



## Assessing the stability of polio eradication after the withdrawal of oral polio vaccine

Michael Famulare, Christian Selinger, Kevin A Mccarthy, Philip A Eckhoff,  
Guillaume Chabot-Couture

### ► To cite this version:

Michael Famulare, Christian Selinger, Kevin A Mccarthy, Philip A Eckhoff, Guillaume Chabot-Couture. Assessing the stability of polio eradication after the withdrawal of oral polio vaccine. PLoS Biology, 2018, 16, 10.1371/journal.pbio.2002468 . hal-03471239

**HAL Id: hal-03471239**

**<https://hal.science/hal-03471239>**

Submitted on 8 Dec 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

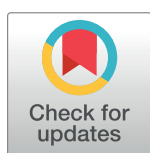
RESEARCH ARTICLE

# Assessing the stability of polio eradication after the withdrawal of oral polio vaccine

Michael Famulare\*, Christian Selinger, Kevin A. McCarthy, Philip A. Eckhoff, Guillaume Chabot-Couture

Institute for Disease Modeling, Bellevue, Washington, United States of America

\* [mfamulare@idmod.org](mailto:mfamulare@idmod.org)



## Abstract

The oral polio vaccine (OPV) contains live-attenuated polioviruses that induce immunity by causing low virulence infections in vaccine recipients and their close contacts. Widespread immunization with OPV has reduced the annual global burden of paralytic poliomyelitis by a factor of 10,000 or more and has driven wild poliovirus (WPV) to the brink of eradication. However, in instances that have so far been rare, OPV can paralyze vaccine recipients and generate vaccine-derived polio outbreaks. To complete polio eradication, OPV use should eventually cease, but doing so will leave a growing population fully susceptible to infection. If poliovirus is reintroduced after OPV cessation, under what conditions will OPV vaccination be required to interrupt transmission? Can conditions exist in which OPV and WPV reintroduction present similar risks of transmission? To answer these questions, we built a multi-scale mathematical model of infection and transmission calibrated to data from clinical trials and field epidemiology studies. At the within-host level, the model describes the effects of vaccination and waning immunity on shedding and oral susceptibility to infection. At the between-host level, the model emulates the interaction of shedding and oral susceptibility with sanitation and person-to-person contact patterns to determine the transmission rate in communities. Our results show that inactivated polio vaccine (IPV) is sufficient to prevent outbreaks in low transmission rate settings and that OPV can be reintroduced and withdrawn as needed in moderate transmission rate settings. However, in high transmission rate settings, the conditions that support vaccine-derived outbreaks have only been rare because population immunity has been high. Absent population immunity, the Sabin strains from OPV will be nearly as capable of causing outbreaks as WPV. If post-cessation outbreak responses are followed by new vaccine-derived outbreaks, strategies to restore population immunity will be required to ensure the stability of polio eradication.

## OPEN ACCESS

**Citation:** Famulare M, Selinger C, McCarthy KA, Eckhoff PA, Chabot-Couture G (2018) Assessing the stability of polio eradication after the withdrawal of oral polio vaccine. *PLoS Biol* 16(4): e2002468. <https://doi.org/10.1371/journal.pbio.2002468>

**Academic Editor:** Steven Riley, Imperial College London, United Kingdom of Great Britain and Northern Ireland

**Received:** March 16, 2017

**Accepted:** March 28, 2018

**Published:** April 27, 2018

**Copyright:** © 2018 Famulare et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** All relevant data and software are provided in the Supporting information files, and Interactive tools to explore the digitized primary data are available at [famulare.github.io/cessationStability/](https://github.io/cessationStability/).

**Funding:** Global Good. This work was supported by Bill and Melinda Gates through Global Good, Bellevue, WA, USA. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## Author summary

Oral polio vaccine (OPV) has played an essential role in the elimination of wild poliovirus (WPV). OPV contains attenuated (weakened) yet transmissible viruses that can spread from person to person. In its attenuated form, this spread is beneficial as it generates population immunity. However, the attenuation of OPV is unstable and it can, in rare

**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:** bOPV, bivalent type 1 and 3 OPV; CI, confidence interval; CID50, the culture infectious dose that induces a cytopathic effect in 50% of infected cell or tissue cultures; cVDPV, circulating vaccine-derived poliovirus; HID50, the dose (measured in CID50) that infects 50% of orally exposed and immunologically naive humans; IPV, inactivated polio vaccine; MLE, maximum likelihood estimate; mOPV, monovalent OPV; OPV, oral polio vaccine; tOPV, trivalent OPV; UP, Uttar Pradesh; WPV, wild poliovirus.

instances, revert to a virulent form and cause vaccine-derived outbreaks of paralytic poliomyelitis. Thus, OPV is both a vaccine and a source of poliovirus, and for complete eradication, its use in vaccination must be ended. After OPV is no longer used in routine immunization, as with the cessation of type 2 OPV in 2016, population immunity to polioviruses will decline. A key question is how this loss of population immunity will affect the potential of OPV viruses to spread within and across communities. To address this, we examined the roles of immunity, sanitation, and social contact in limiting OPV transmission. Our results derive from an extensive review and synthesis of vaccine trial data and community epidemiological studies. Shedding, oral susceptibility to infection, and transmission data are analyzed to systematically explain and model observations of WPV and OPV circulation. We show that in high transmission rate settings, falling population immunity after OPV cessation will lead to conditions in which OPV and WPV are similarly capable of causing outbreaks, and that this conclusion is compatible with the known safety of OPV prior to global cessation. Novel strategies will be required to ensure the stability of polio eradication for all time.

## Introduction

Wild polioviruses (WPVs) have been eliminated from all but three countries [1,2] by mass vaccination with the oral polio vaccine (OPV). The annual burden of paralytic polio infections has been reduced 10,000-fold since the start of vaccination efforts [1]. OPV has been the preferred vaccine for polio eradication because it costs less, can be reliably delivered by volunteers without medical training, and is more effective against poliovirus infection, relative to the inactivated polio vaccine (IPV) [3,4]. Unique among current human vaccines, the live-attenuated Sabin poliovirus strains in OPV are transmissible. This transmissibility provides additional passive immunization that enhances the effectiveness of OPV for generating herd immunity. However, the attenuation of Sabin OPV is unstable and so it can, in rare instances, cause paralytic poliomyelitis [5] and lead to outbreaks of circulating vaccine-derived poliovirus (cVDPV) with virulence and transmissibility comparable to that of WPV strains [6]. Thus, to complete the task of poliovirus eradication, vaccination with Sabin OPV must eventually cease [7].

The dual role of Sabin OPV as both a vaccine and a source of poliovirus is responsible for key uncertainties surrounding the ability of the Global Polio Eradication Initiative to achieve and sustain poliovirus eradication. Since the widespread introduction of polio vaccination, 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 outbreaks have been rare consequences of the hundreds of millions of OPV doses administered every year [9].

However, after vaccination with OPV is stopped, population immunity against infection will progressively decline. If polioviruses are reintroduced, whether because of accidental or deliberate release [10–12] or because of sustained yet undetected transmission [2,13–15], then large outbreaks may again occur. Outbreak control would require vaccination campaigns in affected countries and perhaps much more broadly, as has been done following recent type 2 cVDPV detections in Nigeria, Pakistan, the Democratic Republic of Congo, and Syria [16–19].

In this paper, we explore the implications of the accumulated evidence about polio infection and transmission for the long-term stability of polio eradication. Will it be possible to interrupt all polio outbreaks without restarting widespread OPV vaccination, now and at all times in the future? Fundamental to this question is the ability of the Sabin polioviruses to circulate in low

immunity populations. After OPV cessation, under what conditions will Sabin OPV remain the most effective tool for eliminating outbreaks without significant risks of causing more?

To address these questions, and building from primary literature and previous reviews and models [4,20–25], we developed a comprehensive synthesis of the evidence for how within-host immunity, viral infectivity, and transmission dynamics fit together to explain the epidemiology of poliovirus transmission. We built a within-host model that summarizes the effects of immunization on poliovirus shedding and susceptibility. We then incorporated the within-host dynamics into a poliovirus transmission model using a household–community network framework, and we calibrated the model to field transmission studies. With the model, we explored how the average transmission rate in exposed communities varies with immunity, sanitation, number of social contacts, and poliovirus type. We identified conditions required for the Sabin strains to remain indefinitely as highly effective vaccines with low risks of causing outbreaks, and conditions in which they can be expected to transmit nearly as efficiently as WPV. Our results are discussed in the context of the established stability of OPV cessation in the developed world and the ongoing global Sabin 2 cessation.

Previous models have also explored the effects of OPV cessation on Sabin and WPV transmission [20,26–33]. Our work shares a similar emphasis on individual immunity and infection dynamics [20,24,34], but it differs in model structure, use of transmission data sources, and approach to epidemiological inference. The earlier work used compartmental models that assume individuals in large populations interact randomly [20,26,27,33]. Models of specific settings—places and times—were based on national polio surveillance data [27,33], and poliovirus evolution was modeled by extrapolation between Sabin and WPV end points based on assumed intermediate transitions [26,27,33]. In contrast, our model is based on person-to-person transmission among family members and extrafamilial contacts. We calibrate specific settings to contact transmission data from field studies designed for that purpose [35–37]. We explore the effects of evolution by focusing on differences between the Sabin and WPV end points, and not the largely unstudied population genetics in between. In short, our model takes a bottom-up approach to modeling poliovirus transmission that complements existing work. Instead of drawing inferences about the unobserved conditions that affect transmission from observed outbreaks [27,33], we draw inferences about unobserved properties of possible outbreaks from observed conditions that directly affect transmission.

## Methods

### Overview

To integrate knowledge of within-host immunity, shedding, and acquisition with between-host transmission, we built a multi-scale mathematical model. We first performed a quantitative literature review of clinical trial data to determine the impact of polio vaccination schedules containing OPV and/or IPV on poliovirus shedding after challenge with OPV. This resulted in an indirect measure of immunity—the OPV-equivalent antibody titer—which was used to model the associations between polio vaccination and shedding duration, concentration of virus in stool, and oral susceptibility to infection. Second, we reviewed in detail three historical transmission studies to parameterize a model of poliovirus transmission within households and between close extrafamilial contacts. We then extended the person-to-person model by defining the local reproduction number—a threshold parameter that summarizes the potential for epidemic transmission within a community that has homogeneous demographics, immune histories, and sanitation practices. The model was implemented in Matlab 2015b (The Mathworks, Natick, MA) and is available in [S1 Code](#) and at [famulare.github.io/cessationStability](https://github.com/famulare/cessationStability). For all model parameters, see [S1 Text Table A](#).

We made simplifying assumptions while developing the model. First, we did not include the oral–oral transmission route. The studies known to us show that oral shedding occurs for shorter durations than fecal shedding and most often in individuals with low immunity [38–41], and this route is likely more important in high sanitation settings [34,39,42]. Second, we ignored fascinating questions about the effects of genetic evolution on Sabin strain transmission, and so our Sabin transmission parameters are most applicable in the first few weeks after OPV vaccination [43–45]. Third, our model focuses on transmission from children to family members and extrafamilial contacts, and it ignores other person-to-person interactions and possible environmental transmission routes, all of which influence the absolute probability and severity of outbreaks [46–50]. In the Results, we explore how the limitations of a model with these assumptions are informative about the roles of transmission route, viral evolution, and contact structure in various settings. Fourth, because paralysis has no direct influence on transmission, we did not model the impact of vaccination on paralysis (see Vidor and Plotkin [51] for a review).

All model features that describe the fraction of subjects shedding after live poliovirus exposure were fit by maximum likelihood assuming binomial sampling. Models for positive-definite quantities (concentration of poliovirus in stool, antibody titer) were estimated by ordinary least squares on  $\log(\text{quantity})$ , and 95% confidence intervals (CIs) assume log-normality. Ninety-five percent CIs were estimated by parametric bootstrap with 1,000 replicates. To estimate bootstrap CIs of parameters that are conditionally dependent on previously estimated parameters, we propagated uncertainty by resampling known parameters from the 95% CIs prior to resampling the data and re-estimating the parameters under investigation. Model equations and more detailed discussions of design decisions and calibration results can be found in [S1 Text](#). Differences in comparable quantities are considered statistically significant at  $\alpha = 0.05$ .

## Within-host model

Our within-host model describes shedding from and susceptibility to poliovirus infection. In the model, the ability of an infected individual to transmit polio depends on the duration of shedding and the concentration of poliovirus in their stool. Oral susceptibility to infection depends on the dose–response relationship for the probability that poliovirus ingested orally results in an infection, as detected by subsequent fecal shedding. Shedding duration, concentration, and oral susceptibility all depend on pre-exposure immunity and the poliovirus source, vaccine or wild.

Immunity in our model is represented by the OPV-equivalent antibody titer (denoted  $N_{\text{Ab}}$ )—an indirect measure of immunity that is inferred from measurements of shedding duration and/or dose response (first introduced by Behrend and colleagues [25] and called "mucosal immunity" therein). Previous reviews have demonstrated that when immunity is due to prior OPV immunization or natural WPV infection, homotypic (of the same serotype) serum neutralizing antibody titers (measured as the geometric mean reciprocal dilution of serum that is able to neutralize 100 CID50 [the culture infectious dose that induces a cytopathic effect in 50% of infected cell or tissue cultures] of poliovirus) are predictive of fecal shedding and susceptibility [25,52]. However, serum antibody titers induced by IPV alone, and heterotypic titers against type 2 from bivalent type 1 and 3 OPV (bOPV) are not predictive of shedding and susceptibility [25,53,54]. The OPV-equivalent antibody titer describes the impacts of vaccination histories containing IPV or bOPV on shedding and susceptibility in terms of equivalent serum antibody titers from homotypic OPV vaccination in children. This model is agnostic about the biophysical mechanisms of immunity that prevent fecal shedding and is not

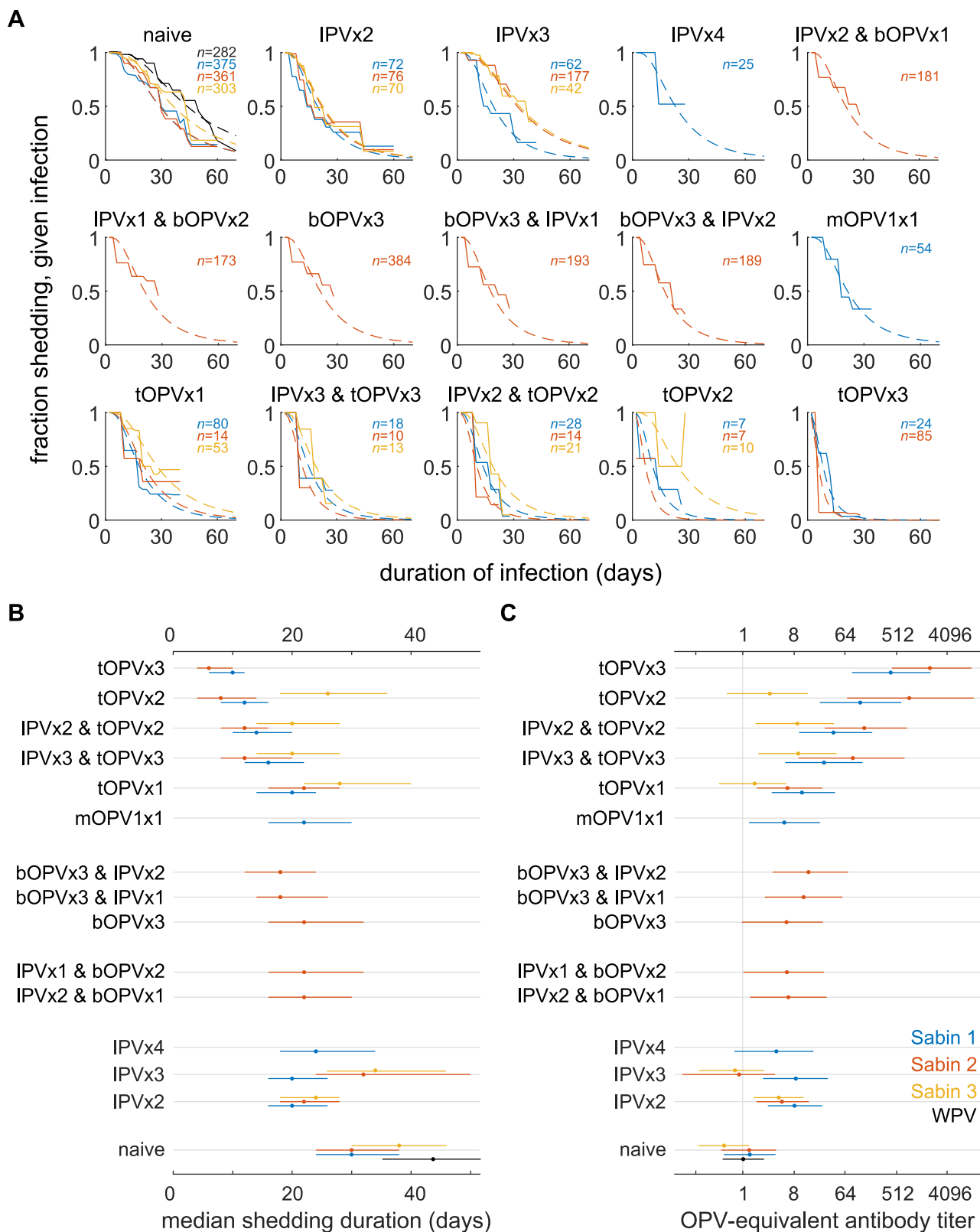
intended to represent immunoglobulin A concentration or other direct correlates of mucosal immunity [55]. Following the results of Behrend and colleagues [25], we assumed that the typical immunologically naive individual with no history of poliovirus exposure ("unvaccinated") and no measurable humoral immunity ("seronegative") has an OPV-equivalent antibody titer of  $N_{Ab} = 1$  by definition, that the typical OPV-equivalent titer at maximum achievable individual immunity is  $N_{Ab} = 2,048 (= 2^{11})$ , and that homotypic antibody titers for each poliovirus serotype are independent.

