

A COMPARTMENTAL SIMULATION MODEL TO IMPROVE INTERVENTIONS FOR CONTROLLING POLIOVIRUS OUTBREAKS

Yuming Sun
Pinar Keskinocak
Lauren N. Steimle

Stephanie D. Kovacs
Steven G. Wassilak

H. Milton Stewart School of Industrial and Systems
Engineering
Georgia Institute of Technology
755 Ferst Drive NW
Atlanta, GA 30332, USA

Global Immunization Division, Center for Global
Health
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333, USA

ABSTRACT

Poliomyelitis (polio) is an infectious disease that paralyzed millions of people worldwide before polio vaccines were available. Despite the successes of the Global Polio Eradication Initiative, there are circulating vaccine-derived poliovirus outbreaks that require improved interventions. We built a compartmental model to simulate the spread of polio that considers mutation of the live-attenuated virus (in the oral polio vaccine) to evaluate the effectiveness of interventions. We validated the model in a case study of northern Nigeria and tested the impact of interventions that varied in the number of vaccination rounds and the target regions. Results indicated that the model captures polio dynamics by matching the case counts and their spatiotemporal and age distributions in the data. To stop the outbreaks, stakeholders should conduct aggressive interventions with more rounds and broader coverage, especially in the under-vaccinated regions, compared to the current practice.

1 INTRODUCTION

Poliomyelitis (polio) is caused by poliovirus infections, which can lead to severe and incurable paralysis. The Global Polio Eradication Initiative and its partners have made significant progress towards a polio-free world. For the wild forms of poliovirus, two serotypes have been eradicated (Global Polio Eradication Initiative 2015; World Health Organization 2019), and the global cases of the one remaining serotype have decreased significantly (Roberts 2022).

However, there has been an increase in the outbreaks of circulating vaccine-derived poliovirus (cVDPV) infections, especially for serotype 2 (cVDPV2). In under-vaccinated regions, the live-attenuated virus from traditional oral polio vaccine (OPV) can circulate and accumulate enough mutations to revert to cVDPV. Similar to the wild forms, cVDPV infects susceptible individuals and causes paralysis. The Global Polio Eradication Initiative has planned a phased cessation of OPV after global eradication of the wild forms by serotype (Global Polio Eradication Initiative 2013). As a first step, in April 2016, serotype 2-containing OPV (OPV2) cessation was achieved in the preventive vaccination by a “switch” from an OPV containing all serotypes to an OPV containing no serotype 2. However, due to the persistent cVDPV2 transmission that emerged before the switch, since May 2016, there have been 2,417 cVDPV2 paralytic cases reported in more than 30 countries.

The efforts towards preventing and stopping cVDPV2 transmission face many challenges. The inactivated polio vaccine, which was introduced in the preventive vaccination in 2015 to provide some protection against serotype 2 for post-switch birth cohorts, unlike OPV, does not induce intestinal mucosal

immunity that stops person-to-person cVDPV2 transmission. In addition, the preventive vaccination coverage remains low in some areas, e.g., due to insurgency (Bolu et al. 2018). Although a novel OPV2 which has a lower risk of virus reversion was rolled out in 14 countries' outbreak response vaccination in March 2021 to control cVDPV2 outbreaks, some of these countries (e.g., Nigeria) failed to vaccinate all target children to stop the outbreaks (Roberts 2022).

To quantify the impact of interventions on cVDPV2 transmission, we built a differential-equation-based model of live poliovirus transmission. Our model considers the reversion from the live-attenuated virus (in traditional OPV) to cVDPV, separates individuals' immunity levels based on their vaccination/infection history, and parameterizes interventions by preventive vaccination and outbreak response vaccination. We validated the model in a case study of northern Nigeria and evaluated the effectiveness of various outbreak response vaccination scenarios, such as no response (i.e., only preventive vaccination), planned outbreak response vaccination, and other scenarios that all used novel OPV2 but varied in the number of rounds and the target regions of the outbreak response vaccination. Our analyses suggested stakeholders to implement outbreak response vaccination with more rounds of high coverage rates and a special focus on the under-vaccinated regions.

The rest of the article is organized as follows: Section 2 gives the model overview and the case study of northern Nigeria. Sections 3 and 4 present and discuss the results, respectively. Section 5 concludes the insights and future works.

