinated goes to $N_{\text{Ab}} = 2$). The probability of propagating to both contacts is reduced to 33%. (C) Same transmission chain if WPV exposure follows shortly after an IPV campaign (6+ tOPV goes to $N_{\text{Ab}} = 2048$ and unvaccinated remains $N_{\text{Ab}} = 1$). The probability of propagating to both contacts is reduced to 19%.

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The changing landscape of Sabin 2 transmission potential after OPV cessation

The totality of evidence for predicting how Sabin 2 transmission potential will change after OPV cessation is summarized in Fig. 13. In the tOPV era, wherever tOPV was delivered in sufficient quantities to achieve durable immunity against infection, transmission of Sabin 2 was rare even among intimate contacts in settings with very poor sanitation and high population densities.

At the time of writing, the world is six months into the bOPV era, in which infants who have received bOPV in routine immunization are surrounded by older tOPV-immunized household contacts (Fig. 13 B,F,J). While the shift to bOPV has increased the transmission potential of Sabin 2, well-vaccinated communities are likely still protected from Sabin 2 transmission—local $R_{\text{eff}} \lesssim 1$ at all levels of fecal-oral exposure, and so the community reproduction number almost certainly remains below one.

However, many households will soon have multiple children who receive only bOPV (and possibly one or more doses of IPV), and so the ability of Sabin 2 to transmit in poor sanitation settings will be very different (Fig. 13 C,G,I). Because of the substantially weaker immunity against type 2 infection provided by bOPV, re-introduced Sabin 2 will eventually transmit through well-vaccinated communities with inadequate sanitation as if they had not been vaccinated at all (Fig. 13 D,H,L). In moderate transmission settings, the protection from bOPV will still be substantial, but only because Sabin 2 local $R_{\text{eff}} \lesssim 1$ even in the absence of immunity in children.

This represents a fundamental shift in the risk of Sabin 2 transmission. Prior to OPV cessation, Sabin 2 could only transmit easily in pockets of low vaccination coverage and surrounded by high immunity, thus severely limiting epidemic spread of Sabin 2 and curtailing cVDPV risk almost everywhere. But in communities with poor sanitation, within the next one to five years (depending on total birth rates and birth-interval preferences), Sabin 2 will be capable of epidemic transmission upon re-introduction, and cVDPV outbreaks will thus only be limited by the weakness of distant network contacts and the fact that many thousands of infections in unvaccinated children are required to generate a paralytic case with high probability [28, 29].

Toward a more quantitative understanding of cVDPV emergence

To better understand the distinction between epidemic spread of Sabin 2 "out of the vial" and cVDPV outbreaks that require genetic reversion to regain wild phenotype, we examined how local

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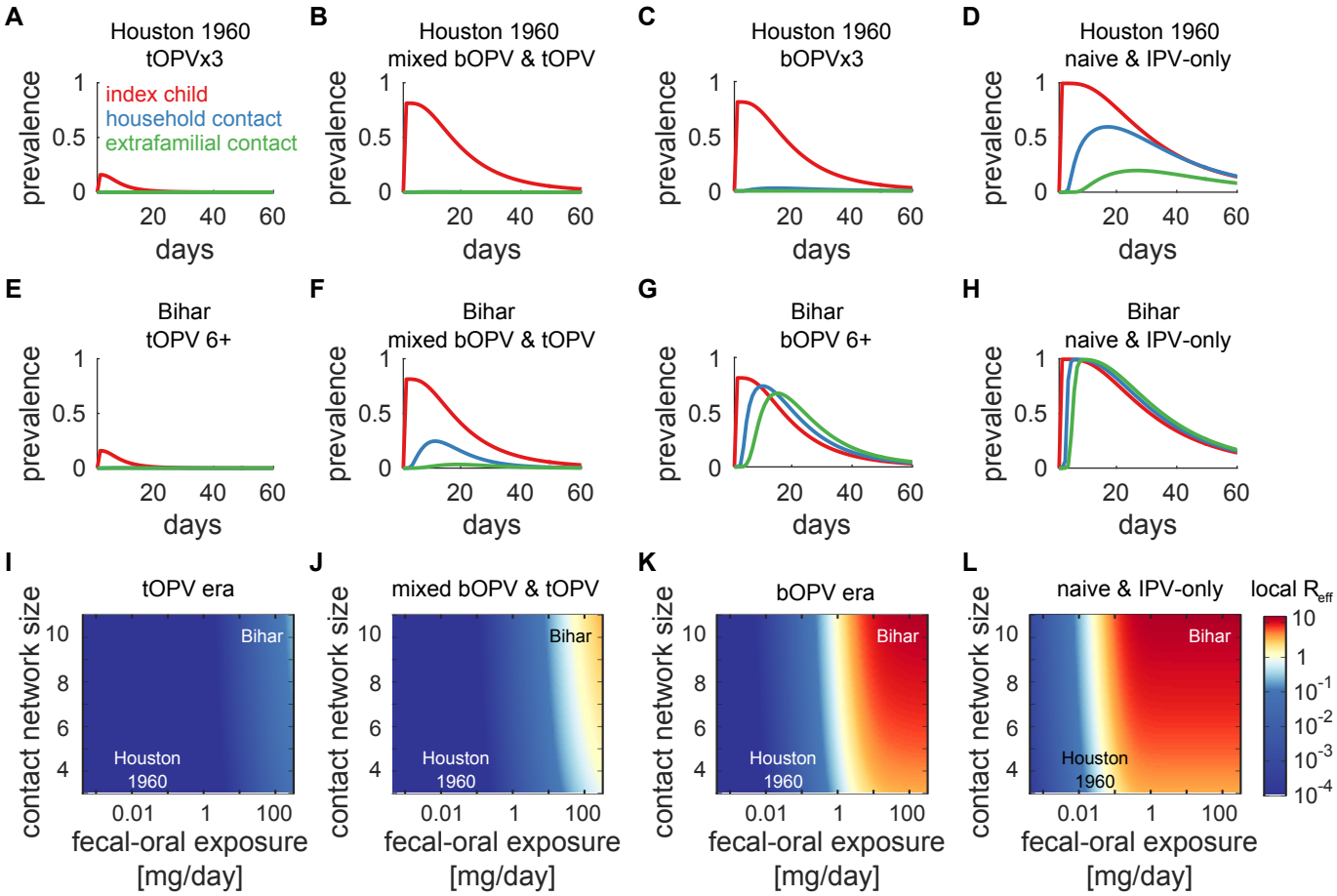

Figure 13. Sabin 2 transmission potential after OPV cessation. Model results for the stool prevalence of chidlren along the essential transmission chain (Fig. 10) from from an index child dosed with mOPV2 to a household contact to an extrafamilial contact for moderate transmission settings like Houston 1960 (A–D) and very high transmission settings like Bihar (E–H). Local reproduction number across all settings as a function of daily fecal-oral exposure between extrafamilial contacts and contact network size (I–L). For the tOPV era (A,E,I), we assume all children have an OPV-equivalent antibody titer of $N_{\mathrm{Ab}} = 512$. For the mixed bOPV & tOPV era (B,F,J), we assume index children have $N_{\mathrm{Ab}} = 8$ against type 2 and contacts had $N_{\mathrm{Ab}} = 256$ to reflect partial waning. For the bOPV-only era (C,G,K), we assume all children have $N_{\mathrm{Ab}} = 8$, and for the IPV-only or immunologically-naive era (D,H,L), $N_{\mathrm{Ab}} = 1$. Any measurable immunity against infection protects against transmission in settings of moderate fecal-oral exposure, but only high levels of immunity are protective against transmission in high transmission settings. For WPV, the images are similar but for a shift of the boundary region of local $R_{\mathrm{eff}} = 1$ to approximately ten-fold lower daily fecal-oral exposures (see Fig. S6).

reproduction numbers depend on poliovirus infectiousness, ranging from Sabin 3 to WPV (Fig. 14).

Moderate transmission settings. In settings with moderate transmission intensity like Houston 1960, the Sabin strains are not capable of epidemic transmission among close contacts if any childhood immunity against infection is present (Sabin 2 local $R_{\mathrm{eff}} = 1.3$ at $N_{\mathrm{Ab}} = 1$), whereas

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WPV is likely to transmit through communities that haven't recently been immunized with tOPV or swept by outbreaks (WPV local $R_{\text{eff}} = 3.4$ at $N_{\text{Ab}} = 1$). Under these circumstances, Sabin 2 is unlikely to persistently transmit for the three to twelve months required to fully regain wild phenotype [36] and thus become robustly capable of sustained transmission and neurovirulence.