The studies used to calibrate the within-host model span many countries, years, and types of immunization history. All included studies describe the fraction of subjects positive for poliovirus in stool after OPV challenge or WPV exposure as equal to the number of subjects shedding divided by the number tested at each time point. In many cases, the data were digitized from published figures that do not report variation in the number of samples for each time point, and so our sample sizes at each time point are often approximate. A summary of all included studies, with details about which studies contributed to which components of the model and reasons for study exclusion, appears in [S1 Text Part B \[36,41,53,54,56–72\]](#), and the data are in [S1 Code](#).

**Shedding duration.** In [Fig 1](#), we summarize available data for and our model of the impact of different immunization histories on shedding duration [36,41,53,54,56,57,59–62,64–67,69–71]. [Fig 1A](#) shows the average shedding duration survival distribution for all included trial arms by poliovirus strain (Sabin 1, 2, 3 or WPV) and pre-challenge immunization history (formulation and number of vaccine doses). All included subjects were 5 years of age or younger and from the Americas, Europe, the Middle East, or East Asia. We averaged across differences in vaccination schedule (i.e., trivalent OPV [tOPV] at 6, 10, and 14 weeks of age [54] was grouped with tOPV at 7, 8, and 9 months [61]) and age at challenge because our goal was to model levels of immunity that describe typical conditions among children in practice—in which vaccination schedules are not rigorously adhered to and natural oral challenge has no schedule. We also averaged over differences in the exact dose given (i.e., Salk vaccine [61] versus enhanced IPV [41]), as dose effects on shedding were insignificant relative to differences in the type and number of vaccinations. At this stage in model building, we ignored waning and setting-specific variations in OPV take, both of which are addressed in later sections. Because individual-level data were not available, we could not construct proper Kaplan-Meier estimates of the survival distribution for each immunization history. Rather, we assumed that the fraction shedding at each time point for each trial arm represented an approximate survival distribution, and the aggregated distributions shown in [Fig 1](#) are the sample-size-weighted averages of the fraction shedding at each time point from the original papers. Thus, in rare instances in which the sample sizes are small, the empirical distribution is not monotonically decreasing, as is necessary for a true survival model (i.e., [Fig 1A](#): tOPV×2, Sabin 3). We used the data and our log-normal survival model for shedding duration ([S1 Text Eq A](#)) to inform estimates of typical OPV-equivalent antibody titers in children under 5 years of age with various immunization histories. Additional details about the data used, the shedding duration model, and model calibration can be found in [S1 Text Part B.2](#).

Our shedding duration model ([S1 Text Eq A](#)) summarizes the following observations. In immunologically naive individuals, there were no statistically significant differences by serotype in shedding duration after OPV challenge. The maximum likelihood estimate (MLE) of the median shedding duration for immunologically naive individuals shedding any Sabin strain is 30.3 (23.6–38.6) days, significantly shorter than the median shedding duration for WPV, 43.0 (35.7–51.7) days (see also [S1 Text Fig A](#)). The median shedding duration associated with maximum OPV-equivalent antibody titer ( $N_{Ab} = 2,048$ ) is 6 (4–10) days for the Sabin strains and is modeled to be 8 (6–13) days for WPV. Repeated immunization with tOPV has a





**Fig 1. Effect of vaccination on shedding duration after OPV challenge and pre-challenge immunity.** Labels describe vaccines received and number of doses (i.e., bOPVx2 and IPVx1: two doses of bOPV and one dose of IPV). (A) Sheddling duration after OPV challenge: shedding duration survival curves from aggregated trial data (solid lines) and maximum likelihood model fit (dashed) for each immunization schedule and poliovirus type.

(Infection with Sabin 1, blue; Sabin 2, red; Sabin 3, orange; WPV, black). (B) Median shedding durations after infection because of OPV challenge or WPV transmission estimated from model fits in panels A and (C), corresponding pre-challenge homotypic OPV-equivalent antibody titers (see, also, S1 Text Fig A, and an interactive visualization of shedding duration data is available at <https://famulare.github.io/cessationStability/>). bOPV, bivalent type 1 and 3 OPV; IPV, inactivated polio vaccine; OPV, oral polio vaccine; WPV, wild poliovirus.

<https://doi.org/10.1371/journal.pbio.2002468.g001>

cumulative effect on shedding duration. tOPV has weaker effects on shedding duration for type 3 than types 1 and 2, reflecting known per-dose efficacy differences [73]. At the level of aggregation examined here, limited data suggest monovalent OPV (mOPV) is comparable to tOPV. Repeated vaccination with IPV alone shows no cumulative effect on shedding duration, and study-to-study variation shows little or no effect overall. bOPV produces a decrease in shedding duration against heterotypic Sabin 2 challenge, and this effect may be weakly enhanced by IPV after bOPV, but not IPV before bOPV.

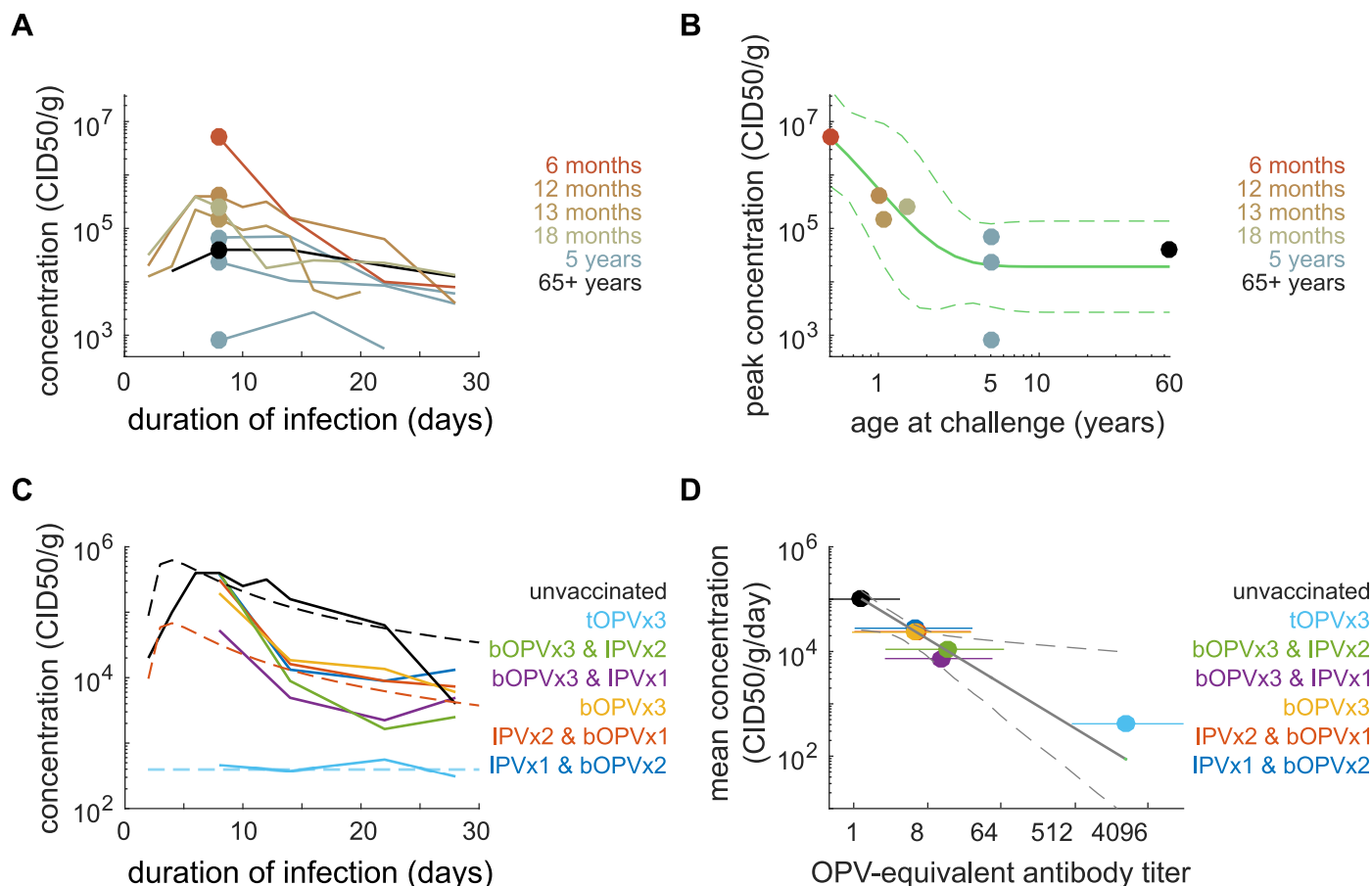
The transformation from median duration (Fig 1B) to titer (Fig 1C) serves as the definition of the OPV-equivalent antibody titer in our model—short post-challenge shedding duration implies high pre-challenge OPV-equivalent immunity. Having used the typical post-vaccination shedding duration distributions to define the OPV-equivalent antibody titer model, for the rest of this article, we do not rely on immunization histories to determine immunity. Rather, we calibrate to setting-specific data on shedding duration to infer the appropriate OPV-equivalent immunity for each data source. This allows us to generalize from the aggregated results in Fig 1 to incorporate variation in post-vaccination immunity without having to model mechanisms of variation, such as enterovirus interference or enteropathy [25, 74–77].

**Concentration of poliovirus in stool.** In Fig 2, we show available data for and our model of the concentration of poliovirus in stool while shedding after OPV challenge [53,54,56–58,67,68]. The included studies all reported concentration as the CID50 per gram of stool (CID50/g) averaged across all subjects positive for poliovirus at each time point, and individual-level variation was generally not reported. Ages at OPV challenge ranged from 6 months to 65 years or more. The majority of trial arms challenged subjects with mOPV2 (mOPV1,  $n = 5$ ; mOPV2,  $n = 11$ ; mOPV3,  $n = 5$ ). Data exploration revealed no systematic differences in concentration by serotype. We are not aware of similar longitudinal data for WPV shedding. OPV-equivalent antibody titers were estimated from the corresponding shedding duration data for each trial arm (see S1 Text Part B.2), and trial arms considered immunologically naive reported no history of live poliovirus exposure, contained confirmed seronegative subjects, or had OPV-equivalent antibody titers consistent with  $N_{Ab} = 1$ .

Our model of poliovirus concentration in stool summarizes the following observations. Poliovirus concentrations peak 5–8 days after acquiring infection and decline slowly thereafter (Fig 2A). Data from immunologically naive subjects revealed an unexpected dependence of peak concentration with age (Fig 2B). Peak concentration declines by roughly two orders of magnitude over the first 3 years of life, with an exponential aging constant of 12 (1–45) months, consistent with major developmental milestones, including the transition to solid food and immune system maturation [78,79], after which the limited data indicate stability of peak shedding concentration for life. The concentration of poliovirus in stool is correlated with vaccination history (Fig 2C) and decreases by roughly a factor of 10 with each 8-fold increase in OPV-equivalent titer (Fig 2D). The shedding concentration model is described in S1 Text Eqs B–D.

**Oral susceptibility to infection.** To inform our dose–response model for oral susceptibility to infection, we first examined studies of healthy children that measured the probability of fecal shedding after receiving oral droplets with doses ranging from  $10^1$  to  $10^6$  CID50 and for which pre-challenge immunization histories were known. Three studies challenged with Sabin



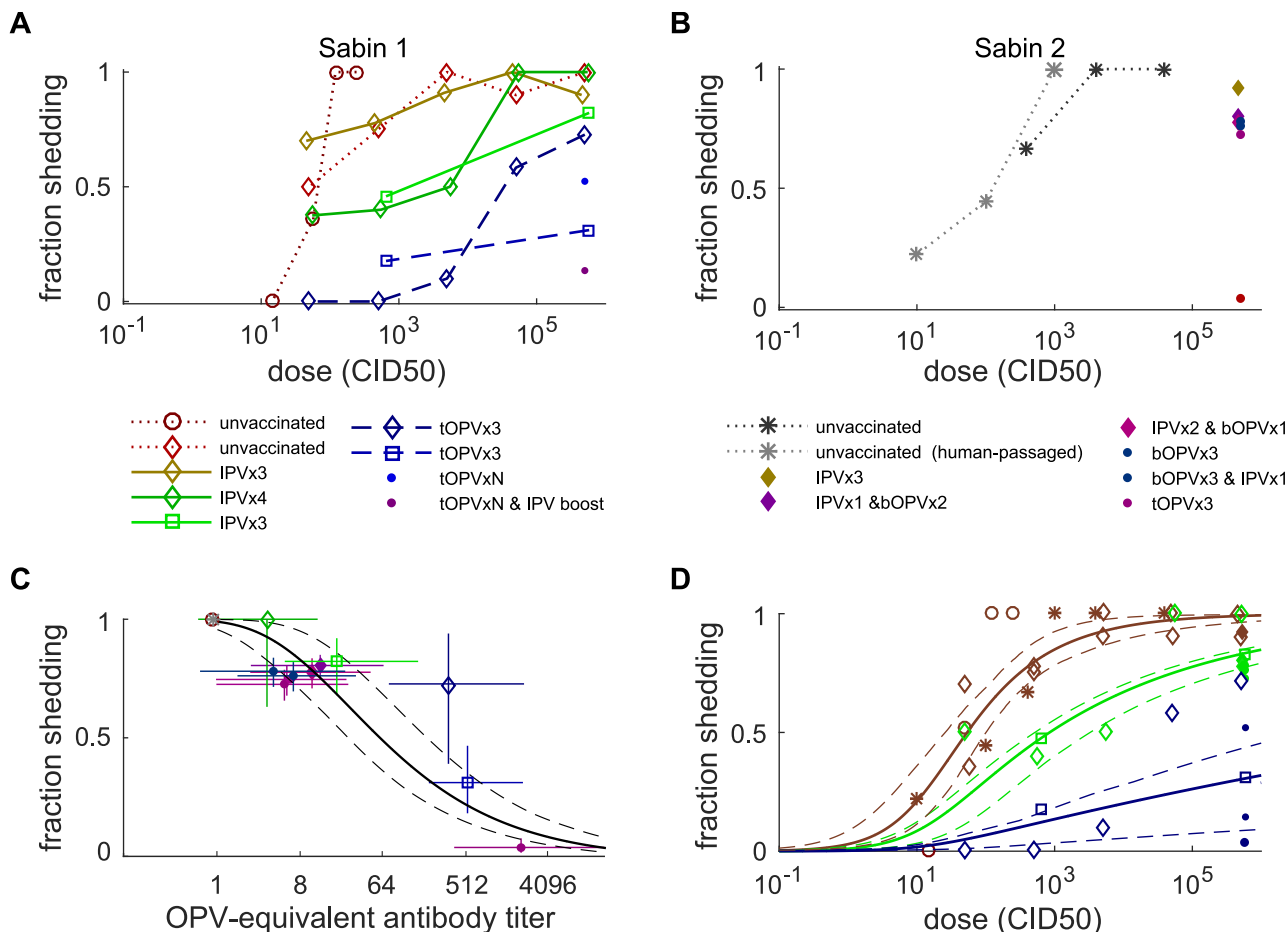


**Fig 2. Concentration of poliovirus in stool: effects of age and immunity.** (A) Mean concentration of poliovirus in stool (CID50/g) versus time after OPV challenge for immunologically naive subjects (color by age at challenge). (B) Peak concentration depends on age (dot color by age at challenge, corresponding to data from panel A at 1 week post-challenge; green line, model MLE and 95% CI, S1 Text Eq B). (C) Mean concentration after mOPV2 challenge for subjects with various vaccination histories (dashed, model MLE; solid, trial data age adjusted to 12 months using S1 Text Eq C). The concentration of poliovirus in stool depends on pre-challenge vaccination history. (D) The mean daily concentration (culture infectious doses per gram per day; CID50/g/day) declines by one order of magnitude for every 8-fold increase in OPV-equivalent antibody titer (OPV-equivalent titers [color, MLE, and 95% CI] for each trial arm shown in panel C; black, model [S1 Text Eq D, MLE, and 95% CI]). Interactive data visualization is available at <https://famulare.github.io/cessationStability/>. CI, confidence interval; CID50, the culture infectious dose that induces a cytopathic effect in 50% of infected cell or tissue cultures; IPV, inactivated polio vaccine; MLE, maximum likelihood estimate; mOPV, monovalent OPV; OPV, oral polio vaccine; tOPV, trivalent OPV.