2 METHODS

In this section, we describe our poliovirus transmission model and the case study. In Section 2.1.1 and 2.1.2, we describe our model's compartments and characterize the transitions between them; Sections 2.1.3 and 2.1.4 explain other model dynamics and outcome measures, respectively. In Section 2.2, we detail a case study of northern Nigeria, with Sections 2.2.1, 2.2.2, 2.2.3, and 2.2.4 for data, model setup, calibration and validation, and analyses of outbreak response vaccination scenarios, respectively.

2.1 Live Poliovirus Transmission Model

2.1.1 Model Compartments

To simulate the live poliovirus (LPV) transmission, we adapted a deterministic differential-equation-based model (Duintjer Tebbens et al. 2013) which follows an extended susceptible (S), exposed (E), infectious (I) - susceptible compartmental framework, with the addition of an inactivated polio vaccine-injected (H) compartment. The compartment H represents individuals who have received a dose of the inactivated polio vaccine (IPV) but have not acquired the corresponding immunity. There are multiple (partially) susceptible, exposed, infectious, and IPV-injected compartments in the model that differ in terms of immunity levels, virus strains, ages, and geographic locations.

Immunity groups: The model includes one immunity group ($i = 0$) to represent unimmunized individuals and seven immunity groups ($i = 1, \dots, 7$) depending on the source of immunity (from LPV or IPV), the timing of the most recently acquired immunity (to incorporate waning immunity), and the number of exposures to LPV or the number of IPV doses received by an individual. "IPV-immunized" stands for individuals who only have the humoral immunity induced by IPV and includes those who received their most recent IPV doses more than two years ago ($i = 1$) and those who received their most recent IPV doses within the last two years and had one, or two, or at least three IPV doses ($i = 2, 3, \text{ or } 4$ respectively). "LPV-immunized" stands for individuals who have intestinal mucosal immunity induced by LPV and includes those who acquired immunity more than two years ago ($i = 5$), who acquired immunity within the last two years and had only one exposure to LPV ($i = 6$), and who acquired immunity within the last two years and had at least two exposures to LPV or both LPV exposures and IPV doses ($i = 7$).

Virus strains: Different strains of LPV have different virological properties; hence, the model includes 21 hypothetical virus strains LPV_j ($j = 0, \dots, 20$), with strain 0 representing the genetically stabilized virus

in novel OPV (assuming no reversion); strain 1 represents the live-attenuated virus in traditional OPV (i.e., Sabin OPV); strains 2-19 represent the partially and progressively reverted forms of the virus in Sabin OPV during community circulation; and strain 20 represents cVDPV. The model simulates the transmission of one serotype at a time.

Age groups and subpopulations: The studied population is stratified by non-overlapping age groups ($a = 1, \dots, n_a$) and subpopulations ($s = 1, \dots, n_s$) based on geography, vaccination coverage, and accessibility. The vaccination coverage is the estimated percentage of individuals who have received polio vaccines from vaccination interventions. The accessibility is evaluated by the probability that the polio vaccines can be delivered and administered. Both n_a and n_s depend on the studied population.

Compartments: $S_{i,a,s}$ and $H_{i,a,s}$ correspond to (partially) susceptible and IPV-injected individuals, respectively, in immunity group i , age group a , and subpopulation (SP) s . $E_{i,j,a,s}$ and $I_{i,j,a,s}$ correspond to exposed (i.e., infected but not infectious) and infectious (i.e., infected and infectious) individuals, respectively, in immunity group i , infected by LPV_j , and in age group a and SP s . D corresponds to dead individuals.

2.1.2 Transitions between Compartments

Transitions between compartments happen due to infection, intervention through preventive vaccination and outbreak response vaccination, disease dynamics, virus reversion, waning of immunity (see Figure 1), aging, birth, and death.