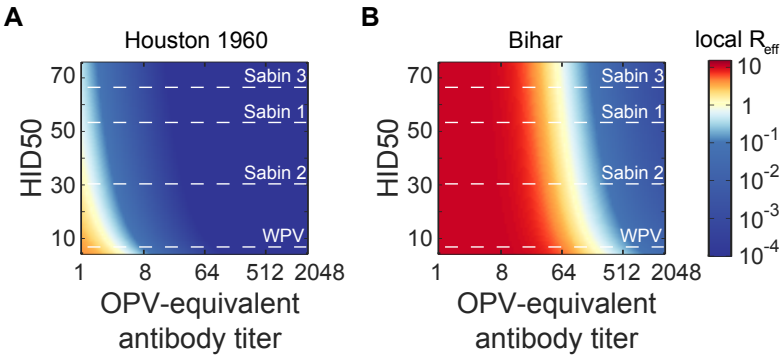

Figure 14. Changing infectivity from Sabin to cVDPV. Local reproductive number as a function of infectiousness (HID50) and OPV-equivalent antibody titer of children in a transmission chain for a (A) moderate transmission setting and a (B) very high transmission setting. Genetic reversion of the Sabin strains to wild phenotype increases the infectiousness (reducing the HID50) over time. In moderate transmission settings, both reversion and low immunity are essential for cVDPV emergence to occur with non-negligible probability when Sabin virus is introduced to a population. In contrast, in very high transmission settings, cVDPV emergence is only prevented by widespread high immunity throughout the child population. Genetic reversion is of minor importance in comparison to population immunity and cVDPV would likely be common in low immunity settings.

Israel. The crucial quantitive differences in transmission between the Sabin strains and WPV likely explain why Israel was susceptible to WPV importation [22] but has never experienced a cVDPV outbreak despite evidence for regular Sabin importation [84]. Recent modeling work has estimated that the community reproduction number of WPV among children ages 0–10 years in the Bedouin community in Israel during the 2013 outbreak was approximately 1.8 [15]. Given our inferred differences in infectivity between Sabin 2 and WPV, the equivalent community reproduction number for Sabin 2 is likely no more than 0.7, bounded from above by the assumption that all community transmission is reduced only in proportion to the change among the most intimate contacts. Thus, Israel behaves like a moderate transmission setting. The reduced infectivity of Sabin 2 relative to WPV is sufficient to explain why Sabin importations that have not regained wild phenotype prior to arriving in Israel are unlikely to spark endogenous cVDPV emergences.

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Low transmission settings. At daily stool exposures below 1 to 10 micrograms of stool per day (roughly ten-fold less than we estimated for low-SES families in Houston in 1960), our model shows that the fecal-oral route cannot sustain poliovirus transmission, wild or vaccine. This observation supports the long-held hypothesis that oral-oral transmission is important in settings with high socioeconomic status and corresponding good sanitation, supported by many observations that IPV alone—an effective blocker of oral shedding [64, 85]—can block transmission and prevent outbreaks from importation in middle- and high-SES communities [8, 85].

High transmission settings. In contrast, our model indicates that epidemic Sabin transmission "out of the vial" in settings like Uttar Pradesh and Bihar in the 2000s can only be prevented by high immunity against infection. High immunity was common prior to OPV cessation: we inferred from reported estimates of shedding duration that the typical OPV-equivalent immunity in healthy children who reported six or more doses of tOPV is roughly $N_{\mathrm{Ab}} = 512$. This conclusion of high immunity despite high WPV risk, due to both comprehensive vaccination and endemic WPV transmission, is supported by serosurveys as well [86]. With that immunity, we estimate local $R_{\mathrm{eff}} = 0.05$ for Sabin 2. However, once families have more than one child who received only bOPV immunization, because of the ability of both children to shed high quantities of poliovirus, we estimate the local reproduction number of Sabin 2 will jump to $R_{\mathrm{eff}} = 9.3$, bounded by the number of intimate contacts (assumed $N_h = 10$) and not by immunity against infection. Demographic transitions [87] will reduce local R_{eff} roughly in proportion to declining birth rates, but local R_{eff} will remain above protective levels without significant reductions in fecal-oral exposure in currently high-transmission settings.

The pre-OPV-cessation experience that cVDPV is non-existent in moderate transmission settings and rare in high transmission settings relies on the dual rarities of sustaining transmission prior to recovering wild phenotype and of finding under-vaccinated communities of sufficient size and social integration to connect thousands of immunologically-naive children such that cases of paralytic polio result. Within a few years of OPV cessation, cVDPV emergence will require neither rarity—the Sabin strains will be capable of epidemic transmission in many settings even under perfect vaccination coverage.

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Discussion

We have covered a great deal of information in pursuit of a single question: when all the evidence is considered, should OPV cessation fundamentally change how we think about the Sabin polio vaccine? We conclude that the answer is yes. The Sabin strains became the preferred live-attenuated vaccine because of their low neurovirulence and high vaccine efficacy [4, 88]. In pursuit of both goals, we arrived at vaccine strains that are 1,000–10,000 times less neurovirulent than wild polioviruses [5], but only five to ten times less infectious. The Sabin vaccine strains are fundamentally infectious polioviruses with very low virulence—less capable of causing paralysis but not categorically different from the naturally-occurring low-virulence strains once found in the wild [88]. However, like for the naturally-occurring low-virulence strains, neurovirulence is not a stable phenotype. In the absence of widespread population immunity, the difference between vaccine and wild virus is small in settings where community transmission of the vaccine strains is possible.

The safety and effectiveness of tOPV in the pre-eradication era. Prior to the advent of polio vaccination, the vast majority of people possessed immunity against polio infection due to natural exposure to WPV at young ages. When first introduced, Sabin OPV lowered the rate of paralysis everywhere it was used because it replaced WPV infection as the source of first exposure in previously unimmunized vaccine recipients. As coverage expanded and neonatal vaccination began, OPV use artificially increased the force of infection of the Sabin viruses above the highest historical levels of wild poliovirus transmission. In doing so, it displaced WPV from the human population while achieving unprecedented levels of immunity and dramatically reduced risk of paralysis. With high levels of population immunity, significant poliovirus transmission is impossible, and so OPV vaccination could be continued indefinitely with risks very small in comparison to WPV.

The safety and stability of OPV cessation in middle- and high-income countries. In the absence of widespread WPV transmission, the non-zero neurovirulence of Sabin strains causes a non-negligible public health burden. Because IPV is highly effective against viremia, and thus oral shedding and paralysis, many countries now precede OPV with IPV or use IPV alone to provide immunity against polio. Due to the high cost of IPV relative to OPV, only middle- and high-income countries currently rely solely on IPV vaccination [7, 89]. Because increases in socioeconomic status are accompanied by improvements in sanitation and reductions in family size, it is likely that many countries that were once capable of sustaining endemic polio transmission are now unable to support

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transmission of even wild poliovirus via the fecal-oral route, and thus IPV alone is sufficient to protect from transmission in most of the places that have already ceased OPV use.

The metastability of OPV cessation in Israel. The 2013 WPV1 outbreak in Israel [22] shows the limits of IPV as a vaccine against poliovirus transmission. The observation that importation of the Sabin strains does not cause cVDPV while importation of WPV can cause a national outbreak, as well as the estimated community reproduction number of WPV near 1 [15], indicate that transmission intensity during the WPV1 outbreak was similar to that once common in low-SES parts of the USA. In such circumstances, mass vaccination with OPV is necessary to eliminate WPV transmission, but the Sabin strains are not capable of widespread transmission prior to complete genetic reversion, and so OPV cessation can resume safely after outbreak interruption.