<https://doi.org/10.1371/journal.pbio.2002468.g002>

1 [41,61,63]; none used Sabin 3 or WPV, and one study challenged with Sabin 2 and type 2 poliovirus derived from Sabin 2 after 5 days of replication in vaccinated children [58]. There were no statistically significant differences between Sabin 1 and Sabin 2 across these trials, but statistical power at low doses is poor. We also included modern studies of vaccine doses ( $10^{5-6}$  CID50) that provided information about the effects of heterotypic immunity against type 2 from bOPV [53, 54] and IPV boosting on prior OPV immunization [72]. OPV-equivalent antibody titers were estimated from the corresponding shedding duration data for each trial arm.

Our dose-response model summarizes the following observations (Fig 3A and 3B). The typical Sabin 1 dose required to infect 50% of immunologically naive healthy children (the dose [measured in CID50] that infects 50% of orally exposed and immunologically naive humans [HID50]) is 54 (26–100) CID50, and the fraction shedding approaches 1 for doses greater than  $10^4$  CID50. Immunity has similar effects on susceptibility as it does on shedding duration and concentration. IPV-only immunization reduces susceptibility to infection in



**Fig 3. Oral susceptibility to infection after OPV challenge.** (A) Fraction shedding after Sabin 1 oral challenge at different doses (color by trial arm, symbol by source study). (B) Fraction shedding after Sabin 2 oral challenge at different doses (color by trial arm, symbol by source study; data for doses  $\leq 10^3$  CID50 are for human-passaged Sabin 2 isolated from stool 5 days after vaccination). (C) Fraction shedding at vaccine doses ( $10^{5-6}$  CID50) decreases with increasing OPV-equivalent antibody titer (color and symbols as in panels A–B; black lines are model MLE and 95% CI using S1 Text Eq E). (D) Beta-Poisson dose–response model MLE and 95% CI. Three model scenarios shown correspond to immunologically naive ( $N_{Ab} = 1$ , red), heterotypic bOPV and upper-bound IPV-only ( $N_{Ab} = 8$ , green), and typical tOPV or post-IPV-boosting ( $N_{Ab} = 256$ , blue). Data from panels A–B (symbols as above, colored by corresponding model scenario). bOPV, bivalent type 1 and 3 OPV; CI, confidence interval; CID50, the culture infectious dose that induces a cytopathic effect in 50% of infected cell or tissue cultures; IPV, inactivated polio vaccine; MLE, maximum likelihood estimate; OPV, oral polio vaccine; tOPV, trivalent OPV.

<https://doi.org/10.1371/journal.pbio.2002468.g003>

some studies but not all, and the effect is at most comparable to that provided by heterotypic immunity against type 2 from immunization with bOPV. tOPV reduces susceptibility across all doses. Not addressed in previous sections on shedding is that IPV boosting in subjects with prior OPV immunization is highly effective for reducing susceptibility—as is now well known [72,80,81]. OPV-equivalent antibody titer has a monotonic relationship with oral susceptibility (Fig 3C). The data are consistent with an immunity-dependent beta-Poisson dose–response model [82] (Fig 3D and S1 Text Eq E).

To inform our model of strain-specific differences in dose response, we examined two transmission studies from similar settings in the United States. The first study in Houston in 1960 [36] measured transmission among immunologically naive close contacts of vaccinees for each of the Sabin strains, and another in Louisiana from 1953–1955 [35] measured close contact transmission of WPV (combined across all serotypes); these studies and our transmission model are described in detail in a later Methods section. Under the assumptions that

**Table 1. Infectivity by strain.** MLE and 95% CI of the HID50—the oral dose that infects 50% of immunologically naive people.

Strain	HID50
Sabin 1	54(26–100) CID50
Sabin 2	30(15–54) CID50
Sabin 3	67(34–120) CID50
WPV	7(2–41) CID50

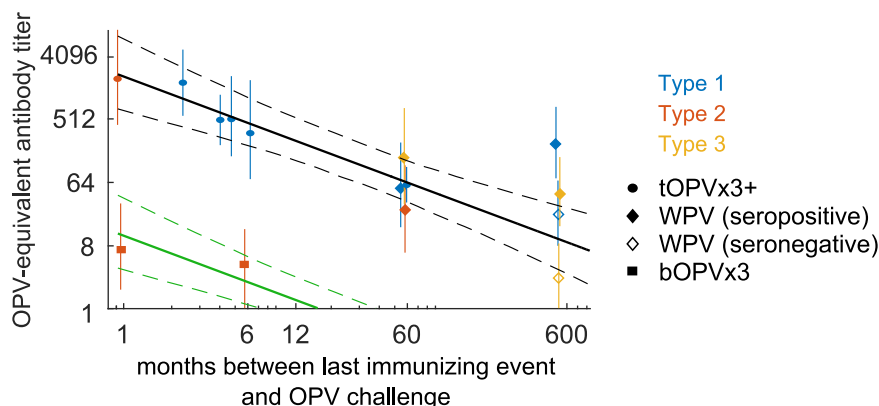
Abbreviations: CI, confidence interval; CID50, the culture infectious dose that induces a cytopathic effect in 50% of infected cell or tissue cultures; HID50, the dose (measured in CID50) that infects 50% of orally exposed and immunologically naive humans; MLE, maximum likelihood estimate; WPV, wild poliovirus.

<https://doi.org/10.1371/journal.pbio.2002468.t001>

Sabin 1 is well described by the OPV challenge model above and that sanitation and contact patterns are similar across the four trial arms, differences in transmission are attributable to the virus-specific differences in infectivity shown in Table 1.

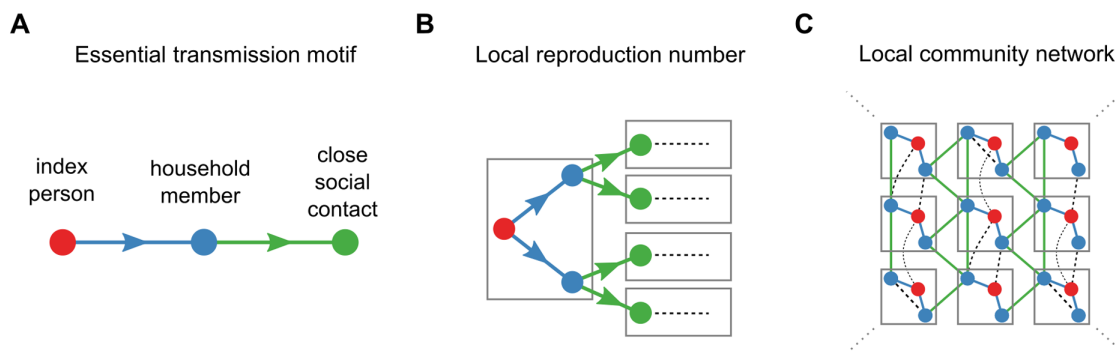
**Waning immunity.** We built a composite picture of waning immunity against infection from analysis of OPV-equivalent antibody titers across studies. We considered data for individuals that were likely maximally immune after their last poliovirus exposure, either due to immunization with three or more doses of tOPV [41,54,72] or accumulated natural immunity through 15 years of age during the endemic era [56,68]. The included trial arms involved subjects from 6 months to 65+ years of age and with between 1 month and likely 45+ years from last immunizing event to OPV challenge (see S1 Text Part B.5 for additional details).

Our waning model summarizes the following observations (Fig 4). Absent reinfection or vaccination, immunity declines over many years, possibly with increasing variation in adults. We modeled waning as a power-law decay [83] during the months since last immunization,  $N_{Ab}(t) \propto t^{-\lambda}$ , with exponent  $\lambda = 0.87$  (0.73–1.02) (S1 Text Eq F). The limited relevant data after bOPV vaccination [54] are consistent with the hypothesis that heterotypic and homotypic immunity share waning dynamics (bOPV data only,  $\lambda = 0.52$ [0–1.2]).



**Fig 4. Waning immunity against infection.** OPV-equivalent antibody titer versus time between last exposure and mOPV challenge (color by serotype and symbol by source of immunity). Power-law model of waning from peak homotypic immunity (MLE and 95% CI, black lines) and heterotypic immunity against type 2 from bOPV (MLE and 95% CI assuming homotypic waning exponent, green lines). bOPV, bivalent type 1 and 3 OPV; CI, confidence interval; MLE, maximum likelihood estimate; mOPV, monovalent OPV; OPV, oral polio vaccine; tOPV, trivalent OPV; WPV, wild poliovirus.

<https://doi.org/10.1371/journal.pbio.2002468.g004>



**Fig 5. Network motifs of poliovirus transmission.** (A) The essential motif of poliovirus transmission is index person to household member to close social contacts (dot color gives subject type; line color describes relationship). (B) The local reproduction number describes the expected number of secondary households infected by an index person based on sanitation, individual immunity, and the number of close social contacts. The house-to-house transmission motif represents this first generation of local transmission (color as in panel A; gray boxes denote households, and dashed lines indicate relationships beyond the first generation). (C) Our definition of the local reproduction number captures transmission among household members and close social contacts (solid colored lines) but does not include all relationships that may contribute to transmission (dashed black).

<https://doi.org/10.1371/journal.pbio.2002468.g005>

## Transmission model

Our model describes the effects of within-host dynamics on transmission among people who share a household and close social contacts outside the household. We assumed that transmission from infected person to recipient occurs by oral exposure to infected feces, for which the amount of poliovirus transmitted per exposure is determined by the shedding duration and concentration models, and recipient susceptibility is determined by the dose–response model.

**Person-to-person transmission.** The population structure of the model is based on the essential transmission network motif examined by the field transmission studies (Fig 5A): an index person transmits to household contacts (typically family members), who in turn transmit to their close social contacts outside the household. For each of the three individuals along the transmission chain, the person-to-person model calculates daily incidence (the probability of becoming infected each day), prevalence (the probability of shedding poliovirus in stool each day), and concentration of poliovirus shed (CID50 per gram of stool).

Our model focuses on person-to-person transmission because it allows us to study factors that causally affect transmission probability within and between households, with contact tracing data collected for that purpose (as described in detail below). Although we rely in this paper on calibration to poliovirus transmission data, each parameter has biophysical meaning and can in principle be measured directly in the absence of live poliovirus. This model building approach offers a complementary alternative to more classical models that focus on population-wide measures of disease transmission and for which key transmission rate parameters lack biophysical meaning [84]. Our focus on specific within- and between-household relationships follows the available data and emphasizes the roles of the strongest links in the transmission network to determine community susceptibility to poliovirus transmission.

Infections in index persons are defined to begin on day  $t = 1$  due to either mOPV or WPV exposure on day  $t = 0$ . Incidence is determined by the dose–response model,

$$P_{\text{index}}(\text{infected at } t) = \begin{cases} p_x P(\text{infection} | \text{dose}, N_{\text{Ab, index}}) & t = 1 \text{ days} \\ 0 & t > 1 \text{ days} \end{cases} \quad (1)$$

where  $p_x$  (serotype  $x = 1, 2, 3$ ,  $p_x \in (0, 1]$ ) is a setting-specific susceptibility modifier that accounts for non-immunological host factors such as non-polio enterovirus infection or

enteropathy that can reduce the probability of shedding [25, 74, 77], and the second term is defined in S1 Text Eq E. The prevalence for  $t > 0$  after exposure is given by:

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

where the first term is Eq 1 and the second is the shedding duration model in S1 Text Eq A. Household members are infected with probabilities determined by the dose–response model, the size of the fecal dose, and the amount of virus shed by the index person. Daily incidence derives from exposure to index shedding as:

$$P_{\text{household}}(\text{infected at } t) = P_{\text{household}}(\text{transmission at } t | \text{index shedding}) \times P_{\text{index}}(\text{shedding at } t | N_{\text{Ab,index}}; \text{infected at } t = 1),$$

with

$$P_{\text{household}}(\text{transmission at } t | \text{index shedding}) = \beta(t) \prod_{t'=1}^{t-1} (1 - \beta(t'))$$

$$\beta(t) = 1 - (1 - P(\text{infection} | \text{dose}(t), N_{\text{Ab,household}}))^{D_{ih}},$$

$$\text{dose}(t) = T_{ih} \times (\text{index concentration}(t) | N_{\text{Ab,index}}),$$

where  $P_{\text{household}}(\text{transmission at } t | \text{index shedding})$  is the household member incidence on day  $t$  given contact with a shedding index person,  $\beta(t)$  is the infection probability determined by the dose–response model,  $D_{ih}$  is the interaction rate for an index and household member pair (average number of fecal–oral exposures per day),  $T_{ih}$  is the fecal–oral dose (micrograms of stool per exposure), and index concentration (CID50 per gram) is given by the fecal concentration model in S1 Text Eq D. Household member prevalence follows from convolving daily incidence (assuming no reinfection) with the shedding duration distribution:

$$P_{\text{household}}(\text{shedding at } t) = \sum_{t'=1}^t P_{\text{household}}(\text{infected at } t') \times P(\text{shedding at } (t - t') | N_{\text{Ab,household}}; \text{infected at } t').$$

The model assumes all transmission to close social contacts occurs only through household members of index cases, depending on contact susceptibility and fecal exposure to and the amount shed by the contacted household member. Daily incidence derives from exposure to household contact shedding as:

$$P_{\text{social}}(\text{infected at } t) = \sum_{t'=1}^t P_{\text{social}}(\text{transmission at } t | \text{household shedding since } t') \times P_{\text{household}}(\text{infected at } t')P(\text{shedding at } (t - t') | N_{\text{Ab,household}}; \text{infected at } t'),$$

with

$$P_{\text{social}}(\text{transmission at } t | \text{household shedding since } t') = \beta(t - t') \prod_{t''=t'}^{t-1} (1 - \beta(t'' - t'))$$

and

$$\beta(t - t') = 1 - (1 - P(\text{infection} | \text{dose}(t - t'), N_{\text{Ab, social}}))^{D_{hs}},$$

$$\text{dose}(t - t') = T_{hs} \times (\text{household contact concentration}(t - t') | N_{\text{Ab, family}}), \quad (2)$$

where  $D_{hs}$  is the interaction rate for a household-to-close-social-contact pair,  $T_{hs}$  is the fecal-oral dose, and  $(t - t')$  is the time interval since the household contact became infected. The convolution over household member incidence accounts for all the times at which household members can become infected. Close social contact prevalence follows from convolving daily incidence with the shedding duration distribution:

$$P_{\text{social}}(\text{shedding at } t) = \sum_{t'=1}^t P_{\text{social}}(\text{infected at } t') \\ \times P(\text{shedding at } (t - t') | N_{\text{Ab, social}}; \text{infected at } t').$$

**Local reproduction number.** We defined the local reproduction number ( $R_{loc}$ ) as the expected number of close social contacts infected by an index person due to transmission along the index-household-social-contact essential transmission motif,

$$R_{loc} = p_{is} N_s, \quad (3)$$

$$p_{is} = \frac{\sum_{t=1}^{\infty} P_{\text{social}}(\text{infected at } t)}{\sum_{t=1}^{\infty} P_{\text{index}}(\text{infected at } t)},$$

where  $N_s$  is the average number of close social contacts outside the index household and  $p_{is}$  is the total probability that an index person transmits through a household member to a close social contact in another household, as determined by the ratio of total incidences in Eqs 1 and 2.  $R_{loc}$  describes the first generation of household-to-close-social-contact transmission following infection of an index person (Fig 5B).

Within close-knit communities where all households have similar demographic, behavioral, and immunological patterns,  $R_{loc}$  provides a lower bound on the total transmission rate because it does not include all possible transmission routes (Fig 5C). Across large, heterogeneous communities, the a priori relationship between  $R_{loc}$  and the true average transmission rate across all contacts is unclear. The model can be extended to describe any set of relationships—for example, a household member may have many more socially distant contacts who receive smaller doses less often—but the model complexity that needs to be constrained increases rapidly with the number of relationships. For these reasons, this iteration of the model cannot make predictions about the absolute probability or severity of outbreaks, for which model specification is critical [46–50]. Rather,  $R_{loc}$  is a useful threshold parameter for categorizing outbreak risk with data from contact-tracing studies.