(1) Transitions within IG i :

Infection: Individuals in $S_{i,a,s}$ transition to $E_{i,j,a,s}$ based on the force of infection of LPV_j in age group a and SP s ($\lambda_{j,a,s}$) and the relative susceptibility of individuals in immunity group i (σ_i). The $\lambda_{j,a,s}$ depends on the basic reproductive number of LPV_j (R_{0j}) with seasonal changes and the proportion of infectious individuals who can spread LPV_j to susceptible individuals in age group a and SP s ($EIP_{j,a,s}$). The model

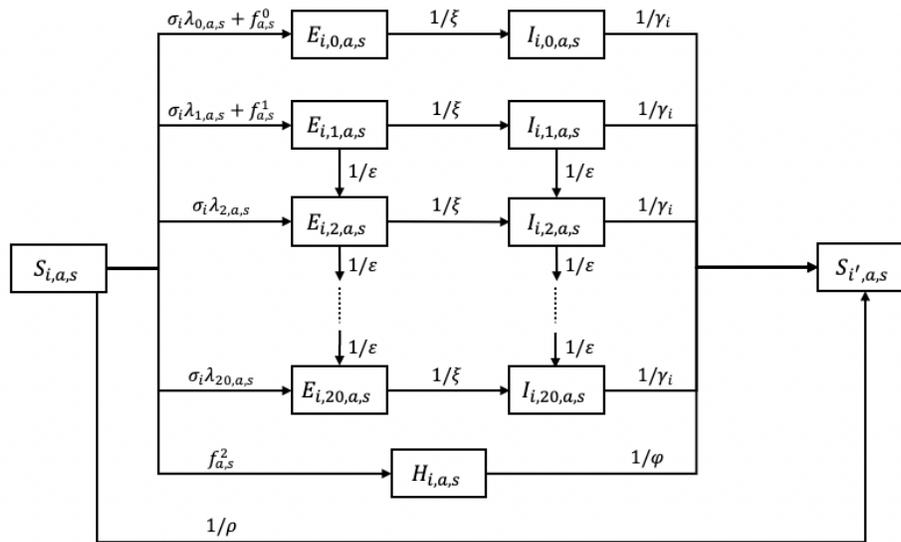


Figure 1: Transitions among the susceptible (S), exposed (E), infectious (I), and inactivated polio vaccine (IPV)-injected (H) due to infection, intervention through outbreak response vaccination, disease dynamics, virus reversion (through strains $j = 1, \dots, 20$), and waning immunity for immunity group i . Transitions due to intervention through preventive vaccination, aging, birth, and death are not shown.

includes a die-out threshold (EIP^*) to force the die-out of transmission when there is a fractional number of infections (Thompson and Kalkowska 2020), i.e., if $EIP_{j,a,s} < EIP^*$, the model sets $\lambda_{j,a,s}$ to 0.

Intervention through outbreak response vaccination: Outbreak response vaccination happens in the form of supplementary immunization activities (SIAs) which vaccinate individuals of wide ages (e.g., 0-4 years) in a short period (e.g., 4 days). In the model, individuals in $S_{i,a,s}$ transition to $E_{i,0,a,s}$, $E_{i,1,a,s}$, and $H_{i,a,s}$, given the effective vaccination coverage of novel OPV, Sabin OPV, and IPV through SIAs in age group a and SP s , respectively ($f_{a,s}^v$; $v = 0$ (novel OPV), 1 (Sabin OPV), and 2 (IPV)). The $f_{a,s}^v$ depends on the implementation period and the coverage of SIAs using vaccine v in age group a and SP s , and the efficacy of vaccine v .

Disease dynamics: Individuals in $E_{i,j,a,s}$ transition to $I_{i,j,a,s}$ at a rate of $1/\xi$, where ξ denotes the duration of being latent (i.e., the time between LPV exposure and becoming infectious).

Virus reversion: For $j = 1, \dots, 19$, individuals in $E_{i,j,a,s}$ and $I_{i,j,a,s}$ transition to $E_{i,j+1,a,s}$ and $I_{i,j+1,a,s}$, respectively, at a rate of $1/\varepsilon$ where ε denotes the duration of virus reversion from LPV_j to LPV_{j+1} .

Aging and intervention through preventive vaccination: For $a = 1, \dots, n_a - 1$, individuals in $E_{i,j,a,s}$, $I_{i,j,a,s}$, and $H_{i,a,s}$ transition to $E_{i,j,a+1,s}$, $I_{i,j,a+1,s}$, and $H_{i,a+1,s}$, respectively, at a rate of $1/w_a$ where w_a is the number of days contained by age group a (e.g., w_a is 365 days for $a = 1$ year).