The instability of OPV cessation in low-income countries. In settings with low-SES and accompanying inadequate sanitation, our synthesis of the evidence accumulated over decades makes clear that the ability of the Sabin strains to transmit has been limited by population immunity and not by the attenuated phenotype. In the absence of substantial population immunity, the Sabin strains will be capable of widespread transmission "out of the vial" prior to any genetic reversion, and so, with respect to transmission, the Sabin strains will behave like wild poliovirus. If Sabin OPV has to be used in outbreak response once population immunity has fallen below historically protective levels, synchronized vaccination campaigns with coverage sufficiently high to saturate local contact networks can limit cVDPV risk within target populations. However, export into unvaccinated populations will only be limited by the weakness of social ties that are difficult to characterize or control. WPV outbreaks demonstrate that poliovirus is able to rapidly traverse the world despite immunity in the majority of people [8, 90, 91]. If mOPV used in outbreak response campaigns is found to seed more cVDPV outbreaks than can be prevented with further campaigns, then OPV will need to be re-introduced to routine immunization to maintain the pre-cessation successes of the polio eradication program—successes that have limited poliomyelitis to only hundreds of paralytic cases per year [2, 5], down from hundreds of thousands [4].

Timeline for cascading cVDPV2 outbreak risk. Global Sabin 2 cessation began in April 2016, when it was believed that all persistent cVDPV2 transmission had ceased [7]. At the same time, a cVDPV2 lineage thought eliminated was detected in environmental surveillance in Borno, Nigeria, and it is continuing to circulate at the time of writing in September 2016 [7, 92]. In response,

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mOPV2 campaigns are being conducted in the Lake Chad region, but due to the impacts of violent conflict on surveillance and vaccination, there is currently no timeline for the expected interruption of the cVDPV2.

Six months after tOPV cessation, the conditions supporting Sabin 2 transmission have likely not changed substantially. Type 2 immunity throughout sub-Saharan Africa was rapidly increased in preparation for tOPV cessation [7, 93, 94]. Almost all households contain only at most one child born after cessation, and our model of transmission among intimate contacts predicts that one unimmunized child is insufficient to support local epidemic transmission. At this time, focal mOPV2 campaigns are not likely to seed cVDPV2 outside of the target population. However, our models show that once families have more than one child born after tOPV cessation, the potential for Sabin 2 transmission will increase substantially to near WPV levels. The median birth spacing in most currently-OPV-using countries is between 24 and 36 months [95]. Thus, we predict that in 2018–2019, the risk of establishing cVDPV2 in the many regions of the developing world that have not received mOPV2 campaigns will increase substantially. The meager cross-immunity of bOPV (and one or more doses of IPV) against type 2 does not alter this conclusion.

Our estimate of 2 to 3 years to increased cVDPV2 risk are compatible with the known epidemiology of cVDPV2 outbreaks. Although only understood in 2003, the first known example of widespread circulation of Sabin 2 after a small release took place in Belarus in 1965 [96]. Two years after a local experiment in OPV cessation, tOPV given to 40 children likely spread type 2 poliovirus throughout a city of 160,000 people for at least 10 months. In Northern Nigeria, after a political vaccination ban and widespread vaccine refusal in 2003 [97], twelve independent VDPV lineages were detected in the following one to three years in association with the restoration of tOPV campaigns, including the largest known outbreak of cVDPV2 in history [98].

The importance of IPV. We echo the recommendation of the WHO Strategic Advisory Group of Experts on Immunization to introduce IPV into global routine immunization [7, 99]. While IPV in RI will have little direct impact on transmission in settings with poor sanitation, IPV boosting campaigns will remain effective interventions against transmission until a few years after cessation when a lack of primary immunity in young children will dominate transmission everywhere. Expanded IPV coverage will prevent paralysis from polio outbreaks and OPV use. Long-term, if poliovirus transmission cannot be interrupted globally without using OPV in RI, then IPV followed by OPV provides superior protection against paralysis and all the immunological benefits of OPV

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vaccination without the associated risks. In all scenarios, in a population well-immunized with IPV, live poliovirus re-introduction does not pose substantial risks to human health.

Conflicting with this recommendation is a severe IPV shortage. Despite coordinated global effort to introduce at least one dose of IPV everywhere, currently 50 countries have either not done so or are experiencing stockouts that will not be replenished until at least the end of 2017 [7]. Our analysis of how IPV affects poliovirus transmission supports the current Global Polio Eradication Initiative (GPEI) IPV prioritization in which supply flows first to the endemic countries, where paralysis risk is highest and the ability of IPV boosting to induce herd immunity is greatest; then to countries at high risk of cVDPV, where IPV will prevent the paralytic consequences of uncontrolled Sabin transmission; and then to outbreak responses, where IPV will play a secondary role to OPV in interrupting transmission; and finally to countries currently at lower risk of polio transmission, where IPV provides a safe and effective insurance policy against all forms of poliovirus importation. Given the evolving landscape of cVDPV2 risk, the IPV shortage should be viewed as a global public health emergency, and all efforts to achieve adequate supply must be accelerated. These efforts should include attempting to procure donations and shift allocations from middle- and high-income countries that currently give four or more doses of IPV in RI.

Sufficient OPV manufacturing capacity must be maintained until OPV cessation is secure. Even in the absence of IPV supply, we reiterate that resuming OPV vaccination is vastly preferable to the widespread resurgence of WPV or cVDPV transmission. It is thus imperative that sufficient Sabin manufacturing capability be maintained until we can be confident that all polio transmission has ceased or that Sabin vaccine is no longer necessary. This recommendation is in conflict with the limitations that the GAPIII policy on poliovirus containment places on vaccine manufacturers in low-income countries [100], and so it is critical that the GPEI coordinate with vaccine manufacturers now to insure that adequate supply for OPV re-introduction in RI will be available if necessary. One creative route to securing sustained OPV supply capacity would be to develop contigency plans to repurpose Sabin IPV supplies into OPV should the need arise [101].

The long-term stability of polio eradication requires a new vaccine. Given the realities of IPV supply constraints and costs, inadequate routine immunization coverage, the necessity of Sabin containment, and the long-term risks of poliovirus re-introduction, the difficulty of achieving and sustaining polio eradication with the current vaccines speaks to the importance of developing

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improved vaccines that produce infection-blocking immunity without the risks of Sabin OPV [102–106]. Genetically-stabilized engineered live vaccines (new OPV) are closest to reaching the clinic and are most promising for retaining the benefits of Sabin OPV [107]. To enable new OPV developers to secure long-term polio eradication, regulatory agencies should support pathways to approval based on genetic and animal correlates of neurovirulence and the shedding index correlate of person-to-person transmissibility to assess the safety of new OPV candidates, without requiring direct evidence from massive field trials of reduced rates of vaccine-associated paralytic poliomyelitis and cVDPV. Because attenuation of neurovirulence and transmission can be achieved in many ways [108–111], and adjuvanted IPV provides a complementary route to a new vaccine [106], funding agencies should support continued research until a new vaccine with the necessary properties achieves clinical success.

Conclusion. The totality of evidence accumulated over the last 75 years indicates that OPV cessation will not be stable in high transmission countries if poliovirus outbreaks continue after cessation for more than two to three years. By keeping our analysis very close to the best clinical and epidemiological data on the impacts of polio vaccination on transmission, and by quantifying our predictions for the future potential for widespread Sabin transmission in terms of the known potential of WPV transmission, we hope to emphasize that the conclusion that cVDPV risk will rise well above historical norms within a few years of OPV cessation follows from the deeply understood epidemiology of polio and not the particular assumptions of our model. It follows from the simple facts that the Sabin strains are infectious polioviruses by design and that doses acquired via fecal-oral exposure can be much higher in the poorest parts of the developing world than they were in the countries where Sabin OPV was first studied and where OPV cessation has already been successful. OPV cessation must be secured quickly for OPV re-introduction to be avoided. If OPV re-introduction is required, securing IPV supply is critical for achieving the dual goals of maintaining population immunity against transmission without risks of paralysis. Given the costs and complexity of sustaining dual vaccination with IPV and OPV, both financial and regulatory support for new polio vaccines must be sustained until viable candidates are found to guarantee the stability of polio eradication for the indefinite future.

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Acknowledgments

We would like to thank Laina Mercer and Steve Kroiss (IDM) for critical feedback on the manuscript, Benoît Raybaud and Qinghua Long (IDM) for developing the online interactive data visualization tools, and Hao Hu (IDM) [and others pending approval of acknowledgement] for useful discussions that motivated this work.

Funding

This work was supported by Bill and Melinda Gates through the Global Good Fund, Bellevue, WA, USA. The Institute for Disease Modeling (which is funded by Global Good) provided support in the form of a salary for authors, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of the authors are articulated in the "author contributions" section.