**Calibration.** While the data on within-host aspects of polio infection showed remarkable coherence across studies from different eras and settings, this is not the case for literature on community transmission of poliovirus. The 18 transmission studies reviewed by Tebbens and colleagues [24] exhibit varying thoroughness in their reporting of pre-exposure immunity and contact relationships. In lieu of a comprehensive review, we based our transmission model on specific studies capable of identifying important model parameters. The studies took place in

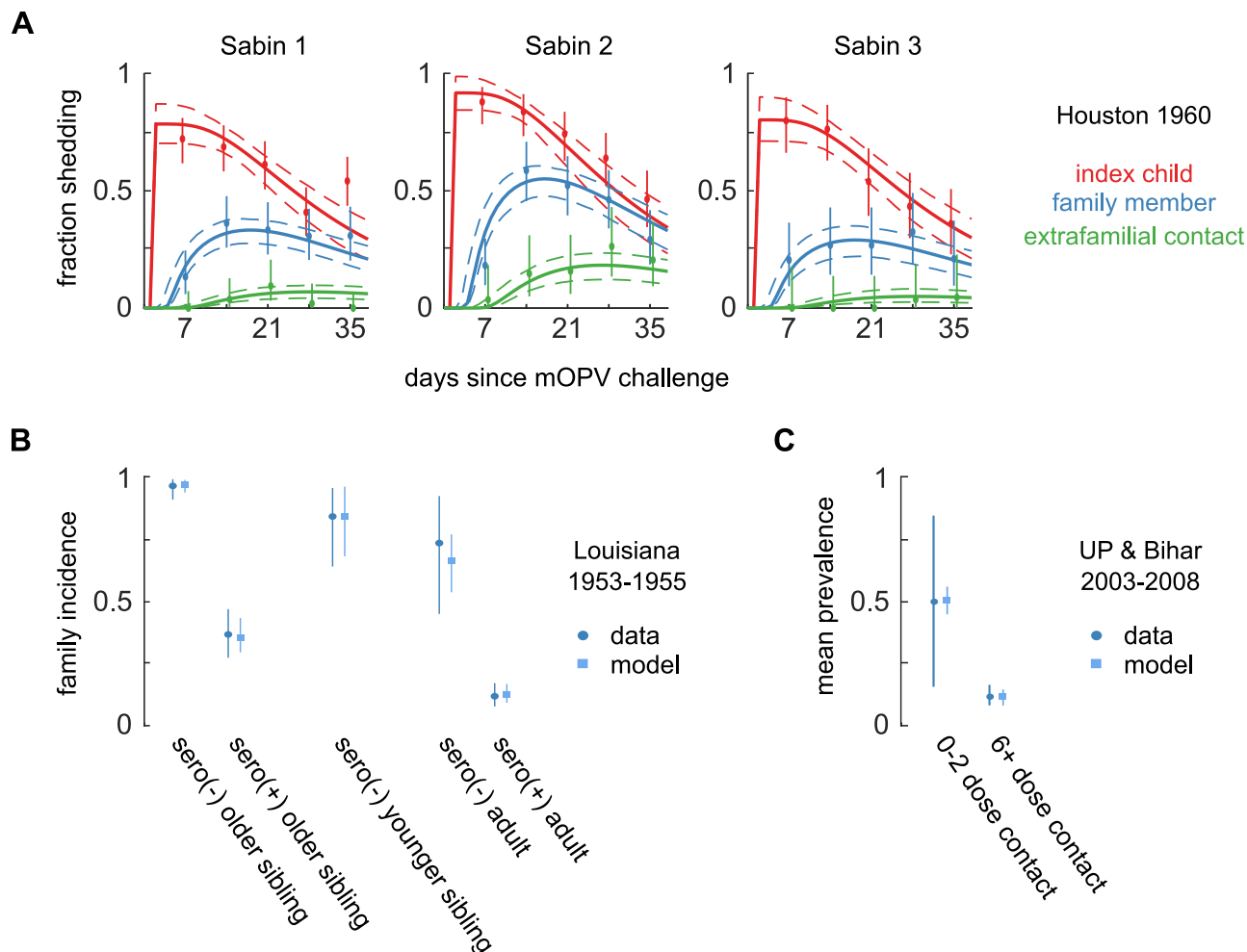


the US between 1953 and 1960 [35,36] and in India between 2003 and 2008 [37]; all had large sample sizes and carefully reported demographic and social contact attributes, and provided sufficient information to infer pre-exposure OPV-equivalent immunity (either directly through vaccination histories or serostatus, or indirectly via shedding duration). The fraction of subjects positive for poliovirus after OPV challenge or WPV exposure was given by the number of subjects shedding in stool [36, 37] or recently seroconverted [35] divided by the number tested. Additional information about calibration methods are provided in [S1 Text Part C](#).

We assumed that the serotype-specific dose–response model parameters ([Table 1](#), [S1 Text Eq E](#)) are independent of setting. The setting-specific free parameters are the pre-challenge OPV-equivalent antibody titers for each subject type ( $N_{Ab}$ ), the average fecal–oral dose (micrograms of stool ingested per interaction,  $T_{ih}$  and  $T_{hs}$ ), the interaction rates (number of fecal–oral contacts per day for each person-to-person pair,  $D_{ih}$  and  $D_{hs}$ ), the setting-specific dose response modifiers ( $p_x$ ), and the typical number of close social contacts ( $N_s$ ). The interaction rate and fecal–oral dose parameters are not separately identifiable from the available data, and so we fixed the index-to-household-member interaction rate to once per day ( $D_{ih} = 1$ ) and assumed that fecal–oral dose is independent of relationship type ( $T_{ih} = T_{hs}$ ).

From the Sabin transmission study conducted in Houston 1960 [36], we calibrated the serotype-specific dose–response parameters, and the fecal–oral dose and between-household interaction rate representative of a typical endemic setting with low socioeconomic status in the pre-elimination US. Additional study-specific parameters described OPV-equivalent immunity and trial-to-trial variation in post-vaccination shedding in index children. Briefly, children aged 2–18 months were enrolled to receive a dose of mOPV. Weekly stool samples were collected from the vaccine-recipient index children, their siblings, and primary extrafamilial social contacts of siblings. The majority of index children had prior serological immunity either due to maternal antibodies or IPV vaccination. Pre-challenge serology was not presented for siblings or extrafamilial contacts. The authors observed no significant differences in shedding by IPV immunization history or pre-challenge serologic immunity. Family members and extrafamilial contacts 5–9 years of age shed significantly less from transmission, and there was essentially no shedding in subjects older than 10 years of age ([S1 Text Fig B](#)). From joint calibration across the three mOPV trial arms ([Fig 6A](#)), we inferred that children under 5 years of age who shed poliovirus, regardless of position in the transmission chain, had OPV-equivalent antibody titers of  $N_{Ab} = 1$ , and the fraction of infants shedding 1 week after receiving mOPV was high: type 2, 0.92 (0.85–1.0); type 1, 0.79 (0.70–0.88), and type 3, 0.81 (0.71–0.91). Thus, it is likely that most children under 5 years of age had no experience with WPV. (See [S1 Text Part C.1](#) for additional details.) From the differences in transmission by serotype in this immunologically naive population, we estimated the infectiousness of each serotype (shown above in [Table 1](#)). The estimated fecal–oral dose was microscopic at 5 (1–31) micrograms per day ( $\mu\text{g/day}$ ), and the estimated interaction rate in a family member and extrafamilial contact pair—the average number of fecal–oral exposures per day—was 9.0 (2.6/46), possibly reflecting higher rates of social interaction in peer versus infant–sibling pairs [85].

From the WPV transmission study conducted in Louisiana from 1953–1955 [35], we calibrated WPV dose response and the age dependence of the fecal–oral dose, under the assumption that the fecal–oral dose between index children and older siblings was the same as in Houston 1960. Briefly, Gelfand and colleagues enrolled families with newborn children to undergo monthly surveillance for naturally acquired polio infections. Whenever a newly infected index child was identified, household contacts were tested for subsequent polio infection, most reliably through evidence of seroconversion. This measure of incidence was reported for siblings and parents, stratified by serostatus and age relative to the index child.



**Fig 6. Transmission model calibration.** Each study measured the amount of transmission from index persons in different ways. (A) Houston 1960: fraction of children under 5 years of age shedding each week after mOPV challenge to an index child and subsequent transmission. (Color by subject type; weekly data MLE and 95% CI, dot and whiskers; model MLE and 95% CI, lines). Eight free parameters are jointly identified across the nine calibration targets. (B) Louisiana 1953–1955: incidence in household contacts of index children naturally infected by WPV, measured by seroconversion approximately 30 days after the index child became infected. Three free parameters are jointly identified by the five calibration targets. (C) Uttar Pradesh and Bihar 2003–2008: mean prevalence of WPV in stool measured in household contacts after the onset of paralysis in index children. One free parameter is jointly identified by the two calibration targets. See S1 Text Fig C for additional information about model fit. CI, confidence interval; MLE, maximum likelihood estimate; mOPV, monovalent OPV; WPV, wild poliovirus.

<https://doi.org/10.1371/journal.pbio.2002468.g006>

We assumed that the OPV-equivalent antibody titer of seronegative subjects was  $N_{Ab} = 1$ , and we reconstructed from the published serological data that the median seropositive titer was  $N_{Ab} = 93$  in this naturally immunized population (see S1 Text Part C.2 for additional details.) Joint calibration of incidence 30 days after index infection across the five reported index-family relationships (Fig 6B) confirmed the expected outcome that WPV is more infectious than any Sabin strain (Table 1). We inferred that the fecal-oral dose transmitted from index children to adults was 26 (16–41)% of that passed to siblings under 5 years of age; a similar age-related decline in fecal-oral dose was inferred with this same model for a recent Sabin 2 transmission study in Bangladesh [86]. The estimated fecal-oral dose transmitted from older index children to younger siblings was 46 (26–104)% of the reverse.

To estimate an upper bound for fecal-oral dose in regions of extremely high polio transmission intensity [87], we examined WPV surveillance data from 2003–2008 in India reported by

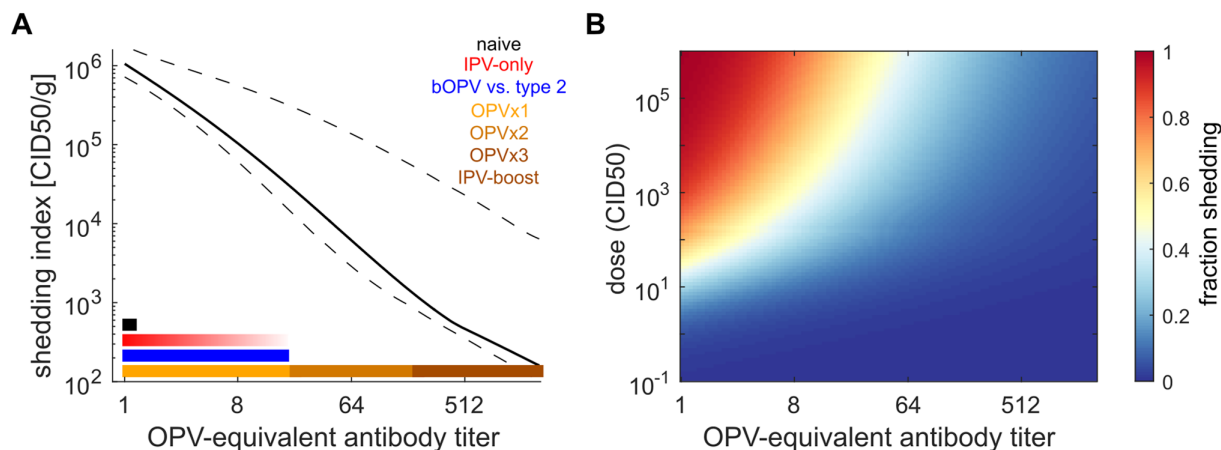
Grassly and colleagues [37]. The authors examined the fraction of stools positive for WPV from children under 5 years of age who were household contacts (siblings, residents of the same household, or playmates [37]) of paralytic WPV cases (mostly from Uttar Pradesh [UP] and Bihar). Household contacts with low immunity (0–2 reported tOPV doses) and high immunity (6+ reported doses) were grouped for analysis. They estimated that 51 (16–84)% of low immunity and 12 (8–16)% of high immunity contact stool samples were positive for WPV when sampled once during the 10 weeks after paralysis of the index child. For our model, we assumed that the high immunity cohort had an OPV-equivalent antibody titer of  $N_{Ab} = 512$  corresponding to their estimate of an 11-day mean shedding duration, and that the low immunity cohort had  $N_{Ab} = 1$  in this setting known for low tOPV efficacy [75]. Given the assumptions, and after accounting for the unobserved time infected prior to paralysis (see [S1 Text Part C.3](#) and [S1 Text Eq G](#)), we inferred from joint calibration to both targets ([Fig 6C](#)) that the fecal–oral dose transmitted from index children to household contacts 230 (1–1,800)  $\mu\text{g/day}$ , roughly 50 times higher than in Houston 1960.

**Additional assumptions.** The calibration studies did not report sufficient information to constrain the average number of close social contacts outside the household ( $N_s$ ), and only the Houston study provided information about the household-to-close-social-contact interaction rate ( $D_{hs}$ ). Except when explicitly exploring sensitivity to these parameters, we made the following assumptions. For Houston/Louisiana, we assumed that the typical number of close social contacts is  $N_s = 4$  (3–5), reflecting the average number of close friends in American childhood social networks [88]. For UP and Bihar, we assumed  $N_s = 10$  (8–12) based on scaling Houston in proportion to the 2–3 times larger typical classroom sizes [89,90] and population densities [91,92] in northern India. For all settings, the value for the household-to-close-social-contact pair interaction rate ( $D_{hs}$ ) estimated from Houston was used.

To simplify the presentation of results below, we chose to ignore adults. First, calibration showed that changes in childhood immunity from vaccination policy choices have larger effects on immunity than waning ([Figs 1C](#) and [4](#)), and so typical adults alive near OPV cessation will make small contributions to the local transmission rate relative to children. Second, unimmunized adult family members of infected children have a similar (albeit slightly lower) likelihood of infection from index persons than unimmunized children ([Fig 6B](#)) [35,86]. Absent immunity, including adults in our model is roughly equivalent to increasing the number of child contacts.

## Results

[Fig 7](#) summarizes our within-host model for the effects of immunity on shedding and susceptibility and how typical immunity levels relate to specific vaccination schedules. The shedding index ([Fig 7A](#)) is the expected total amount of virus shed per gram of stool after mOPV challenge. For a typical healthy child under 5 years of age—averaged over vaccination timing and waning—each of the first three doses of OPV increases the OPV-equivalent antibody titer by roughly a factor of 8 and decreases the expected amount of virus shed by a factor of 10. To characterize settings with low OPV effectiveness [25, 74–77], we found that children who received at least six doses of tOPV in UP and Bihar [37] had similar OPV-equivalent antibody titers to healthy clinical trial subjects who received three tOPV doses. In our model, IPV boosting and OPV doses after the first three maintain maximum immunity. The heterotypic protection against type 2 from bOPV immunization is comparable to that of a single homotypic dose but does not accumulate with multiple doses. We inferred from the trial arms reviewed that the OPV-equivalent immunity of IPV-only is at most comparable to heterotypic immunity from bOPV, but we expect that the true impact is closer to none—the trial arms that showed



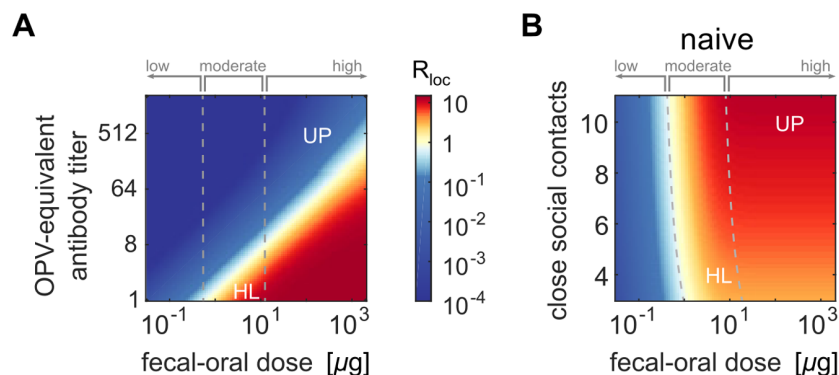
**Fig 7. The effects of pre-exposure immunity on shedding and oral susceptibility to infection in children.** (A) Shedding index versus pre-challenge OPV-equivalent antibody titer (black, model MLE and 95% CI; color, range of immunities expected from vaccination). In the legend, the number of OPV doses equivalent to a titer range assumes healthy child (typical clinical trial) vaccine take rates. (B) Dose-response model versus OPV-equivalent titer (dose measured in culture infectious doses [CID50]). Pre-exposure immunity reduces susceptibility at all doses. bOPV, bivalent type 1 and 3 OPV; CI, confidence interval; CID50, the culture infectious dose that induces a cytopathic effect in 50% of infected cell or tissue cultures; IPV, inactivated polio vaccine; MLE, maximum likelihood estimate; OPV, oral polio vaccine.