Preventive vaccination happens in the form of essential immunization (EI) which vaccinates individuals when they reach certain ages (e.g., at birth, 6, 10, and 14 weeks). The model uses $e_{a,s}^v$ to denote the effective vaccination percentage of the EI (in SP s) that uses vaccine v to vaccinate susceptible individuals when they reach age group a . Therefore, among individuals in $S_{i,a,s}$ that transition to age group $a + 1$, the proportions $e_{a+1,s}^0$, $e_{a+1,s}^1$, and $e_{a+1,s}^2$ of them transition to $E_{i,0,a+1,s}$, $E_{i,1,a+1,s}$, and $H_{i,a+1,s}$, respectively, and the proportion $1 - \sum_{v=0}^2 e_{a+1,s}^v$ of them transition to $S_{i,a+1,s}$. The $e_{a,s}^v$ depends on coverage and efficacy of the vaccine v in EI.

(2) Transitions from immunity group i to immunity group i' (if feasible; see Table 1):

Disease dynamics: Individuals in $I_{i,j,a,s}$ transition to $S_{i',a,s}$ at a rate of $1/\gamma_i$ where γ_i denotes the duration of being infectious for individuals in immunity group i . Individuals in $H_{i,a,s}$ transition to $S_{i',a,s}$ at a rate of $1/\varphi$ where φ denotes the duration of IPV immunity delay (i.e., the brief period following receipt of IPV to the acquisition of the immunity induced by this IPV dose).

Waning of immunity: Individuals in $S_{i,a,s}$ transition to $S_{i',a,s}$ at a rate of $1/\rho$ where ρ denotes the duration of the waning of intestinal mucosal immunity and/or humoral immunity.

Table 1: Feasible transitions from immunity group i to immunity group i' .

	$i' = 0$	$i' = 1$	$i' = 2$	$i' = 3$	$i' = 4$	$i' = 5$	$i' = 6$	$i' = 7$
$i = 0$			H to S				I to S	
$i = 1$				H to S				I to S
$i = 2$		S to S		H to S				I to S
$i = 3$		S to S			H to S			I to S
$i = 4$		S to S			H to S			I to S
$i = 5$								I/H to S
$i = 6$						S to S		I/H to S
$i = 7$						S to S		I/H to S

(3) Transitions due to birth and death:

Among newborns of SP s that enter the model based on the birth rate b , the proportions $e_{1,s}^0$, $e_{1,s}^1$, and $e_{1,s}^2$ of them transition to $E_{0,0,1,s}$, $E_{0,1,1,s}$, and $H_{0,1,s}$, respectively, and the proportion $1 - \sum_{v=0}^2 e_{1,s}^v$ of them transition to $S_{0,1,s}$. Individuals in $S_{i,a,s}$, $H_{i,a,s}$, $E_{i,j,a,s}$, and $I_{i,j,a,s}$ transition to D at the death rate μ .

2.1.3 Other Dynamics

The model allows for the importation of LPV_j into age group a and SP s by transitioning a certain number of individuals in $S_{0,a,s}$ to $I_{0,j,a,s}$ at a specified time point t (in days). The model also considers the influence of COVID-19 lockdown measures (Molodecky et al. 2021), by specifying the percentage decrease in population mixing and the start and end days of the decrease.

2.1.4 Outcome Measures

Outcome measures from the model include *weekly case counts* (i.e., the number of weekly new cVDPV paralytic cases), *outbreak size* (i.e., the total number of cVDPV paralytic cases), and *die-out date* (i.e., the first week when the weekly case counts become 0). The cVDPV paralytic cases in AG a and SP s are calculated from LPV_{20} infections of individuals in $S_{0,a,s}$ according to a paralysis-to-infection rate (PIR) which depends on the simulated serotype (e.g., 1:2000 for serotype 2).

2.2 Case Study: Post-switch cVDPV2 Outbreaks in Northern Nigeria

Data from northern Nigeria include confirmed paralytic poliomyelitis cases (with onset between January 1, 2018, and December 31, 2021) caused by cVDPV2 infections as detected through acute flaccid paralysis (AFP) surveillance. Data from January 1, 2018, to August 1, 2021 (calibration period) was used for model calibration, and data from August 2 to December 31, 2021 (validation period) was used for model validation. The prediction results of using the validated model are presented for January 1, 2022 to December 31, 2023 (prediction period).