Competing Interests

The authors have the following interest: This work was supported by Global Good, Bellevue, WA, USA. The authors are employees of the Institute for Disease Modeling, which is funded by Global Good. This does not alter the authors' adherence to PLOS policies on sharing data and materials.

Abbreviations

WPV, wild poliovirus; OPV, oral polio vaccine; tOPV, trivalent OPV; mOPV, monovalent OPV; bOPV, bivalent type 1 and 3 OPV; VAPP, vaccine-associated paralytic poliomyelitis; cVDPV, circulating vaccine-derived poliovirus; RI, routine immunization; IPV, inactivated polio vaccine; TCID50, the tissue culture infectious dose that induces a cytopathic effect in 50% of infected cells; HID50, the equivalent TCID50 dose that infects 50% of orally-exposed and immunologically-naive humans; SES, socioeconomic status; GPEI, Global Polio Eradication Initiative.

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Supplement: How polio vaccination affects poliovirus transmission

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Table S1. Parameter table.

component	equation	parameter	value (range)	meaning
OPV-equivalent humoral antibody titer	-	N_{Ab}	$(1, 2^{11})$	individual correlate of immunity
probability of shedding duration	(1)	μ_S	$30.3\,(23.6, 38.6)$ days	Sabin median shedding duration ($N_{\mathrm{Ab}} = 1$)
		σ_S	$1.86\,(1.57, 2.27)$ days	Sabin scale parameter
		μ_{WPV}	$43.0\,(35.7, 51.7)$ days	WPV median shedding duration ($N_{\mathrm{Ab}} = 1$)
		σ_{WPV}	$1.69\,(1.21, 1.94)$ days	WPV scale parameter
		δ	$1.16\,(1.13, 1.21)$ days	median reduction per $\log_2(N_{\mathrm{Ab}})$
peak shedding vs age	(2)	$S_{\max}$	$6.7\,(5.9, 7.5)$ TCID50/g	maximum stool concentration at age 7 months
		$S_{\min}$	$4.3\,(3.5, 5.0)$ TCID50/g	maximum stool concentration at older ages
		τ	$10\,(1, 33)$ months	decay time constant of peak concentration with age
peak shedding vs immunity	(3)	k	$0.056\,(0.01, 0.079)$	shedding reduction with $\log_2(N_{\mathrm{Ab}})$
shedding concentration vs time	(4)	η	$1.65\,(1.26, 2.09)$	location parameter
		ν	$0.17\,(0.01, 0.78)$	scale parameter
		ξ	$0.32\,(0.08, 0.71)$	time-dependent scale
dose response	(5)	α	$0.44\,(0.29, 0.83)$	shape parameter
		γ	$0.55\,(0.51, 0.57)$	immunity-dependent shape parameter exponent
		β_{S1}	$14\,(3, 59)$ TCID50	Sabin 1 scale parameter
		β_{S2}	$8\,(2, 30)$ TCID50	Sabin 2 scale parameter
		β_{S3}	$18\,(5, 63)$ TCID50	Sabin 3 scale parameter
		β_{WPV}	$1.8\,(0.2, 29)$ TCID50	WPV scale parameter
waning immunity against infection	(6)	λ	$0.75\,(0.59, 0.89)$	immunity decay exponenent
Houston Sabin transmission	(S1–8)	p_{S1}	10^6	vaccine dose [TCID50]
		p_{S1}	$0.79\,(0.70, 0.88)$	study-specific mOPV1 take
		p_{S2}	$0.92\,(1.0, 0.85)$	study-specific mOPV2 take
		p_{S3}	$0.81\,(0.71, 0.91)$	study-specific mOPV3 take
		A_i	12 months	assumed age of index (infant)
		A_s	48 months	assumed age of sibling and extrafamilial contact
		T_{is}	$5\,(1, 45)\,\mu$g per day	daily fecal exposure from infant to sibling
		T_{sc}	$46\,(2, 92)\,\mu$g per day	daily fecal exposure from sibling to extrafamilial contact
		N_{Ab}	1	pre-challenge immunity (all subjects)
Louisiana WPV transmission	(S1–8)	A_i	12 months	assumed age of index
		A_s	48 months	assumed age of older sibling
		T_{is}	$5\,(1, 45)\,\mu$g per day	daily fecal exposure from infant to sibling
		$N_{\mathrm{Ab,seronegative}}$	1	pre-exposure immunity (index case and seronegative siblings)
		$N_{\mathrm{Ab,seropositive}}$	93	pre-exposure immunity (seropositive siblings)
India WPV transmission	(S1–8)	A_i	12 months	assumed age of index case
		A_s	48 months	assumed age of sibling and extrafamilial contact
		T_{is}	$3.4 \times 10^3\,(30, 3.4 \times 10^5)\,\mu$g per day	daily fecal exposure from infant to sibling
		T_{sc}	$3.2 \times 10^4\,(240, 3.2 \times 10^6)\,\mu$g per day	daily fecal exposure from sibling to extrafamilial contact
		$N_{\mathrm{Ab,tOPV\ 0\text{–}2}}$	1	pre-exposure immunity (tOPV 0–2 doses)
		$N_{\mathrm{Ab,tOPV\ 6+}}$	512	pre-exposure immunity (tOPV 6+ doses)

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Table S2. OPV challenge studies included in analysis. Mean age rounded to nearest month. "Live virus exposure" indicates that some subjects may have prior immunity from natural acquisition of WPV or OPV by contact. More detailed information about the included and considered but excluded studies can be found in the digitized data tables available at `https://github.com/famulare/howPolioVaccinationAffectsPoliovirusTransmission`.
* IPV administered at same time as OPV; † IPV administered alone but after prior OPV.

RI regimen	RI schedule	challenge	age at challenge	location	publication date	live virus exposure	shedding duration	shedding titer	dose response	reference
seronegative natural	-	mOPV1 mOPV2 mOPV3	5 y 20 y	Nether-lands	1959	yes	yes	no	no	Verlinde1959 [1]
seronegative IPVx2	- -	mOPV1 mOPV2	11 m	UK	1961	no	yes	yes	no	Dick1961 [2]
seronegative	-	mOPV2	12 m	UK	1961	no	no	no	yes	Dane1961 [3]
seronegative	-	mOPV1 tOPV	2 y	USA	1961	no	yes	no	no	Horstmann1961 [4]
unvaccinated	-	mOPV1 bOPV	0 m	USA	1962	no	yes	no	no	Holguin1962 [5]
unvaccinated tOPVx3 IPVx3 IPVx4	- 7,8,9 m 2,3,4 m 2,3,4,15 m	mOPV1	6 m 16 m 6 m 16 m	UK	1966	yes	yes	yes	yes	Henry1966 [6]
unvaccinated	-	mOPV1 mOPV2 mOPV3	2 y	Japan	1966	no	yes	no	no	Takatsu1966 [7]
unvaccinated	-	mOPV1 mOPV2 mOPV3 tOPV	1 y	USA	1967	no	yes	no	no	Benyesh-Melnick1967 [8]
unvaccinated	-	mOPV1	2 m	UK	1981	no	no	no	yes	Minor1981 [9]
unvaccinated tOPVx1	- 0 m	tOPV	0 or 2 m 2 m	China	1986	no	yes	no	no	Dong1986 [10]
tOPVx3 IPVx3	2,4,18 m	tOPV	2 y	USA	1991	yes	yes	no	yes	Onorato1991 [11]
unvaccinated IPVx2	- 2,3 m	tOPV	2 m 4 m	Romania	1997	yes	yes	no	no	Ion-Nedelcu1997 [12]
unvaccinated tOPVx1 tOPVx2	- 7 m 7,8 m	tOPV	7 m 8 m 9 m	France	1997	no	yes	no	no	Mallet1997 [13]
IPVx3	4,6,12 m	mOPV3	18 m	Finland	1999	no	yes	yes	no	Piirainen1999 [14]
seronegative natural	-	mOPV1 mOPV3	65 y	Nether-lands	2005	yes	yes	no	no	Abbink2005 [15]
unvaccinated tOPVx2 IPVx2	- 2,4 m 2,4 m	tOPV	2 m 6 m 6 m	USA	2005	yes	yes	no	no	Laassri2005 [16]
mOPV1x1 tOPVx1	0 m	mOPV1	1 m 2 y	Egypt	2008	no	yes	no	no	El-Sayed2008 [17]
IPVx2 & tOPVx2 IPVx3 & tOPVx3	2*,4*,7 m 2*,4*,7,13* m	tOPV	10 m 16 m	Israel	2008	no	yes	no	no	Swartz2008 [18]
tOPVxN IPV boost	campaigns	mOPV1 mOPV3	1,5,10 y	India	2014	yes	no	no	yes	Jafari2014 [19]
IPVx1 & bOPVx2 IPVx2 & bOPVx1 IPVx3	2*,3,4 m 2*,3*,4 m 2*,3*,4* m	mOPV2	5 m	Chile	2015	no	yes	yes	no	O'Ryan2015 [20]
bOPVx3 & IPVx1 bOPVx3 & IPVx2 bOPVx3 tOPVx3	2,3,4* m 2,3,4*,8† m 2,3,4 m 2,3,4 m	mOPV2	5 or 9 m 9 m 5 m 5 m	Latin America	2016	no	yes	yes	no	Asturias2016 [21]