<https://doi.org/10.1371/journal.pbio.2002468.g007>

the highest immunity (Fig 1) likely included some incidental IPV boosting, with larger effects in older [41, 61, 65, 69] versus younger [53, 57, 61] subjects in OPV-using countries, and negligible effects in older subjects in countries where OPV is not ubiquitous [67, 93]. Susceptibility is also strongly impacted by immunity, with the expected fraction shedding after Sabin 2 challenge dropping below half at all relevant doses for  $N_{Ab} \geq 64$  (Fig 7B).

Our waning model (S1 Text Eq F, Fig 4) predicts that without reinfection, typical peak OPV-equivalent antibody titers ( $N_{Ab} = 2,048$ ) decline to typical three-dose healthy child immunity ( $N_{Ab} = 512$ ) in 5 (4–7) months and to typical two-dose immunity ( $N_{Ab} = 64$ ) in an additional 4 (2–10) years. However, the model also predicts that it takes an additional 45 (15–160) years to fall to the equivalent of one-dose childhood immunity ( $N_{Ab} = 8$ ) and that residual immunity persists for life, as has been suspected previously [24, 94]. This result is in disagreement with the conclusions of Abbink and colleagues [68]. They argued from the lack of correlation between serological boosting responses and shedding duration after OPV challenge that memory immunity in seronegative elderly does not protect against poliovirus shedding, but the study lacked a control group of never-exposed subjects to contrast deeply waned and truly naive immunity. As seen through metastudy, the OPV-equivalent immunity of the Abbink and colleagues seronegative elderly cohorts is similar to that of children who have received one dose of OPV. For heterotypic immunity against type 2 from bOPV, we predict that protection from shedding will be lost 13 (9–22) months after bOPV vaccination is stopped [95].

Fig 8 shows MLEs from our transmission model for the local reproduction number of WPV,  $R_{loc}$  (Eq 3), as functions of immunity and daily fecal–oral dose (Fig 8A), and fecal–oral dose and the number of close social contacts outside the household (Fig 8B). The value of  $R_{loc}$ , a measure of the average transmission rate in a community, depends linearly on the number of social contacts but varies across four orders of magnitude because of the strong effects of immunity and dose. Assuming one fecal–oral exposure per day (see Methods: Transmission model: Calibration), the physiological range for the average fecal–oral dose maxes out at two milligrams of stool, corresponding to the upper bound of our estimate from UP and Bihar in 2003–2008. When all children have typical three-dose childhood immunity or more ( $N_{Ab} \geq 512$ ), we



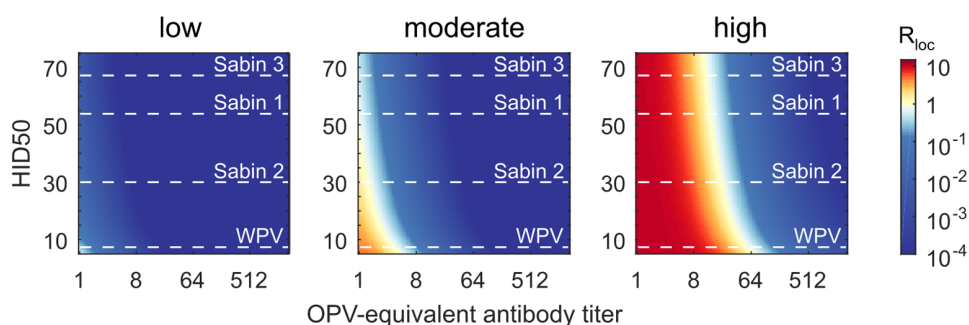
**Fig 8. WPV local reproduction number depends on immunity, sanitation, and contact network size.** (A) Local reproduction number versus immunity and fecal–oral dose (assuming 12 close social contacts outside the household per index child and that everyone has equal immunity) (color map,  $R_{loc}$ ; dashed lines, transmission rate category boundaries). (B) Local reproduction number versus fecal–oral dose and number of close social contacts (assuming all are immunologically naive; legend as in panel A). HL, Houston/Louisiana; OPV, oral polio vaccine; UP, Uttar Pradesh and Bihar; WPV, wild poliovirus.

<https://doi.org/10.1371/journal.pbio.2002468.g008>

estimated  $R_{loc} < 1$  over the entire physiological range and thus that WPV persistence is impossible under universal tOPV immunization. In the absence of immunity, WPV epidemics are possible in all settings where sanitation practices permit the ingestion of roughly one microgram of stool per day or more.

We identified three categories describing the transmission rate in different settings: low, where the fecal–oral route alone cannot sustain WPV transmission ( $R_{loc} < 1$  for all  $N_{Ab} \geq 1$ ); moderate, where WPV epidemics can occur in immunologically naive communities but not where at least one-dose OPV-equivalent immunity is common ( $R_{loc} \geq 1$  only for  $N_{Ab} < 8$ ); and high, where WPV can persist despite at least one-dose OPV-equivalent immunity in everyone ( $R_{loc} \geq 1$  when  $N_{Ab} \geq 8$  but less than a protective threshold).

Fig 9 shows the dependence of the local reproduction number on poliovirus strain and immunity for example low, moderate, and high transmission rate settings. In low transmission rate settings, epidemic transmission of any strain cannot occur without contributions from the unmodeled oral–oral transmission route. This result supports the long-held hypothesis that oral–oral transmission is critical in settings with good sanitation, supported



**Fig 9. Effects of poliovirus strain on the local reproduction number.**  $R_{loc}$  versus HID50 and OPV-equivalent antibody titer for low (fecal–oral dose  $T_{th} = 0.5 \mu\text{g/day}$  and number of close social contacts  $N_s = 3$ ), moderate (Houston 1960,  $T_{th} = 5 \mu\text{g/day}$  and  $N_s = 3$ ), and high (UP and Bihar,  $T_{th} = 230 \mu\text{g/day}$  and  $N_s = 10$ ) transmission rate settings (color map,  $R_{loc}$ ; dashed lines, MLE for the HID50 of each strain [Table 1]). HID50, the dose (measured in CID50) that infects 50% of orally-exposed and immunologically-naive humans; MLE, maximum likelihood estimate; OPV, oral polio vaccine; UP, Uttar Pradesh; WPV, wild poliovirus.

<https://doi.org/10.1371/journal.pbio.2002468.g009>



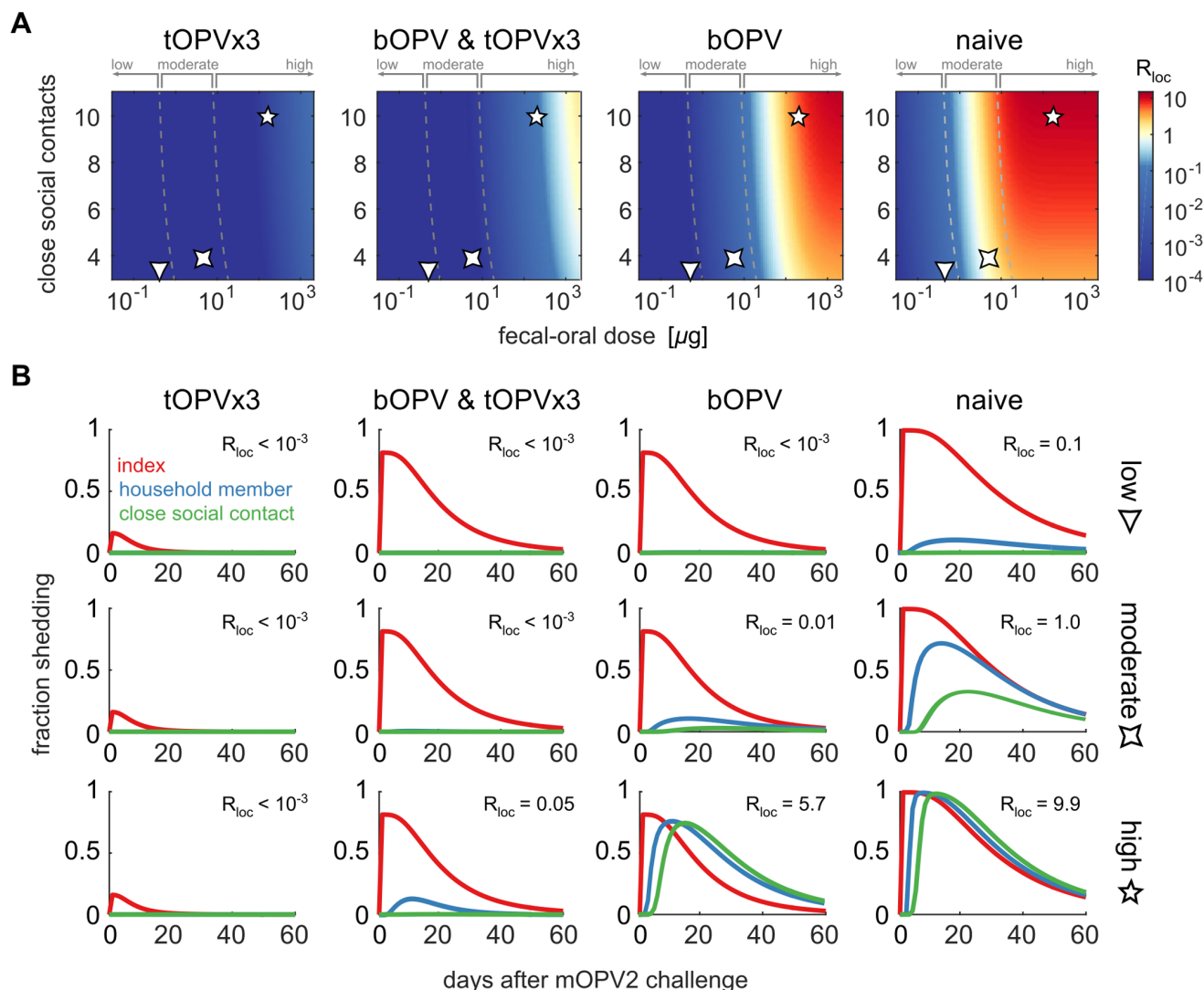
by many observations that IPV alone—an effective intervention against oral shedding [38–42]—can block transmission and prevent outbreaks from importation in communities with high socioeconomic status [8,42,96]. In moderate transmission rate settings (such as Houston 1960 [36], Louisiana 1953–1955 [35], or Matlab, Bangladesh 2015 [86]), immunologically naive populations can support WPV epidemics, but  $R_{loc} \lesssim 1$  for the Sabin strains and one-dose OPV-equivalent immunity ( $N_{Ab} = 8$ ) are sufficient to block epidemic transmission of all strains. This result is consistent with the historical experience in middle- and high-development countries that WPV elimination rapidly follows the introduction of OPV vaccination [22,97–99] and that cVDPV outbreaks are unknown [9,43] outside of isolated communities with atypical immunological and social conditions [100–102].

In high transmission rate settings (such as UP and Bihar 2003–2008 [37]), reinfection of previously immunized people can permit community-wide epidemics if typical immunity is below a threshold level. In the example shown, one-dose OPV-equivalent immunity ( $N_{Ab} = 8$ ) has little or no impact on  $R_{loc}$  for any poliovirus strain, and WPV elimination requires  $N_{Ab} > 64$  for all. This result, that WPV could persist despite  $N_{Ab} > 8$  for most children in UP and Bihar 2003–2008, is supported by serosurveillance [103]. Prior to WPV elimination, the endemic dynamics of natural infection and vaccination conspire to maintain typical immunity levels near  $R_{loc}^{(WPV)} \approx 1$  [84], and thus the Sabin strains must have  $R_{loc}^{(Sabin)} < 1$ , with Sabin 2 highest and Sabin 3 lowest. This result is consistent with the historical experience that vaccine-derived outbreaks have only been observed after genetic reversion has restored WPV-like properties in places where the WPV serotype has been eliminated [43, 44], and that type 2 cVDPVs are most common [9]. However, if poliovirus is reintroduced after elimination into a high transmission rate setting with insufficient immunity, our model predicts that epidemic dynamics will be similar for all strains:  $R_{loc}^{(Sabin)} \approx R_{loc}^{(WPV)} > 1$  is determined by the number of social contacts and is insensitive to differences in infectiousness of the Sabin strains.

Our results above, combined with the observation that cVDPV outbreaks have only been observed at rates of roughly one per year per 250 million children at risk under 15 years of age [9], indicate that settings where the transmission rate for the Sabin strains is high have been rare. To evaluate how community susceptibility to Sabin 2 transmission will change due to anticipated vaccination policy changes after WPV eradication [95], we considered four scenarios for childhood immunity against type 2 poliovirus in Fig 10A. The tOPV×3 scenario describes pre-cessation populations in which all index persons, household members, and close social contacts had achieved maximum immunity prior to waning. The bOPV and tOPV×3 scenario applies in the first 2–3 years after type 2 cessation, when birth spacing [104] is such that the likely index child in a family has only received bOPV (and possibly IPV), but older household members and their contacts have had tOPV. The bOPV scenario applies when two or more children in a typical household are born after type 2 cessation, and the naive scenario applies in settings where all OPV immunization has stopped. Prior and up to a few years after type 2 cessation,  $R_{loc}^{(Sabin2)} < 1$  almost everywhere. However, our model predicts that  $R_{loc}^{(Sabin2)} > 1$  will be common when typical households have more than one child born after type 2 cessation and where hygienic practices are comparable to those of UP and Bihar in the years preceeding WPV elimination. Some moderate transmission settings may also become susceptible to Sabin 2 outbreaks once all OPV vaccination is stopped.

To relate local reproduction number to data that can be collected in the field, Fig 10B shows our MLEs for the fraction of index children, household members, and close social contacts who shed after mOPV2 challenge of the index child. In well-protected communities ( $R_{loc} \ll 1$ ), the model predicts little to no measurable transmission from index children infected with



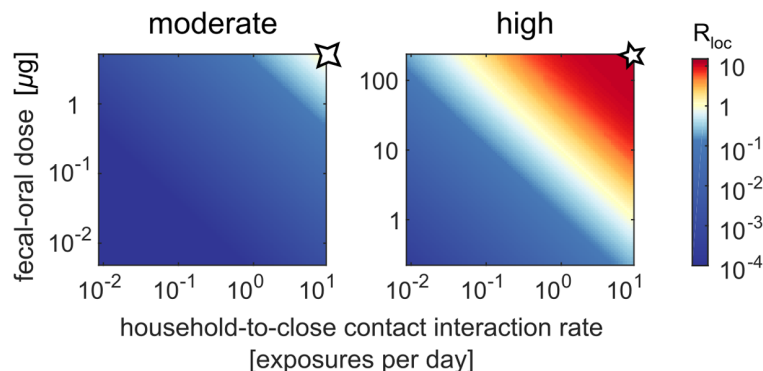


**Fig 10. The effects of vaccination policy on Sabin 2 transmission for four immunity scenarios:** tOPVx3 (index and household/social contact  $N_{Ab} = 512$ ), bOPV and tOPVx3 (index  $N_{Ab} = 512$  and household/social contact  $N_{Ab} = 256$ ), bOPV (index  $N_{Ab} = 8$  and household/social contact  $N_{Ab} = 2$ ), and naive (index and household/social contact  $N_{Ab} = 1$ ). (A) Local reproduction number versus fecal–oral dose and number of close social contacts (color map,  $R_{loc}$ ; dashed lines, transmission rate category boundaries from Fig 8B; symbols, example low, moderate, and high transmission rate settings). (B) Maximum likelihood estimates of the fraction shedding for each subject type after mOPV2 challenge in young index children, for each immunity scenario and example transmission rate setting in panel A. bOPV, bivalent type 1 and 3 OPV; mOPV, monovalent OPV; tOPV, trivalent OPV.

<https://doi.org/10.1371/journal.pbio.2002468.g010>

Sabin 2, but when  $R_{loc} \gg 1$ , Sabin 2 transmission from index children to unvaccinated contacts will be nearly indistinguishable from WPV [24, 35, 37].