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Shedding duration after OPV challenge

Figure S1 shows the reverse cumulative shedding duration distributions that describe estimates of the probability an individual is still shedding after successful OPV take. Each curve represents the sample-size weighted average of the curves from the individual studies; disaggregated data is provided in the supplementary data files. All original data were presented as estimates of prevalence over time, sampled on discrete days that often differ across studies, and variations in sample size due to missing data or dropout were often impossible to reconstruct. These distributions are thus not proper Kaplan-Meier estimates of the survival functions, and due to different censoring patterns across studies, the average curves are not guaranteed to decrease monotonically, although deviations from monotonicity are rare and only found with small total sample sizes.

Figure S2 reprises the estimated median shedding durations and model OPV-equivalent humoral immunity for all RI regimens shown in Figures 2–4.

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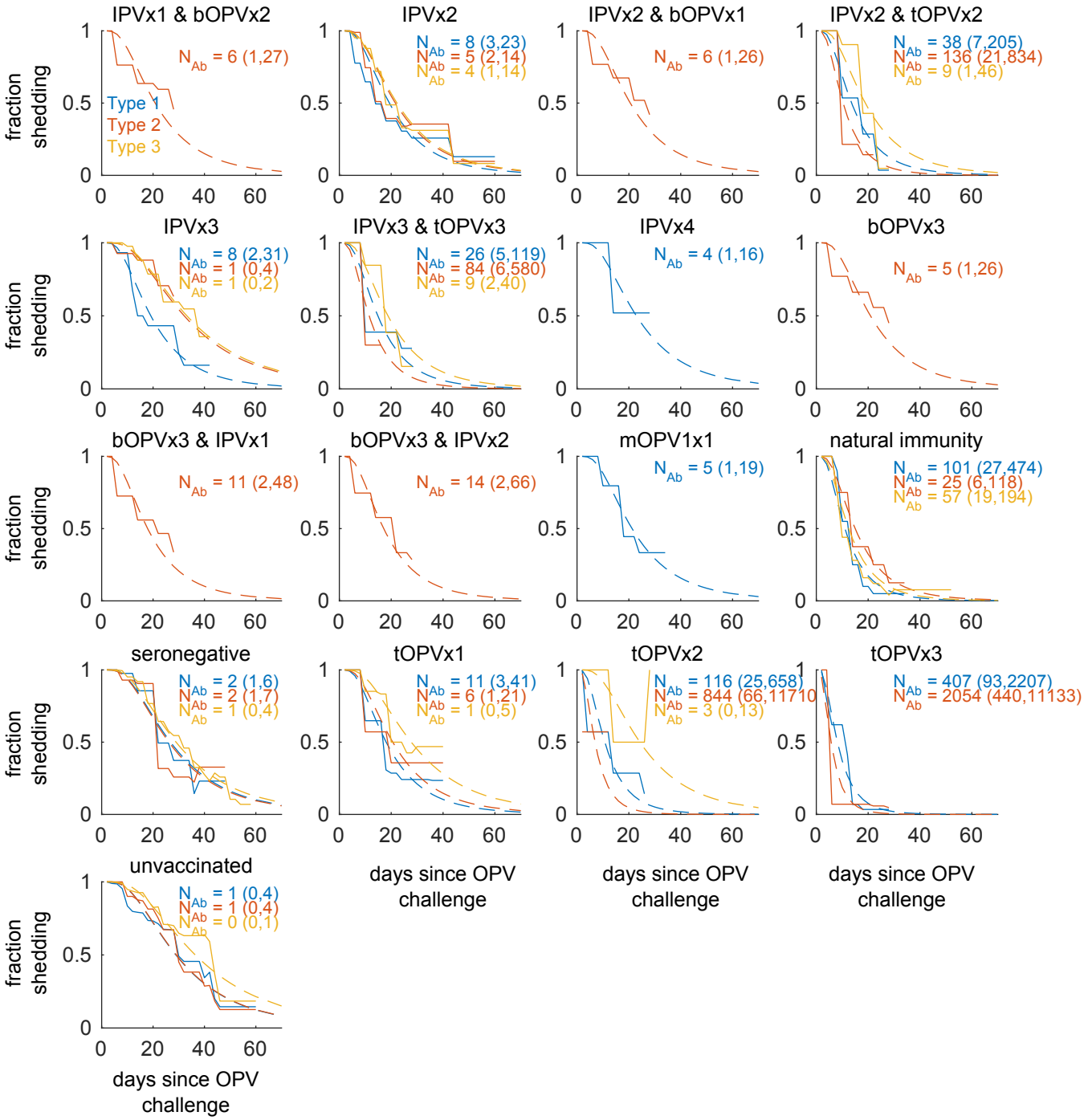

Figure S1. Shedding duration data and model best-fits for all studied vaccination schedules. Color encodes serotype (Sabin 1, blue; Sabin 2, red; Sabin 3, orange) and model estimates of the OPV-equivalent humoral antibody titers against challenge serotype, mean (95% CI), are shown. (Interactive online.)

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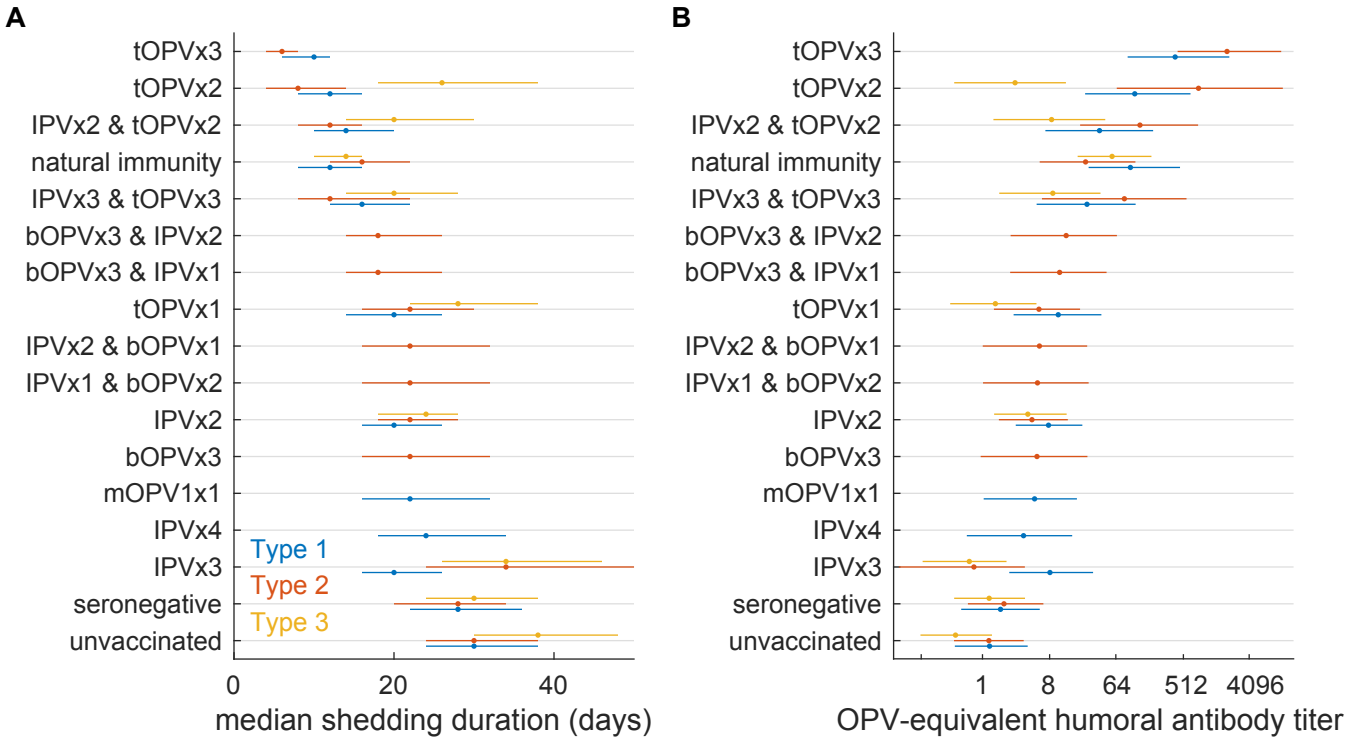

Figure S2. Median shedding duration and inferred antibody titers following all studied vaccination schedules and 95% confidence interval. Color encodes challenge serotype, and antibody titers are homotypic to the challenge serotype.

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Concentration of poliovirus in stool after OPV challenge

Figure S3 shows the geometric mean poliovirus concentration in stool (TCID50/g) for all included trial arms. Seronegative, unvaccinated, IPVx2, and IPVx3 data also appear in Figure 5, and all type 2 data appear age-adjusted to 12 months in Figure 6.

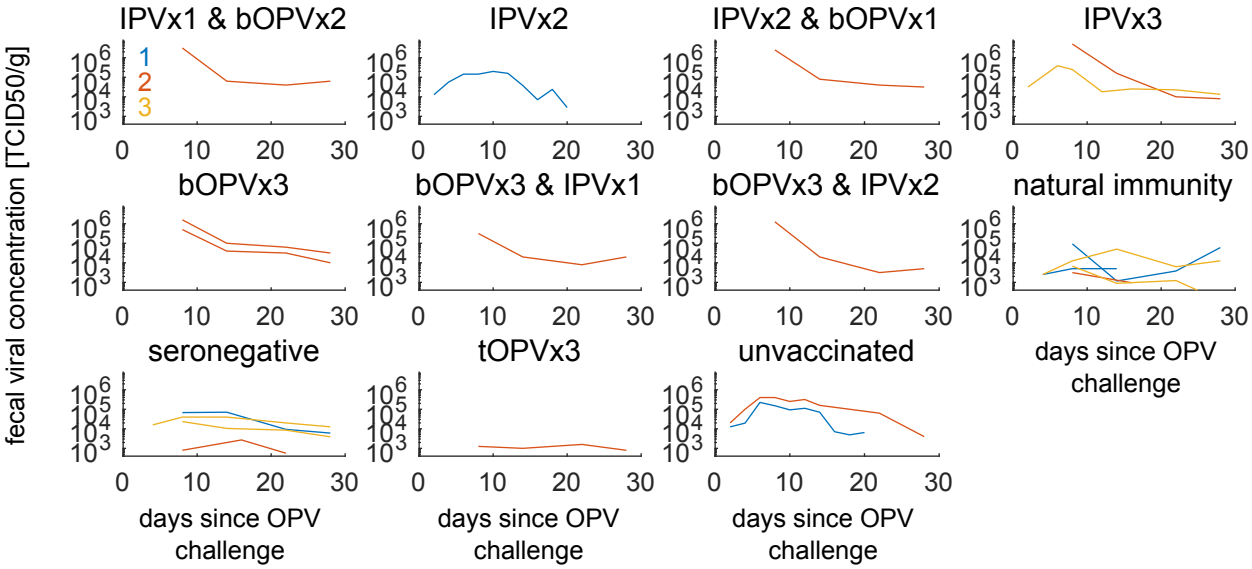

Figure S3. Concentration in stool vs. time for all trial arms. Geometric mean poliovirus concentration in stool (TCID50/g) vs. time since OPV challenge for all included trial arms. (Interactive online.)

Figure S4 shows the average concentration, age-adjusted to 120 months for all immunologically-naive trial arms (seronegative, unvaccinated, IPVx2, and IPVx3) and the best fit temporal profile described in equation (4).

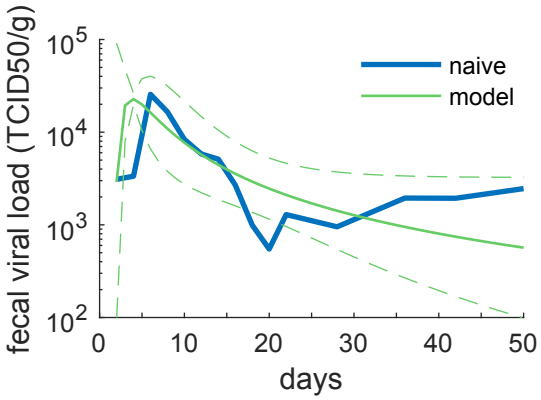

Figure S4. Concentration vs. time for immunologically-naive individuals. Data combined for all immunologically-naive trial arms (seronegative, unvaccinated, IPVx2, and IPVx3), and model best-fit and 95% confidence interval, equation (4).

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Determining the interval between last immunization and OPV challenge to assess waning immunity against infection

For individuals from tOPVx3 vaccine trials, intervals between last immunization and mOPV challenge ranged from 1 month [21] to 6 months [11]. To assess waning of tOPV-based immunity in older children, one study in Uttar Pradesh compared mOPV vaccine take rates in children 1, 5, or 10 years of age [19] who had previously recieved an unknown but high number of tOPV doses. To estimate the likely interval between last immunization and challenge, we assumed that children are offered up to 5 doses in the first year of life (3 RI plus 5 campaigns at 60% coverage), corresponding to roughly 2.5 months on average between last vaccination and mOPV challenge at 1 year of age. We assumed campaigns delivered 3 doses per year in ages two through four, corresponding to roughly 4 months between last vaccination and challenge at 5 years of age, and no doses after 5 years of age, corresponding to 5 years since last vaccination and challenge at 10 years of age. For this study, OPV-equivalent immunity was inferred via vaccine take rates using equation (5). Data on adult shedding after natural immunity were taken from studies in the Netherlands. From the study by Verlinde *et al* [1] in 1959, the average seropositive subject in the study was 20 years of age, and we assumed that their last infection was 5 years earlier at 15 years of age when maximum seropositivity was first achieved in the population. From the study by Abbink *et al* [15] from 2005 that measured shedding in elderly individuals upon mOPV challenge, we assumed last exposure was 45 years earlier in 1960, at roughly the year in which widespread endemic transmission ceased in the Netherlands. We included data for both seropositive and seronegative adults from the Abbink *et al* study because seronegative adults showed evidence of memory immunity and reduced shedding durations in comparison to immunologically-naive children.

Houston 1960: detailed exploration of shedding fraction by age

As shown in Fig. S5, older index children shed slightly less after mOPV challenge than younger children for types 2 and 3 (type 1 $p = 0.105$; type 2 $p = 0.016$; type 3 $p = 0.025$). The reduction may be influenced by three effects. One possibility is a small fraction of older children experienced natural exposure prior to the start of the study and so have more immunity than suggested by their lack of vaccination history. We believe this is unlikely as it is unlikely wild polio transmission would affect a small fraction of a geographically, demographically, and immunologically similar cohort. A second possibility is a small influence from prior IPV

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immunization. As described in Table 1 of Benyesh-Melnick *et al* [8], older index children were more likely to have received at least one dose of IPV. However, it should be noted that the original authors who had access to the individual-level data reported that they found no significant differences between IPV and unvaccinated index subjects, as is compatible with our metastudy. A third possibility is that stool concentrations of poliovirus are higher in young infants who are not yet eating solid foods and may not have mature immune systems, and so stool culture may be more sensitive to shedding in younger children. This third possibility is suggested by the observations summarized in equation (2) that shedding in children under 8 months of age shed systematically higher viral concentrations than comparable children 15 to 18 months of age [6, 11].