Fig 11 shows the sensitivity of the local reproduction number in immunologically naive settings to social distance, measured in terms of the fecal–oral dose ( $T_{hs}$ ) and the household member to social contact interaction rate ( $D_{hs}$ ). In moderate transmission rate settings, such as Houston 1960,  $R_{loc}$  declines rapidly with increasing social distance, even in the absence of immunity. Relative to the calibrated parameters that describe transmission among close contacts, a 10-fold reduction in either fecal–oral dose or interaction rate reduces  $R_{loc}$  from near 1 to less than 0.1. In moderate transmission rate settings, significant transmission requires regular, undiluted contact, and so Sabin 2 is unlikely to spread outside of the communities it is



**Fig 11. Effects of increasing social distance on the local reproduction number of Sabin 2 in immunologically naive populations ( $N_{Ab} = 1$ ).** Local reproduction number versus household member to social contact interaction rate and fecal–oral dose for moderate ( $N_s = 4$ ,  $T_{ih} = 5$  µg/day,  $T_{ih} \leq 5$  µg/day) and high ( $N_s = 10$ ,  $T_{ih} = 230$  µg/day,  $T_{ih} \leq 230$  µg/day) transmission rate settings (color map,  $R_{loc}$ ; symbols, example parameter values from Fig 10).

<https://doi.org/10.1371/journal.pbio.2002468.g011>

delivered to. However, in high transmission rate settings such as UP and Bihar 2003–2008,  $R_{loc}$  can remain above 1 across two orders of magnitude in fecal–oral dose or interaction rate—and above 0.1 across three. Under these conditions, transmission does not require undiluted fecal–oral contact, and Sabin 2 can escape local communities via social interactions that take place only a few times per year.

## Discussion

We have shown how the effects of immunity on poliovirus shedding and susceptibility to infection interact with sanitation and local interfamilial relationships to determine community susceptibility to poliovirus transmission. We found that the local reproduction number is a useful threshold statistic for characterizing the transmission rate. The highest typical levels of OPV-equivalent immunity in our model predict  $R_{loc} < 1$  for all strains in all settings. In low and moderate transmission rate settings, we inferred that the Sabin strains have  $R_{loc}^{(Sabin)} < 1$  because of attenuated infectiousness relative to WPV (9), and thus significant person-to-person Sabin transmission is unlikely regardless of population immunity. Moderate transmission rate settings are at risk of outbreaks from WPV or imported (wild-like) cVDPV but are unlikely to generate indigenous Sabin-derived outbreaks. However, in high transmission rate settings with low population immunity—a situation that can only exist in the absence of endemic transmission and OPV vaccination—our model predicts that the transmission rate of the Sabin strains, if reintroduced, will exceed all levels experienced prior to OPV cessation, approaching that of WPV and with highest risk for Sabin 2.

Other published mathematical models known to us have explored the effects of immunity on Sabin transmission [20,26,31,32]. Despite substantial methodological differences, all are in agreement that the Sabin strains will have reproduction numbers above one in high transmission rate settings with low population immunity. In addition to novel results for dose response and waning, the key innovation of our work is its direct connection from individual-level measures of shedding and susceptibility obtained by stool surveys to assessment of community susceptibility (Fig 10). A recent application of this model to a field transmission study in Matlab, Bangladesh [86], found that moderate transmission rate conditions exist in a low-income, high-density community in the developing world, where comprehensive maternal and child healthcare and improved sanitation systems are in place [105]. The key limitation of our model is that, while it can predict when the outbreak risk from OPV

vaccination is negligible, it cannot address the absolute probability, severity, or geographic scope of outbreaks when they are possible without incorporating additional structural assumptions and calibration data about socially distant transmission. We discuss the relevance of our results for interpreting the history of and implications for vaccination policy in the polio eradication endgame [95] below.

Before polio vaccination, most people were immunized against subsequent polio infection by natural exposure to WPV at young ages. The Sabin strains dramatically lowered the burden of paralytic disease by producing unprecedentedly high levels of immunity and displacing WPV. OPV cessation is intended to eliminate the residual disease burden caused by the Sabin strains [5, 18], but stopping OPV vaccination will reduce global immunity against poliovirus transmission to unprecedentedly low levels.

Many high-income countries with good sanitation and smaller family sizes have maintained polio elimination solely through the routine use of IPV [7, 106, 107]. Although IPV alone has little to no impact on susceptibility or shedding in stool (Fig 7), our results show that the fecal–oral route alone is incapable of supporting epidemic transmission in low transmission rate settings (Fig 8). When the oral–oral route is required to permit significant transmission, our results indicate that it is possible for IPV alone to prevent outbreaks by reducing oral shedding [34, 38–41]. The Netherlands is an example of a country where IPV alone has been sufficient. In 1978 and 1992, there were outbreaks of WPV, but virus was found almost exclusively within high-risk groups who refused vaccination, and no evidence of circulation in the well-vaccinated population was found [96, 108–110]. Furthermore, many countries that could not have eliminated WPV with IPV alone a few decades ago appear now to be adequately protected. The US is an example. While there is some evidence that IPV alone could reduce WPV transmission among middle- and upper-class families in 1960 [39], IPV vaccination of subjects with no prior exposure to live poliovirus had no impact on transmission for both Sabin and WPV strains in communities with low socioeconomic status [36, 111]. However, since 2000, the US has only used IPV [106] and yet has remained polio-free in all vaccinated populations [101] despite extensive international connections and cross-border mixing with OPV-using countries [112].

The 2013 WPV outbreak in Israel shows the limits of IPV to prevent transmission. Eight years after Israel switched from using both OPV and IPV to using IPV only, a type 1 WPV outbreak was tracked via sewage surveillance from February 2013 until April 2014 [113,114]. Most infections were found in children born after the switch despite 93+% coverage with two or more doses of IPV and waning immunity in older people [15,115]. A recent model estimated that the effective reproduction number of WPV among children in the Bedouin community in which transmission was most common was 1.8 [15]; the corresponding reproduction numbers for the Sabin strains, assuming our model of infectivity, are 0.4 and below. Our interpretation is that Israel in 2013 was an example of a moderate transmission rate setting where WPV can persist despite comprehensive IPV vaccination but the Sabin strains cannot [116–118].

In the above scenarios, our model predicts that OPV cessation is stable. OPV can be used to interrupt outbreaks of WPV or imported (WPV-like) cVDPV, and the persistence of vaccine-derived strains is unlikely within (Fig 10A) or outside (Fig 11A) the outbreak response zone. However, in high transmission rate settings with low immunity, we expect that Sabin transmission to unvaccinated contacts within outbreak response regions will be common (Fig 10) and significant transmission to socially distant contacts will occur (Fig 11B). In these settings, OPV cessation is inherently unstable—if poliovirus is reintroduced, there is no guarantee that transmission can be stopped and new cVDPV prevented without restarting OPV vaccination in all high transmission rate settings.

Our conclusion that global OPV cessation is unstable follows from the inference that doses acquired via fecal–oral exposure can be much higher in the developing world than they were in the countries where Sabin OPV was first studied and where OPV cessation has already been successful (Fig 8). The time when instability will reveal itself is uncertain. Our model predicts that two or more children per family born after cessation are required to support Sabin 2 outbreaks in most high transmission rate settings (Fig 10). The median birth spacing in most bOPV-using countries is 24–36 months [104]. Thus, we predict that between early 2018 and mid-2019, the risk of establishing type 2 cVDPV will increase substantially in many regions of the developing world that have not received post-cessation mOPV2 campaigns. The cross-immunity from bOPV against type 2 (with or without IPV) does not alter this conclusion.

Our estimate of 2 to 3 years to increased cVDPV2 risk upon Sabin 2 reintroduction is consistent with predictions from other models [20, 26, 32, 33] and is compatible with the known epidemiology of cVDPV2 outbreaks. The first known example of widespread circulation following a small release of Sabin 2 took place in Belarus in 1965 but was only confirmed as such in 2003 [119]. Two years after a local experiment in type 2 OPV cessation, tOPV given to 40 children likely spread Sabin-derived poliovirus throughout a city of 160,000 people for at least 10 months. In northern Nigeria, after widespread vaccine refusal in 2003 and 2004 [120], restoration of tOPV vaccination seeded 12 independent type 2 Sabin-derived outbreaks, including the largest known outbreak of cVDPV2 in history [44].

The introduction of IPV in routine immunization globally between 2014 and 2016 aimed to provide protection against poliomyelitis to children born after OPV cessation [121]. But without substantial improvements in sanitation, IPV supply [7], and routine immunization coverage, we expect that IPV alone is insufficient to protect against poliovirus circulation in all settings. In pursuit of high vaccine efficacy with low virulence [4,122], Sabin selected strains that are 1,000–10,000 times less likely to cause paralysis than WPV [5] but only 4–10 times less infectious (Table 1). In the absence of population immunity, the differences in infectiousness are insufficient to limit transmission and prevent the evolutionary restoration of virulence [43]. As a consequence, Sabin OPV will be insufficient to guarantee protection from circulation in high transmission settings [20,123,124]. To secure polio eradication for all times and in all conditions, we believe improved vaccines that produce infection-blocking immunity without the risks of Sabin OPV are required. Genetically stabilized, engineered live vaccines are in development and promise the benefits of Sabin OPV without the risks [125–127], and adjuvanted IPV may provide a complementary route to a new effective vaccine [128].

Regardless of the challenges detailed above, Sabin OPV vaccination is always preferable to natural infection by WPV or cVDPV. Thus, mass vaccination with OPV remains the most effective intervention to eliminate poliovirus transmission [3], and the continued use of mOPV2 in regions experiencing type 2 outbreaks is warranted [18] despite concerns about poliovirus containment [19]. For risk mitigation, our model shows the value of healthy contact stool surveillance. The fraction of vaccine recipients and unvaccinated contacts shedding is a direct probe of population immunity and the local transmission rate, and our results provide a rubric to categorize the risk of subsequent outbreaks. Furthermore, with data about fecal–oral contamination (whether from studies of other enteric diseases or sanitation), our model can be calibrated to predict transmission rates in the absence of poliovirus and may thus have predictive value far into the post-cessation future. To go from outbreak risk categorization to risk quantification, continuing work to better understand the relationships between local and non-local transmission is needed [129–131].

## Supporting information

**S1 Text. Supporting text, tables, and figures that further describe referenced data and model design, calibration, and parameters.**  
(PDF)

**S1 Code. Digitized data from reviewed studies, and model and analysis code implemented in Matlab 2015b (The Mathworks, Natick, MA) that were used to generate results and figures.** A version that may receive continued post-publication development is available at <https://famulare.github.io/cessationStability/>.  
(ZIP)

## Acknowledgments

We would like to thank Benoit Raybaud and Qinghua Long (IDM) for developing the online interactive data visualization tools; Laina Mercer and Steve Kroiss (IDM) for critical feedback on the manuscript; Ananda Bandyopadhyay, John Modlin, Arend Voorman (Bill & Melinda Gates Foundation), and Hil Lyons (IDM) for useful discussions that motivated this work and critical feedback; and James S. Koopman (University of Michigan) for motivating us to examine waning immunity. We also thank Ananda Bandyopadhyay for early access to data and results from the bOPV challenge studies.

## Author Contributions

**Conceptualization:** Michael Famulare, Christian Selinger, Kevin A. McCarthy, Philip A. Eckhoff, Guillaume Chabot-Couture.

**Data curation:** Michael Famulare.

**Formal analysis:** Michael Famulare.

**Funding acquisition:** Michael Famulare, Christian Selinger, Kevin A. McCarthy, Philip A. Eckhoff, Guillaume Chabot-Couture.

**Investigation:** Michael Famulare, Christian Selinger.

**Methodology:** Michael Famulare.

**Project administration:** Michael Famulare.

**Resources:** Michael Famulare.

**Software:** Michael Famulare.

**Supervision:** Michael Famulare.

**Validation:** Michael Famulare.

**Visualization:** Michael Famulare, Christian Selinger.

**Writing – original draft:** Michael Famulare.

**Writing – review & editing:** Michael Famulare, Christian Selinger, Kevin A. McCarthy, Philip A. Eckhoff, Guillaume Chabot-Couture.

## References

1. Morales M, Tangermann RH, Wassilak SGF. Progress Toward Polio Eradication—Worldwide, 2015–2016.; 2016. 18. <http://www.cdc.gov/mmwr/volumes/65/wr/mm6518a4.htm>.



2. GPEI. Polio this week; 2016. <http://web.archive.org/web/20161010003058/http://polioeradication.org/polio-today/polio-now/this-week/>.
3. Sutter RW, Maher C. Mass vaccination campaigns for polio eradication: an essential strategy for success. *Current topics in microbiology and immunology*. 2006; 304:195–220. PMID: [16989271](#)
4. Sutter RW, Kew OM, Cochi S, Aylward B. Poliovirus vaccine—live. In: Plotkin SA, Orenstein W, Offit PA, editors. *Vaccines*. 6th ed. Elsevier; 2013. p. 598–645.
5. Platt LR, Estívariz CF, Sutter RW. Vaccine-associated paralytic poliomyelitis: a review of the epidemiology and estimation of the global burden. *The Journal of infectious diseases*. 2014; 210 Suppl (suppl\_1):S380–9. <https://doi.org/10.1093/infdis/jiu184> PMID: [25316859](#)
6. Jorba J, Diop OM, Iber J, Sutter RW, Wassilak SG, Burns CC. Update on Vaccine-Derived Polioviruses—Worldwide, January 2015–May 2016. *Morbidity and Mortality Weekly Report*. 2016; 65(30):763–769. <https://doi.org/10.15585/mmwr.mm6530a3> PMID: [27491079](#)
7. Hampton LM, Farrell M, Ramirez-Gonzalez A, Menning L, Shendale S, Lewis I, et al. Cessation of Trivalent Oral Poliovirus Vaccine and Introduction of Inactivated Poliovirus Vaccine—Worldwide, 2016. *MMWR Morbidity and Mortality Weekly Report*. 2016; 65(35):934–938. <https://doi.org/10.15585/mmwr.mm6535a3> PMID: [27606675](#)
8. Patriarca PA, Sutter RW, Oostvogel PM. Outbreaks of paralytic poliomyelitis, 1976–1995. *The Journal of infectious diseases*. 1997; 175 Suppl:S165–72.
9. Duintjer Tebbens RJ, Pallansch MA, Kim JH, Burns CC, Kew OM, Oberste MS, et al. Oral poliovirus vaccine evolution and insights relevant to modeling the risks of circulating vaccine-derived polioviruses (cVDPVs). *Risk analysis*. 2013; 33(4):680–702. <https://doi.org/10.1111/risa.12022> PMID: [23470192](#)
10. Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science (New York, NY)*. 2002; 297(5583):1016–8. <https://doi.org/10.1126/science.1072266> PMID: [12114528](#)
11. Deshpande JM, Nadkarni SS, Siddiqui ZA. Detection of MEF-1 laboratory reference strain of poliovirus type 2 in children with poliomyelitis in India in 2002 & 2003. *Indian Journal of Medical Research*. 2003; 118(DEC.):217–223.
12. Duizer E, Rutjes S, Husman A, Schijven J. Risk assessment, risk management and risk-based monitoring following a reported accidental release of poliovirus in Belgium, September to November 2014. *Eurosurveillance*. 2016; 21(11). <https://doi.org/10.2807/1560-7917.ES.2016.21.11.30169> PMID: [27020766](#)
13. Kalkowska DA, Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassilak SGF, Thompson KM. Modeling undetected live poliovirus circulation after apparent interruption of transmission: implications for surveillance and vaccination. *BMC Infectious Diseases*. 2015; 15(66):1–12. <https://doi.org/10.1186/s12879-015-0791-5> PMID: [25886823](#)
14. Famulare M. Has Wild Poliovirus Been Eliminated from Nigeria? *PLoS ONE*. 2015; 10(8):e0135765. <https://doi.org/10.1371/journal.pone.0135765> PMID: [26317401](#)
15. Yaari R, Kaliner E, Grotto I, Katriel G, Moran-Gilad J, Sofer D, et al. Modeling the spread of polio in an IPV-vaccinated population; lessons learned from the 2013 silent outbreak in Southern Israel. *BMC Medicine*. 2016; 14(95). <https://doi.org/10.1186/s12916-016-0637-z> PMID: [27334457](#)
16. Etsano A, Damisa E, Shuaib F, Nganda GW, Enemaku O, Usman S, et al. Environmental Isolation of Circulating Vaccine-Derived Poliovirus After Interruption of Wild Poliovirus Transmission—Nigeria, 2016. *MMWR Morbidity and Mortality Weekly Report*. 2016; 65(30). <https://doi.org/10.15585/mmwr.mm6530a4> PMID: [27490081](#)
17. Nhadi C, Damisa E, Esapa L, Braka F, Waziri N, Siddique A, et al. Continued Endemic Wild Poliovirus Transmission in Security-Compromised Areas—Nigeria, 2016. *MMWR Morbidity and Mortality Weekly Report*. 2017; 66(7):190–193. <https://doi.org/10.15585/mmwr.mm6607a2> PMID: [28233765](#)
18. Jorba J, Diop OM, Iber J, Henderson E, Sutter RW, Wassilak SGF, et al. Update on Vaccine-Derived Polioviruses—Worldwide, January 2016–June 2017. *MMWR Morbidity and Mortality Weekly Report*. 2017; 66(43):1185–1191. <https://doi.org/10.15585/mmwr.mm6643a6> PMID: [29095803](#)
19. Previsani N, Singh H, St Pierre J, Boualam L, Fournier-Caruana J, Sutter RW, et al. Progress Toward Containment of Poliovirus Type 2—Worldwide, 2017. *MMWR Morbidity and Mortality Weekly Report*. 2017; 66(24):649–652. <https://doi.org/10.15585/mmwr.mm6624a5> PMID: [28640795](#)
20. Fine PEM, Carneiro IAM. Transmissibility and Persistence of Oral Polio Vaccine Viruses: Implications for the Global Poliomyelitis Eradication Initiative. *American Journal of Epidemiology*. 1999; 150(10):1001–1021. <https://doi.org/10.1093/oxfordjournals.aje.a009924> PMID: [10568615](#)
21. Dowdle W, van der Avoort H, de Gourville E, Delpeyroux F, Desphande J, Hovi T, et al. Containment of polioviruses after eradication and OPV cessation: characterizing risks to improve management.