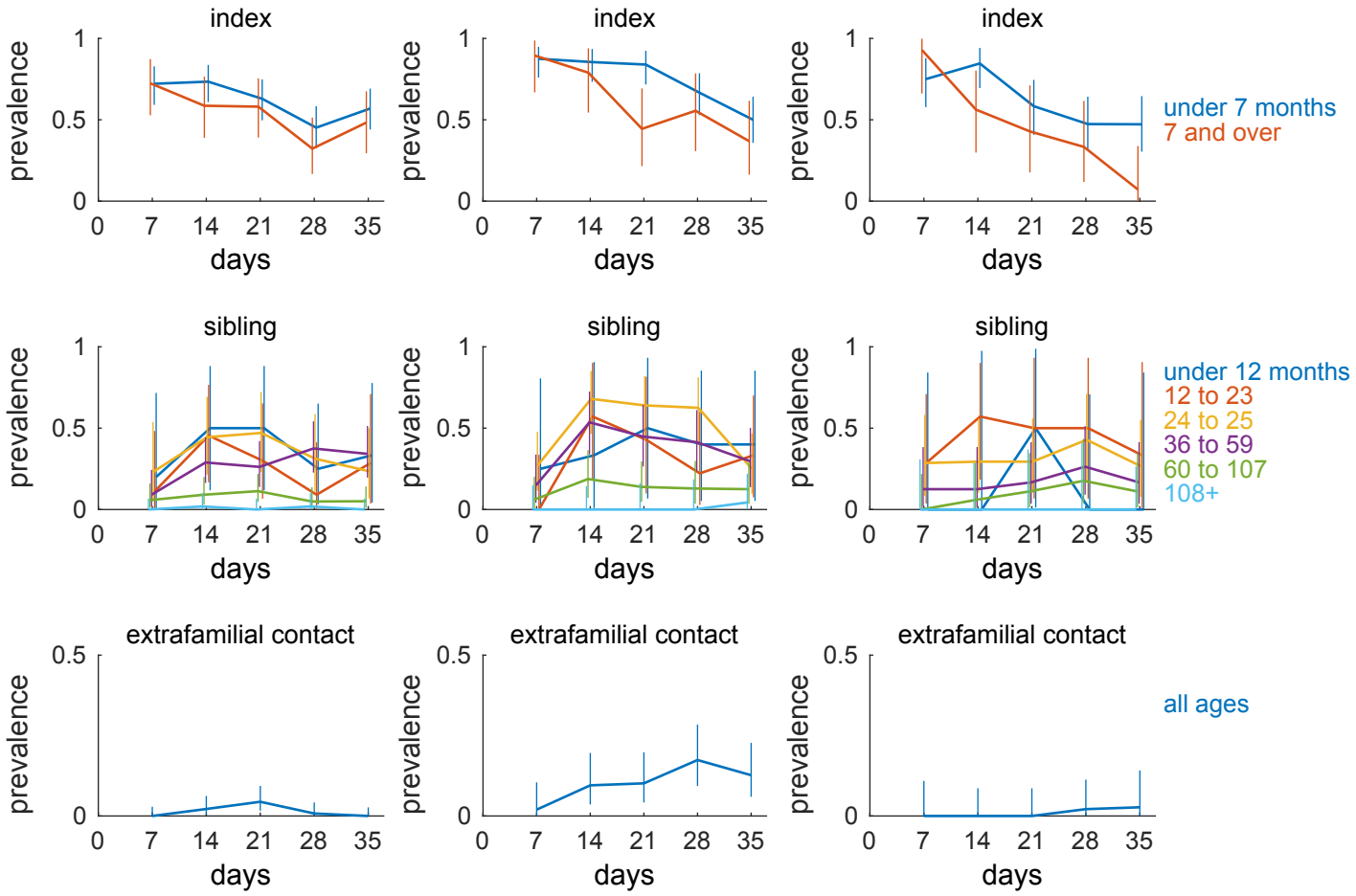

Figure S5. Fraction shedding by cohort and age range as originally reported. Observed fraction shedding and estimated 95% binomial confidence interval for each serotype, subject type, and reported age cohort.

There were no statistically significant differences in shedding among the age groups under 12 months, 12 to 23 months, 24 to 35 months, or 36 to 59 months for any serotype. However, there was significantly less shedding in the 60 to 107 month age group relative to the 36 to 59 age group ($p < 0.001$ for all serotypes).

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As stated in the main text, shedding in siblings age 60 to 107 months (5 to 9 years) is significantly below that of ages less than 5 years for all serotypes (type 1 $p < 0.001$; type 2 $p < 0.001$; type 3 $p = 0.002$).

No breakdown by age was presented by Benyesh-Melnick *et al* [8] for the extrafamilial contacts of the siblings. However, because the contacts are demographically similar to the siblings and age is a significant factor for poliovirus acquisition via transmission in this setting, we used age-adjusted shedding rates in this paper. To estimate the unreported shedding fraction in the age under 5 contact cohort, we adjusted the total reported shedding counts for each serotype as follows:

$$(\text{estimated contacts shedding under 5}) = (\text{total contacts shedding}) \times (\text{fraction siblings shedding under 5})$$

$$(\text{estimated contacts under 5}) = (\text{total contacts}) \times (\text{fraction siblings under 5})\,.$$

The estimated counts were rounded to the nearest integer and confidence intervals presented are based on the rounded estimated counts. The estimated age 5 to 9 years contact data was constructed similarly.

Index-sibling-extrafamilial contact transmission model

The index-sibling-extrafamilial contact model was implemented in Matlab (supplementary file `primarySecondaryTertiaryDoseModel.m`) and all parameters are given in Table S1. For each of the three individuals along the transmission chain, based on specified age and pre-exposure immunity, the model calculates daily incidence (the probability of becoming infected each day), prevalence (the probability of shedding poliovirus in stool each day), and quantity shed (TCID50 per gram).

All infections in index (primary) children begin on day $t = 1$ due to exposure on day $t = 0$. For our analysis of the Houston Sabin transmission study, infection started with vaccination with dose $= 10^6$ TCID50. The incidence due to vaccination is given by

$$P_{\text{index}}\,(\text{infected at } t) = \begin{cases} p_{Sx} P\left(\text{infection}\middle|\text{dose } = 10^6 \text{ TCID50}, N_{\text{Ab,index}}\right) & t = 1 \text{ days} \\ 0 & t > 1 \text{ days} \end{cases} \tag{S1}$$

where p_{Sx} is the study-specific mOPVx (x $= 1, 2, 3$) vaccine take for $N_{\text{Ab}} = 1$ and the second term is given by the dose response model in equation (5). For our analyses of WPV surveillance around index cases, $P_{\text{index}}\,(\text{infection}) = 1$ by definition. In index cases, the prevalence after vaccination is thus

$$P_{\text{index}}\,(\text{shedding at } t) = P_{\text{index}}\,(\text{infected at } t = 1)\, P\left(\text{shedding at } t\middle|N_{\text{Ab,index}}; \text{infected at } t = 1\right), \tag{S2}$$

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where the first term is from eq. (S1) and the second is the shedding duration model in equation (1).

Incidence in siblings (secondary) derives from exposure to index (primary) shedding as:

$$P_{\text{sibling}}\left(\text{infected at } t\right) = P_{\text{sibling}}\left(\text{transmission at } t \middle| \text{index shedding}\right) P_{\text{index}}\left(\text{shedding at } t \middle| N_{\text{Ab,index}}; \text{infected at } t = 1\right) \tag{S3}$$

with

$$\begin{aligned} P_{\text{sibling}}\left(\text{transmission at } t \middle| \text{index shedding}\right) &= \beta(t) \prod_{t'=1}^{t-1} (1 - \beta(t')) \\ \beta(t) &= P\left(\text{infection} \middle| \text{dose at } t, N_{\text{Ab,sibling}}\right) \\ (\text{dose at } t) &= T_{is} \times \left(\text{index concentration } (t) \middle| N_{\text{Ab,index}}; \text{index age}\right), \end{aligned} \tag{S4}$$

where T_{is} is the daily fecal-oral exposure between index and sibling per day (grams of stool), index fecal concentration (TCID50 per gram) is determined by the fecal concentration model in equation (4), $\beta(t)$ is the infection probability determined by the dose response model with sibling pre-exposure immunity, and $P_{\text{sibling}}\left(\text{transmission at } t \middle| \text{index shedding}\right)$ is the probability the sibling is infected on day t given contact with a shedding index child.

Sibling (secondary) prevalence follows from convolving the daily incidence with the shedding duration distribution:

$$P_{\text{sibling}}\left(\text{shedding at } t\right) = \sum_{t'=1}^{t_c} P_{\text{sibling}}\left(\text{infected at } t'\right) P\left(\text{shedding at } (t - t') \middle| N_{\text{Ab,sibling}}; \text{infected at } t'\right). \tag{S5}$$

The cutoff time is for computational convenience; $t_c = 35$ days for Houston and $t_c = 100$ days for Louisiana, and Uttar Pradesh and Bihar.

Extrafamilial contact (tertiary) shedding derives from exposure to sibling (secondary) shedding, after summing over all days at which the sibling may have been infected, as:

$$\begin{aligned} P_{\text{contact}}\left(\text{infected at } t\right) = \sum_{t'=1}^{t_c} \Big[& P_{\text{contact}}\left(\text{transmission at } t \middle| \text{sibling shedding since } t'\right) \\ & \times P_{\text{sibling}}\left(\text{infected at } t'\right) P\left(\text{shedding at } (t - t') \middle| N_{\text{Ab,sibling}}; \text{infected at } t'\right)\Big], \end{aligned} \tag{S6}$$

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with

$$\begin{aligned} P_{\text{contact}}\left(\text{transmission at } t \middle| \text{sibling shedding since } t'\right) &= \beta(t) \prod_{t''=t'}^{t-1} (1-\beta(t'')) \\ \beta(t) &= P\left(\text{infection} \middle| \text{dose at } t, N_{\text{Ab,sibling}}\right) \\ (\text{dose at } t) &= T_{sc} \times \left(\text{sibling concentration } (t-t') \middle| N_{\text{Ab,sibling}}; \text{sibling age}\right), \end{aligned} \tag{S7}$$

where T_{sc} is the daily fecal-oral exposure between sibling and extrafamilial contact per day, and $(t-t')$ is the interval since the sibling became infected. This convolution over sibling incidence accounts for the dependence of the daily dose received by extrafamilial contacts on the start of sibling infection. Extrafamilial contact prevalence follows from incidence in the same manner as for the sibling:

$$P_{\text{contact}}\left(\text{shedding at } t\right) = \sum_{t'=1}^{t_c} P_{\text{contact}}\left(\text{infected at } t'\right) P\left(\text{shedding at } (t-t') \middle| N_{\text{Ab,contact}}; \text{infected at } t'\right). \tag{S8}$$

Local reproduction number

We introduced the local reproduction number to summarize the transmission among clusters of households, based on the index–sibling–contact model described above. In the main text, we define the local reproduction number in equation (7) as:

$$R_{\text{eff}} = p_{hh} N_h,$$

where p_{hh} is the total probability that an index child transmits in one household transmits through its older sibling contacts to an extrafamilial contact in another household, and N_h is the number of intimate extra-familial contacts (and is thus a measure of the number of households exposed). In terms of index to extrafamilial contact transmission, we define p_{hh} as the cumulative incidence in an extrafamilial contact given infection in an index case:

$$p_{hh} = \frac{\sum_{t=1}^{t_c} P_{\text{contact}}\left(\text{infected at } t\right)}{\sum_{t=1}^{t_c} P_{\text{index}}\left(\text{infected at } t\right)}, \tag{S9}$$

with $t_c = 100$ days.

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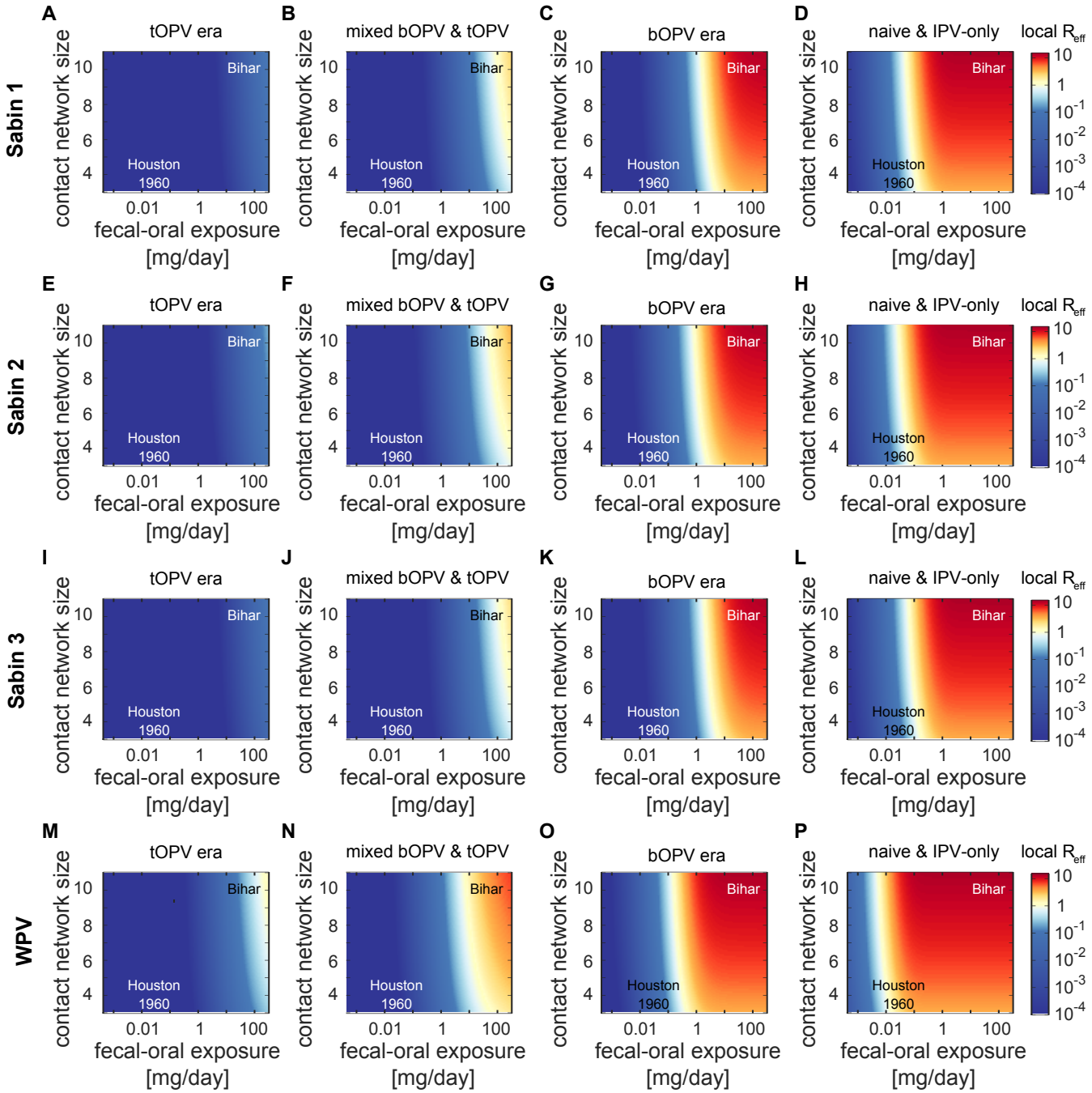

Figure S6. Local reproduction number across all settings as a function of daily fecal-oral exposure and intimate contact network size. (A-D) Sabin 1, (E-H) Sabin 2, (I-L) Sabin 3, (M-P) WPV. As in Figure 13, for the tOPV era (A,E,I,M), we assume all children have an OPV-equivalent antibody titer of $N_{\mathrm{Ab}} = 512$. For the mixed bOPV & tOPV era (B,F,J,N), we assume index children have $N_{\mathrm{Ab}} = 8$ against type 2 and contacts had $N_{\mathrm{Ab}} = 256$ to reflect partial waning. For the bOPV-only era (C,G,K,O), we assume all children have $N_{\mathrm{Ab}} = 8$, and for the IPV-only or immunologically-naive era (D,H,L,P), $N_{\mathrm{Ab}} = 1$. While there is no "bOPV" in use for Sabin 1 and 3, plots with those immune states are included to show how transmission varies by serotype for equivalent incomplete immunity. Differences in transmissibility by serotype and attenuation are due to differences in infectivity (Table 1). In Houston in 1960, WPV was endemic in a pre-OPV population. In settings with higher fecal-oral exposure and larger intimate contact networks, similar and greater levels of transmissibility will be common for all Sabin strains after OPV cessation. In the absence of immunity against infection, the virological differences in transmissiblity between the Sabin strains and WPV are small in comparison to the structural differences between settings.

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