- Risk analysis: an official publication of the Society for Risk Analysis. 2006; 26(6):1449–69. <https://doi.org/10.1111/j.1539-6924.2006.00844.x> PMID: 17184392
22. Nathanson N, Kew OM. From emergence to eradication: the epidemiology of poliomyelitis deconstructed. *American journal of epidemiology*. 2010; 172(11):1213–29. <https://doi.org/10.1093/aje/kwq320> PMID: 20978089
23. Hird TR, Grassly NC. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus challenge. *PLoS Pathog*. 2012; 8(4): e1002599. <https://doi.org/10.1371/journal.ppat.1002599> PMID: 22532797
24. Duintjer Tebbens RJ, Pallansch MA, Chumakov KM, Halsey NA, Hovi T, Minor PD, et al. Expert review on poliovirus immunity and transmission. *Risk Analysis*. 2013; 33(4):544–605. <https://doi.org/10.1111/j.1539-6924.2012.01864.x> PMID: 22804479
25. Behrend MR, Hu H, Nigmatulina KR, Eckhoff P. A quantitative survey of the literature on poliovirus infection and immunity. *International Journal of Infectious Diseases*. 2013; p. 1–10. <https://doi.org/10.1016/j.ijid.2013.09.005> PMID: 24246740
26. Sasaki A, Haraguchi Y, Yoshida H. Estimating the risk of re-emergence after stopping polio vaccination. *Frontiers in microbiology*. 2012; 3(May):178. <https://doi.org/10.3389/fmicb.2012.00178> PMID: 22783231
27. Thompson KM, Pallansch Ma, Tebbens RJD, Wassilak SG, Cochi SL. Modeling population immunity to support efforts to end the transmission of live polioviruses. *Risk analysis*. 2013; 33(4):647–63. <https://doi.org/10.1111/j.1539-6924.2012.01891.x> PMID: 22985171
28. Thompson KM. Modeling poliovirus risks and the legacy of polio eradication. *Risk Analysis*. 2013; 33(4):505–515. <https://doi.org/10.1111/risa.12030> PMID: 23550939
29. Duintjer Tebbens RJ, Pallansch MA, Kalkowska DA, Wassilak SGF, Cochi SL, Thompson KM. Characterizing poliovirus transmission and evolution: Insights from modeling experiences with wild and vaccine-related polioviruses. *Risk Analysis*. 2013; 33(4):703–749. <https://doi.org/10.1111/risa.12044> PMID: 23521018
30. Thompson KM, Tebbens RJD. Modeling the dynamics of oral poliovirus vaccine cessation. *Journal of Infectious Diseases*. 2014; 210(Suppl 1):S475–S484. <https://doi.org/10.1093/infdis/jit845> PMID: 25316870
31. Tebbens RJD, Thompson KM. Modeling the potential role of inactivated poliovirus vaccine to manage the risks of oral poliovirus vaccine cessation. *Journal of Infectious Diseases*. 2014; 210(Suppl 1): S485–S497. <https://doi.org/10.1093/infdis/jit838> PMID: 25316871
32. Duintjer Tebbens RJ, Hampton LM, Thompson KM. Implementation of coordinated global serotype 2 oral poliovirus vaccine cessation: risks of inadvertent trivalent oral poliovirus vaccine use. *BMC infectious diseases*. 2016; 16(1):237. <https://doi.org/10.1186/s12879-016-1537-8> PMID: 27246198
33. McCarthy KA, Chabot-Couture G, Famulare M, Lyons HM, Mercer LD. The risk of type 2 oral polio vaccine use in post-cessation outbreak response. *BMC Medicine*. 2017; 15(1). <https://doi.org/10.1186/s12916-017-0937-y> PMID: 28974220
34. Duintjer Tebbens RJ, Pallansch MA, Chumakov KM, Halsey NA, Hovi T, Minor PD, et al. Review and assessment of poliovirus immunity and transmission: Synthesis of knowledge gaps and identification of research needs. *Risk Analysis*. 2013; 33(4):606–646. <https://doi.org/10.1111/risa.12031> PMID: 23550968
35. Gelfand HM, Leblanc DR, Fox JP, Conwell DP. Studies on the development of natural immunity to poliomyelitis in Louisiana. II. Description and Analysis of Episodes of infection observed in study group households. *American Journal of Hygiene*. 1957; 65:367–385.
36. Benyesh-Melnick M, Melnick JL, Rawls WE, Wimberly I, Oro JB, Ben-Porath E, et al. Studies of the immunogenicity, communicability and genetic stability of oral poliovaccine administered during the winter. *American journal of epidemiology*. 1967; 86(1):112–36. PMID: 4378110
37. Grassly NC, Jafari H, Bahl S, Durrani S, Wenger J, Sutter RW, et al. Asymptomatic wild-type poliovirus infection in India among children with previous oral poliovirus vaccination. *The Journal of infectious diseases*. 2010; 201(10):1535–43. <https://doi.org/10.1086/651952> PMID: 20367459
38. Wehrle PF, Carbonaro O, Day PA, Whalen JP, Reichert R, Portnoy B. TRANSMISSION OF POLIOVIRUSES: III. Prevalence of Polioviruses in Pharyngeal Secretions of Infected Household Contacts of Patients with Clinical Disease. *Pediatrics*. 1961; 27:762–764. PMID: 13783758
39. Marine WM, Chin TD, Gravelle CR. Limitation of fecal and pharyngeal poliovirus excretion in salk-vaccinated children. *American Journal of Hygiene*. 1962; 76:173–195.
40. Ogra PL, Karzon DT. Materials and methods. 1969;(1).
41. Onorato IM, Modlin JF, McBean AM, Thoms ML, Losonsky GA, Bernier RH. Mucosal immunity induced by enhance-potency inactivated and oral polio vaccines. *The Journal of infectious diseases*. 1991; 163(1):1–6. PMID: 1845806

42. Chin TD. Immunity induced by inactivated poliovirus vaccine and excretion of virus. *Reviews of infectious diseases*. 1984; 6 Suppl 2:S369–70.
43. Kew OM, Sutter RW, de Gourville EM, Dowdle WR, Pallansch MA. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. *Annual review of microbiology*. 2005; 59:587–635. <https://doi.org/10.1146/annurev.micro.58.030603.123625> PMID: 16153180
44. Burns CC, Shaw J, Jorba J, Bukbuk D, Adu F, Gumedé N, et al. Multiple independent emergences of type 2 vaccine-derived polioviruses during a large outbreak in northern Nigeria. *Journal of virology*. 2013; 87(9):4907–22. <https://doi.org/10.1128/JVI.02954-12> PMID: 23408630
45. Famulare M, Chang S, Iber J, Zhao K, Adeniji JA, Bukbuk D, et al. Sabin vaccine reversion in the field: a comprehensive analysis of Sabin-like poliovirus isolates in Nigeria. *Journal of Virology*. 2016; 90(1):317–331. <https://doi.org/10.1128/JVI.01532-15> PMID: 26468545
46. Dushoff J, Levin SA. The effects of population heterogeneity on disease spread. *Mathematical Biosciences*. 1995; 128:25–40. PMID: 7606137
47. Kenah E, Miller JC. Epidemic percolation networks, epidemic outcomes, and interventions. *Interdisciplinary perspectives on infectious diseases*. 2011; 2011:543520. <https://doi.org/10.1155/2011/543520> PMID: 21437002
48. Miller JC. A Note on the Derivation of epidemic final sizes. *Bulletin of mathematical biology*. 2012; 74(9).
49. Lahodny GE, Allen LJS. Probability of a disease outbreak in stochastic multipatch epidemic models. *Bulletin of mathematical biology*. 2013; 75(7):1157–80. <https://doi.org/10.1007/s11538-013-9848-z> PMID: 23666483
50. Miller JC, Volz EM. Model hierarchies in edge-based compartmental modeling for infectious disease spread. *Journal of mathematical biology*. 2013; 67(4):869–99. <https://doi.org/10.1007/s00285-012-0572-3> PMID: 22911242
51. Vidor E, Plotkin SA. Poliovirus vaccine-inactivated. In: Plotkin SA, Orenstein W, Offit PA, editors. *Vaccines: Sixth Edition*. 6th ed. Elsevier; 2012. p. 573–597.
52. Alexander JP, Gary HE, Pallansch MA. Duration of poliovirus excretion and its implications for acute flaccid paralysis surveillance: a review of the literature. *The Journal of infectious diseases*. 1997; 175 Suppl:S176–82.
53. O’Ryan M, Bandyopadhyay AS, Villena R, Espinoza M, Novoa J, Weldon WC, et al. Inactivated poliovirus vaccine given alone or in a sequential schedule with bivalent oral poliovirus vaccine in Chilean infants: a randomised, controlled, open-label, phase 4, non-inferiority study. *The Lancet Infectious Diseases*. 2015; 3099(15). [https://doi.org/10.1016/S1473-3099\(15\)00219-4](https://doi.org/10.1016/S1473-3099(15)00219-4)
54. Asturias EJ, Bandyopadhyay AS, Self S, Rivera L, Saez-Ilorens X, Lopez E, et al. Humoral and intestinal immunity induced by new schedules of bivalent oral poliovirus vaccine and one or two doses of inactivated poliovirus vaccine in Latin American infants: an open-label randomised controlled trial. *Lancet*. 2016; 6736(16):1–12. [https://doi.org/10.1016/S0140-6736\(16\)00703-0](https://doi.org/10.1016/S0140-6736(16)00703-0)
55. Nathanson N, Ahmed R, Biron CA, Brinton MA, Gonzalez-Scarano F, Griffin DE, et al. *Viral Pathogenesis and Immunity*. 2nd ed. London: Academic Press; 2007.
56. Verlinde JD, Wilterdink JB. A small-scale trial on vaccination and re-vaccination with live attenuated polioviruses in the Netherlands. In: Preliminary Report on Mass Oral Immunization of Population Against Poliomyelitis with Live Virus from A.B. Sabin’s Attenuated Strains. World Health Organization; 1959. p. 355–367.
57. Dick GW, Dane DS, McAlister J, Briggs M, Nelson R, Field CMB. Vaccination against poliomyelitis with live virus vaccines. 7. Effect of previous Salk vaccination on virus excretion. *British medical journal*. 1961; 2(5247):266–269. PMID: 13722671
58. Dane DS, Dick GW, Briggs M, Nelson R, McAlister J, Connolly JH, et al. Vaccination against poliomyelitis with live virus vaccine: 8. Changes in Sabin Type 1 oral vaccine virus after multiplication in the intestinal tract. *British medical journal*. 1961; p. 269–271. PMID: 13719567
59. Horstmann DM, Paul JR, Godenne-McCrea M, Green RH, Opton EM, Holtz AI, et al. Immunization of Preschool Children with Oral Poliovirus Vaccine (Sabin). *JAMA: The Journal of the American Medical Association*. 1961; 178(7):693–701.
60. Holguin AH, Reeves JS, Gelfand HM. Immunization of infants with the Sabin oral poliovirus vaccine. *American Journal of Public Health*. 1962; 52(4).
61. Henry JL, Jaikaran ES, Davies JR, Tomlinson AJ, Mason PJ, Barnes JM, et al. A study of poliovaccination in infancy: excretion following challenge with live virus by children given killed or living poliovaccine. *The Journal of hygiene*. 1966; 64(1):105–20. PMID: 5219018
62. Vaccine Administration Subcommittee. Evaluation of Sabin live poliovirus vaccine in Japan: II. Clinical, virologic, and immunologic effects of vaccine in children. *Japanese Journal of Medical Science and Biology*. 1966; 19:277–291. PMID: 4293159

63. Minor TE, Allen CI, Tsiatis AA, Nelson DB, D'Alessio DJ. Human infective dose determinations for oral poliovirus type 1 vaccine in infants. *Journal of clinical microbiology*. 1981; 13(2):388–9. PMID: [6259203](#)
64. Dong DX, Hu XM, Liu WJ, Li JS, Jin YC, Tan SG, et al. Immunization of neonates with trivalent oral poliomyelitis vaccine (Sabin). *Bulletin of the World Health Organization*. 1986; 64(6):853–60. PMID: [3493854](#)
65. Ion-Nedelcu N, Strebel PM, Toma F, Biberi-Moroeanu S, Combiescu M, Persu A, et al. Sequential and Combined Use of Inactivated and Oral Poliovirus Vaccines: Dolj District, Romania, 1992–1994. *Journal of Infectious Diseases*. 1997; 175(Suppl1):S241–6.
66. Mallet L, Pelloquin F, Brigaud M, Caudrelier P, Bandet R, Xueref C, et al. Comparative study of poliovirus excretion after vaccination of infants with two oral polio vaccines prepared on vero cells or on primary monkey kidney cells. *Journal of Medical Virology*. 1997; 52(1):50–60. [https://doi.org/10.1002/\(SICI\)1096-9071\(199705\)52:1<50::AID-JMV9>3.0.CO;2-Q](https://doi.org/10.1002/(SICI)1096-9071(199705)52:1<50::AID-JMV9>3.0.CO;2-Q) PMID: [9131458](#)
67. Piirainen L, Stenvik M, Roivainen M, Eskola J, Beuvery EC, Hovi T. Randomised, controlled trial with the trypsin-modified inactivated poliovirus vaccine: assessment of intestinal immunity with live challenge virus. *Vaccine*. 1999; 17(9–10):1084–90. PMID: [10195618](#)
68. Abbink F, Buisman AM, Doornbos G, Woldman J, Kimman TG, Conyn-van Spaendonck MAE. Poliovirus-specific memory immunity in seronegative elderly people does not protect against virus excretion. *The Journal of infectious diseases*. 2005; 191(6):990–9. <https://doi.org/10.1086/427810> PMID: [15717277](#)
69. Laassri M, Lottenbach K, Belshe R, Wolff M, Rennels M, Plotkin S, et al. Effect of different vaccination schedules on excretion of oral poliovirus vaccine strains. *The Journal of infectious diseases*. 2005; 192(12):2092–8. <https://doi.org/10.1086/498172> PMID: [16288372](#)
70. El-Sayed N, Yehia EG, Abbassy AA, Seoud I, Salama M, Kandeel A, et al. Monovalent type 1 oral poliovirus vaccine in newborns. *New England Journal of Medicine*. 2008; 359(16):1655–1665. <https://doi.org/10.1056/NEJMoa0800390> PMID: [18923170](#)
71. Swartz TA, Green MS, Handscher R, Sofer D, Cohen-Dar M, Shohat T, et al. Intestinal immunity following a combined enhanced inactivated polio vaccine/oral polio vaccine programme in Israel. *Vaccine*. 2008; 26(8):1083–90. <https://doi.org/10.1016/j.vaccine.2007.12.021> PMID: [18241962](#)
72. Jafari H, Deshpande JM, Sutter RW, Bahl S, Verma H, Ahmad M, et al. Polio eradication. Efficacy of inactivated poliovirus vaccine in India. *Science (New York, NY)*. 2014; 345(6199):922–5. <https://doi.org/10.1126/science.1255006> PMID: [25146288](#)
73. Patriarca PA, Wright PF, John TJ. Factors affecting the immunogenicity of oral poliovirus vaccine in developing countries: review. *Reviews of infectious diseases*. 1991; 13(5):926–39. PMID: [1660184](#)
74. World Health Organization Collaborative Study Group on Oral Poliovirus Vaccine. Factors affecting the immunogenicity of oral poliovirus vaccine: a prospective evaluation in Brazil and the Gambia. *Journal of Infectious Diseases*. 1995; 171(5):1097–1106.
75. Grassly NC, Fraser C, Wenger J, Deshpande J, Sutter RW, Heymann DL, et al. New strategies for the elimination of polio from India. *Science (New York, NY)*. 2006; 314(5802):1150–3. <https://doi.org/10.1126/science.1130388> PMID: [17110580](#)
76. Grassly NC, Jafari H, Bahl S, Durrani S, Wenger J, Sutter RW, et al. Mucosal immunity after vaccination with monovalent and trivalent oral poliovirus vaccine in India. *J Infect Dis*. 2009; 200(5):794–801. <https://doi.org/10.1086/605330> PMID: [19624278](#)
77. Haque R, Snider C, Liu Y, Ma JZ, Liu L, Nayak U, et al. Oral polio vaccine response in breast fed infants with malnutrition and diarrhea. *Vaccine*. 2014; 32(4):478–482. <https://doi.org/10.1016/j.vaccine.2013.11.056> PMID: [24300591](#)
78. Wan A, Seow W, Purdie D, Bird P, Walsh L, Tudehope D. Immunoglobulins in saliva of preterm and full-term infants. *Oral microbiology and immunology*. 2003; 18:72–78. PMID: [12654094](#)
79. Maheshwari A, Zemlin M. Ontogeny of the intestinal immune system. *Haematologica Reports*. 2006; 2(10):18–26.
80. Herremans TM, Reimerink JH, Buisman AM, Kimman TG, Koopmans MP. Induction of mucosal immunity by inactivated poliovirus vaccine is dependent on previous mucosal contact with live virus. *Journal of immunology*. 1999; 162(8):5011–8.
81. John J, Giri S, Karthikeyan AS, Iturriza-Gomara M, Muliyl J, Abraham A, et al. Effect of a single inactivated poliovirus vaccine dose on intestinal immunity against poliovirus in children previously given oral vaccine: an open-label, randomised controlled trial. *The Lancet*. 2014; 6736(14):1–8. [https://doi.org/10.1016/S0140-6736\(14\)60934-X](https://doi.org/10.1016/S0140-6736(14)60934-X)
82. Furumoto WA, Mickey R. A mathematical model for the infectivity-dilution curve of tobacco mosaic virus: Theoretical considerations. *Virology*. 1967; 32(2):216–223. [https://doi.org/10.1016/0042-6822\(67\)90271-1](https://doi.org/10.1016/0042-6822(67)90271-1) PMID: [6025875](#)

83. Teunis PFM, van Eijkeren JCH, de Graaf WF, Marinović AB, Kretzschmar MEE. Linking the serore-sponse to infection to within-host heterogeneity in antibody production. *Epidemics*. 2016; 16:33–39. <https://doi.org/10.1016/j.epidem.2016.04.001> PMID: 27663789
84. Keeling MJ, Rohani P. *Modeling Infectious Diseases*; 2007. <http://www.sciencedirect.com/science/article/B98GG-4T7XCGF-9D/2/95c40489e0e5ee3c0670ee1cf3f0e65f>.
85. Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing pat-terns relevant to the spread of infectious diseases. *PLoS Med*. 2008; 5(3):e74. <https://doi.org/10.1371/journal.pmed.0050074> PMID: 18366252
86. Taniuchi M, Famulare M, Zaman K, Uddin MJ, Upfill-Brown AM, Ahmed T, et al. Community transmis-sion of type 2 poliovirus after cessation of trivalent oral polio vaccine in Bangladesh: An open-label cluster-randomised trial and modelling study. *The Lancet Infectious Diseases*. 2017; [https://doi.org/10.1016/S1473-3099\(17\)30358-4](https://doi.org/10.1016/S1473-3099(17)30358-4) PMID: 28693854
87. John TJ, Vashishtha VM. Eradicating poliomyelitis: India's journey from hyperendemic to polio Å- free status. *Indian Journal of Medical Research*. 2013; 137(5):881–894. PMID: 23760372
88. Cairns RB, Leung MC, Buchanan L, Cairns BD. Friendships and social networks in childhood and ado-lescence: fluidity, reliability, and interrelations. *Child development*. 1995; 66(8115):1330–1345. <https://doi.org/10.2307/1131650>
89. 120 years of American education: A statistical portrait. National Center for Education Statistics; 1993. <http://nces.ed.gov/pubs93/93442.pdf>.
90. Raghavan TCAS. The poor state of school infrastructure; 2015. <http://www.livemint.com/Politics/h7Wkzl77bMtmN9FLDvyo0M/The-poor-state-of-school-infrastructure.html>.
91. Bihar table data; <http://www.census2011.co.in/census/state/bihar.html>.
92. Population of the 100 largest cities and other urban places in the United States: 1790 to 1990;. <https://web.archive.org/web/20070314031958/http://www.census.gov/population/www/documentation/twps0027.html>.
93. The Cuba IPV Study Collaborative Group. Randomized, placebo-controlled trial of inactivated polio-virus vaccine in Cuba. *The New England journal of medicine*. 2007; 356(15):1536–44. <https://doi.org/10.1056/NEJMoa054960> PMID: 17429085
94. Glezen WP, Lamb GA, Belden EA, Chin TDY. Quantitative relationship of preexisting homotypic anti-bodies to the excretion of attenuated poliovirus type 1. *Am J Epidemiol*. 1966; 83(2):224–237. PMID: 5930775
95. Polio Eradication and Endgame Strategic Plan 2013–2018. World Health Organization; 2016. [www.who.int/about/licensing/copyright\\_form/en/index.html](http://www.who.int/about/licensing/copyright_form/en/index.html).
96. Conyn-van Spaendonck MA, Oostvogel PM, van Loon AM, van Wijngaarden JK, Kromhout D. Circula-tion of poliovirus during the poliomyelitis outbreak in The Netherlands in 1992–1993. *American journal of epidemiology*. 1996; 143(9):929–35. PMID: 8610706
97. Chumakov MP. Some results of the work on mass immunization in the Soviet Union with live poliovirus vaccine prepared from Sabin strains. *Bulletin of the World Health Organization*. 1961; 25:79–91. PMID: 13879389
98. de Quadros CA, Hersh BS, Olivé JM, Andrus JK, da Silveira CM, Carrasco PA. Eradication of wild poliovirus from the Americas: acute flaccid paralysis surveillance, 1988–1995. *The Journal of infec-tious diseases*. 1997; 175 Suppl:S37–S42.
99. Beldarraín E. Poliomyelitis and its elimination in cuba: an historical overview. *MEDICC review*. 2013; 15(2):30–6. PMID: 23686253
100. Cherkasova EA, Yakovenko ML, Rezapkin GV, Korotkova EA, Ivanova OE, Ereemeeva TP, et al. Spread of vaccine-derived poliovirus from a paralytic case in an immunodeficient child: an insight into the natural evolution of oral polio vaccine. *Journal of virology*. 2005; 79(2):1062–1070. <https://doi.org/10.1128/JVI.79.2.1062-1070.2005> PMID: 15613335
101. Alexander JP, Ehresmann K, Seward J, Wax G, Harriman K, Fuller S, et al. Transmission of imported vaccine-derived poliovirus in an undervaccinated community in Minnesota. *The Journal of infectious diseases*. 2009; 199(3):391–7. <https://doi.org/10.1086/596052> PMID: 19090774
102. Korotkova EA, Gmyl AP, Yakovenko ML, Ivanova OE, Ereemeeva TP, Kozlovskaya LI, et al. A cluster of paralytic poliomyelitis cases due to transmission of slightly diverged Sabin-2 vaccine virus. *Journal of Virology*. 2016;(April):JVI.00277–16. <https://doi.org/10.1128/JVI.00277-16> PMID: 27099315
103. Deshpande JM, Bahl S, Sarkar BK, Estivariz CF, Sharma S, Wolff C, et al. Assessing population immunity in a persistently high-risk area for wild poliovirus transmission in India: A serological study in Moradabad, Western Uttar Pradesh. *Journal of Infectious Diseases*. 2014; 210(Suppl 1):S225–S233. <https://doi.org/10.1093/infdis/jiu204> PMID: 25316839

104. Rutstein SO. Trends in Birth Spacing; 2011. September. <http://www.measuredhs.com/pubs/pdf/CR28/CR28.pdf>.
105. icddr:b. Health and Demographic Surveillance System—Matlab. Scientific Report No. 126; 2015.
106. Alexander LN, Seward JF, Santibanez TA, Pallansch MA, Kew OM, Prevots DR, et al. Vaccine policy changes and epidemiology of poliomyelitis in the United States. *JAMA: the journal of the American Medical Association*. 2004; 292(14):1696–701. <https://doi.org/10.1001/jama.292.14.1696> PMID: 15479934
107. Pebody R. Polio vaccination in Europe: the shift from OPV to IPV use. *Eurosurveillance*. 2004; 8(34):2529.
108. Oostvogel PM, van Wijngaarden JK, van der Avoort HG, Mulders MN, Conyn-van Spaendonck MA, Rümke HC, et al. Poliomyelitis outbreak in an unvaccinated community in The Netherlands, 1992–93. *Lancet*. 1994; 344(8923):665–70. PMID: 7915354
109. Oostvogel PM, Rümke HC, Conyn-Van Spaendonck MA, van der Avoort HG, Leeuwenburg J, van Loon aM. Poliovirus circulation among schoolchildren during the early phase of the 1992–1993 poliomyelitis outbreak in The Netherlands. *The Journal of infectious diseases*. 2001; 184(11):1451–5. <https://doi.org/10.1086/324327> PMID: 11709788
110. Rümke HC, Oostvogel PM, Van Steenis G, Van Loon aM. Poliomyelitis in The Netherlands: a review of population immunity and exposure between the epidemics in 1978 and 1992. *Epidemiology and infection*. 1995; 115(2):289–98. PMID: 7589268
111. Gelfand HM, Fox JP, Leblanc DR. Observations on natural poliovirus infections in immunized children. *American journal of public health and the nation's health*. 1957; 47(4 Pt 1):421–31. PMID: 13411317
112. Bebianno Simões M, Jiménez Martínez JM, Lemaitre G, Moreno Antelo MG, Martínez Pizarro J, Reboiras L, et al. International migration in the Americas: First Report of the Continuous Reporting System on International Migration in the Americas (SICREMI). Washington, D.C.: Organization of American States; 2011. <https://www.oecd.org/migration/48423814.pdf>.
113. Anis E, Kopel E, Singer SR, Kaliner E, Moerman L, Moran-Gilad J, et al. Insidious reintroduction of wild poliovirus into Israel, 2013. *Euro surveillance: bulletin Européen sur les maladies transmissibles = European communicable disease bulletin*. 2013; 18(38):1–5.
114. Shulman L, Gavrilin E, Jorba J, Martin J, Burns C, Manor Y, et al. Molecular epidemiology of silent introduction and sustained transmission of wild poliovirus type 1, Israel, 2013. *Eurosurveillance*. 2014; 19(7):20709. <https://doi.org/10.2807/1560-7917.ES2014.19.7.20709> PMID: 24576471
115. Moran-Gilad J, Mendelson E, Burns CC, Bassal R, Gdalevich M, Sofer D, et al. Field study of fecal excretion as a decision support tool in response to silent reintroduction of wild-type poliovirus 1 into Israel. *Journal of Clinical Virology*. 2015; 66:51–55. <https://doi.org/10.1016/j.jcv.2015.03.005> PMID: 25866337
116. Shulman L, Handsheer R, Yang CF, Yang S, Manor J, Vonsover a, et al. Resolution of the pathways of poliovirus type 1 transmission during an outbreak. *Journal of clinical microbiology*. 2000; 38(3):945–52. PMID: 10698978
117. Shulman LM, Mendelson E, Anis E, Bassal R, Gdalevich M, Hindiyeh M, et al. Laboratory challenges in response to silent introduction and sustained transmission of wild poliovirus type 1 in Israel during 2013. *Journal of Infectious Diseases*. 2014; 210(November):S304–S314. <https://doi.org/10.1093/infdis/jiu294> PMID: 25316849
118. Kalkowska DA, Duintjer Tebbens RJ, Grotto I, Shulman LM, Anis E, Wassilak SGF, et al. Modeling options to manage type 1 wild poliovirus imported into Israel in 2013. *Journal of Infectious Diseases*. 2015; 211(11):1800–1812. <https://doi.org/10.1093/infdis/jiu674> PMID: 25505296
119. Korotkova EA, Park R, Cherkasova EA, Lipskaya GY, Chumakov KM, Feldman EV, et al. Retrospective analysis of a local cessation of vaccination against poliomyelitis: a possible scenario for the future. *Journal of virology*. 2003; 77(23):12460–12465. <https://doi.org/10.1128/JVI.77.23.12460-12465.2003> PMID: 14610170
120. Ghinai I, Willott C, Dadari I, Larson HJ. Listening to the rumours: what the northern Nigeria polio vaccine boycott can tell us ten years on. *Global public health*. 2013; 8(10):1138–50. <https://doi.org/10.1080/17441692.2013.859720> PMID: 24294986
121. Sutter RW, Platt L, Mach O, Jafari H, Aylward RB. The New Polio Eradication End Game: Rationale and Supporting Evidence. *Journal of Infectious Diseases*. 2014; 210(suppl 1):S434–S438. <https://doi.org/10.1093/infdis/jiu222> PMID: 25316865
122. Sabin AB. Oral poliovirus vaccine: history of its development and use and current challenge to eliminate poliomyelitis from the world. *The Journal of infectious diseases*. 1985; 151(3):420–436. <https://doi.org/10.1093/infdis/151.3.420> PMID: 2982959



123. Heymann DL, Sutter RW, Aylward RB. A global call for new polio vaccines. *Nature*. 2005; 434 (7034):699–700. <https://doi.org/10.1038/434699a> PMID: 15815604
124. Chumakov K, Ehrenfeld E, Wimmer E, Agol VI. Vaccination against polio should not be stopped. *Nature reviews Microbiology*. 2007; 5(12):952–8. <https://doi.org/10.1038/nrmicro1769> PMID: 17965726
125. Macadam AJ, Ferguson G, Stone DM, Meredith J, Knowlson S, Auda G, et al. Rational design of genetically stable, live-attenuated poliovirus vaccines of all three serotypes: relevance to poliomyelitis eradication. *Journal of virology*. 2006; 80(17):8653–63. <https://doi.org/10.1128/JVI.00370-06> PMID: 16912313
126. Luring AS, Jones JO, Andino R. Rationalizing the development of live attenuated virus vaccines. *Nature biotechnology*. 2010; 28(6):573–9. <https://doi.org/10.1038/nbt.1635> PMID: 20531338
127. Bandyopadhyay AS, Garon J, Seib K, Orenstein WA. Polio vaccination: past, present and future. *Future Microbiology*. 2015; 10(5):791–808. <https://doi.org/10.2217/fmb.15.19> PMID: 25824845
128. Norton EB, Bauer DL, Weldon WC, Oberste MS, Lawson LB, Clements JD. The novel adjuvant dmLT promotes dose sparing, mucosal immunity and longevity of antibody responses to the inactivated polio vaccine in a murine model. *Vaccine*. 2015; 33(16):1909–1915. <https://doi.org/10.1016/j.vaccine.2015.02.069> PMID: 25765967
129. Diop OM, Asghar H, Gavrilin E, Moeletsi NG, Benito GR, Paladin F, et al. Virologic Monitoring of Poliovirus Type 2 after Oral Poliovirus Vaccine Type 2 Withdrawal in April 2016—Worldwide, 2016–2017. *MMWR Morbidity and Mortality Weekly Report*. 2017; 66(20):538–542. <https://doi.org/10.15585/mmwr.mm6620a4> PMID: 28542124
130. Kroiss SJ, Famulare M, Lyons H, McCarthy KA, Mercer LD, Chabot-Couture G. Evaluating cessation of the type 2 oral polio vaccine by modeling pre- and post-cessation detection rates. *Vaccine*. 2017; 35 (42):5674–5681. <https://doi.org/10.1016/j.vaccine.2017.08.048> PMID: 28890193
131. O'Reilly KM, Lamoureux C, Molodecky NA, Lyons H, Grassly NC, Tallis G. An assesment of the geographical risks of wild and vaccine-derived poliomyelitis outbreaks in Africa and Asia. *BMC Infectious Diseases*. 2017; 17(1):367. <https://doi.org/10.1186/s12879-017-2443-4> PMID: 28549485