2.2.1 Model Setup

We defined 7 subpopulations (see Figure 2) with SPs 1-2 in the northwest and SPs 3-7 in the northeast. Given the historic estimated coverage of EI and SIAs, and accessibility, SPs 1 and 3 are “general” (i.e., high level of vaccination coverage and 100% accessibility); SPs 2, 4, and 5 are “under-vaccinated” (i.e., lower level of vaccination coverage; SPs 2, 4 and 5 were assessed as having 100%, 99.4%, and 64.7% accessibility, respectively); and SPs 6 (i.e., Abadam) and 7 (i.e., Marte) are “isolated” with 0% accessibility since 2016 and 2014, respectively, due to the insurgency. 11 age groups were incorporated into the model (i.e., ages 0-2 and 3-11 months; and ages 1, 2, 3, 4, 5-9, 10-14, 15-24, 25-39, and ≥ 40 years) based on

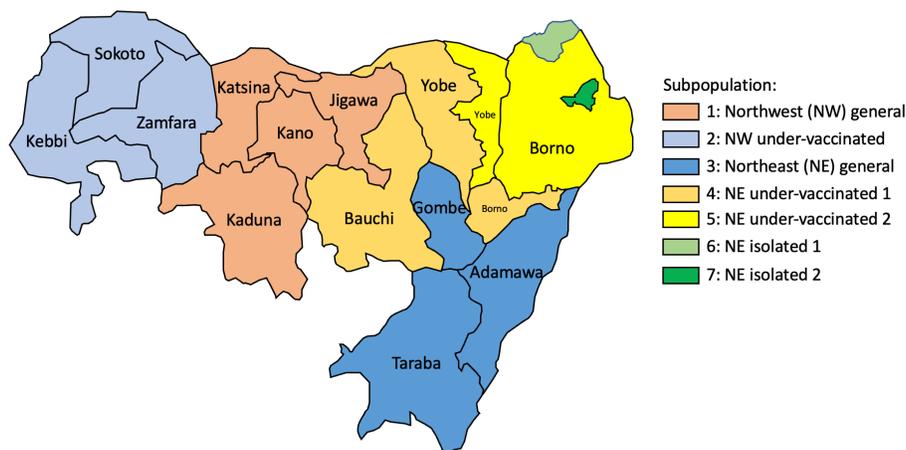


Figure 2: The model’s seven subpopulations of northern Nigeria.

prior modeling studies of polio in Nigeria (Kalkowska et al. 2014; Kalkowska et al. 2020). Most model parameters (e.g., coverage of the one IPV dose in EI) were estimated from prior polio studies (Thompson and Kalkowska 2020) and data on AFP cases and SIAs (personal communication). Parameters that are difficult to estimate from the literature were estimated in model calibration.

2.2.2 Model Calibration and Validation

The model calibration involved extensive iterations and used the idea of walk-forward validation (Hyndman and Athanasopoulos 2018). We stopped the calibration once we found one set of calibrated parameters that produced paralytic cases which generally matched the reported cases in the data in terms of three metrics: (i) the overall trajectory of weekly case counts in each subpopulation; (ii) the total number of case counts in each calendar year in each subpopulation; and (iii) the distribution of case counts across age groups 0-4 years and ≥ 5 years. The calibrated parameters include, for example, the percentage decrease in population mixing (due to COVID-19) and start and end days of the percentage decrease in population mixing, the cVDPV2 importation, die-out threshold, and the coverage of SIAs implemented in the calibration period.

After calibration, we ran the model to simulate weekly cVDPV2 paralytic cases in the validation period. The historical SIAs conducted during the validation period were simulated, where the coverage estimates were adjusted based on the calibrated coverage of SIAs implemented in the calibration period. We compared the simulated weekly case counts and their distributions across subpopulations and age groups 0-4 years and ≥ 5 years to that of the data of the validation period.

2.2.3 Simulating the cVDPV2 Outbreaks in 2022 – 2023

Using the validated model, we evaluated the impact of various outbreak response vaccination scenarios, by simulating cVDPV2 transmission in the prediction period under each scenario. We assumed that in each tested scenario the coverage of the one IPV dose in EI remained constant as that in calibration and validation periods. Figure 3 provides a summary of the outbreak response vaccination scenarios which include:

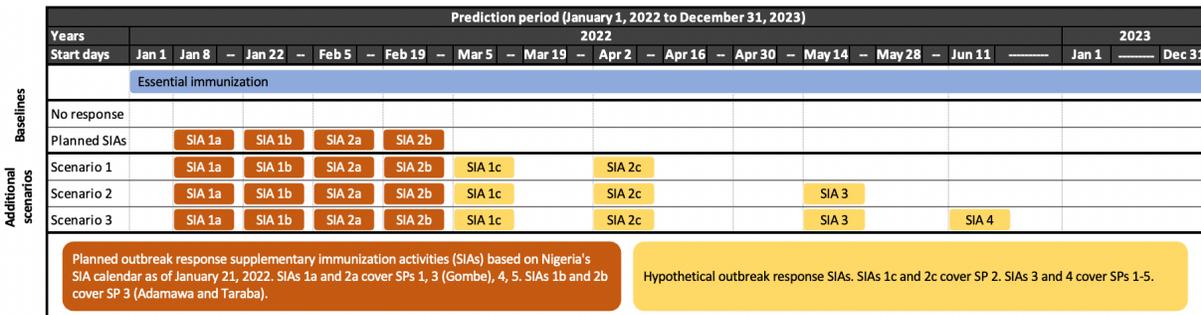


Figure 3: Outbreak response vaccination scenarios tested in the prediction period (2022 – 2023).

- *No Response (NR)*: No SIAs since 2022.
- *Planned SIAs (P-SIAs)*: Two rounds of SIAs (SIAs) target SPs 1, 3, 4, and 5 with a 4-week interval in between (i.e., based on Nigeria’s SIA calendar as of January 21, 2022). Rounds 1 and 2 have two phases. Phase 1 includes two *planned* SIAs (SIAs 1a and 2a) that target SPs 1, 3 (Gombe), 4, and 5. Phase 2 includes two *planned* SIAs (SIAs 1b and 2b) that target SP 3 (Adamawa and Taraba).
- *Scenario 1*: Two rounds of SIAs target SPs 1-5 with a 4-week interval in between. Both rounds 1 and 2 include three phases. Phases 1 and 2 are the same as P-SIAs. Phase 3 includes two *hypothetical* SIAs (SIAs 1c and 2c) for SP 2.
- *Scenario 2*: Three rounds of SIAs target SPs 1-5. Rounds 1 and 2 are the same as in Scenario 1. Round 3 includes one *hypothetical* SIA (SIA 3) that targets SPs 1-5. There is a 6-week interval between Rounds 2 and 3.

- *Scenario 3*: Four rounds of SIAs target SPs 1-5 in 2022. Rounds 1-3 are the same as in Scenario 2. Round 4 includes one *hypothetical* SIA (SIA 4) that targets SPs 1-5. There is a 4-week interval between Rounds 3 and 4.

Based on the guidance in the standard operating procedures (World Health Organization 2022), we assumed that all SIAs used novel OPV2, targeted individuals aged 0-4 years, had a duration of 4 days, and achieved 90% coverage in target areas. More specifically, for an SIA that targets multiple subpopulations, we assumed this SIA vaccinated 90% of susceptible individuals (from all immunity groups) that were aged 0-4 years in each subpopulation. For example, SIA 1a vaccinated 90% of susceptible children aged 0-4 years, in each one of SPs 1, 3 (Gombe), 4, and 5. We set up at least a 4-week interval between every two successive rounds of SIAs to be consistent with the standard operating procedures and the Emergency Use Listing requirements for using novel OPV2 (World Health Organization 2022). Figure 3 shows the start days of all SIAs and Figure 4 summarizes the number of novel OPV2 doses received by individuals in each subpopulation under each scenario.

We considered NR and P-SIAs as baselines for comparison. We tested Scenario 1 to include SP 2 in the outbreak response, given that the planned SIAs did not target SP 2 while SP 2 experienced cVDPV2 outbreaks in 2021. Scenario 1 complies with the requirement in the standard operating procedures that at least two rounds of high-quality large-scale SIAs (i.e., $\geq 90\%$ of children vaccinated) are conducted in outbreak-affected areas. We simulated Scenarios 2 and 3 to study the need for additional rounds of SIAs (i.e., SIAs 3 and 4) to ensure die-out of cVDPV2 in northern Nigeria after the first two rounds of high-quality large-scale SIAs (i.e., the SIAs 1 and 2). We compared the outcomes (i.e., weekly case counts, outbreak size, and die-out date) of NR, P-SIAs, and Scenarios 1-3 in the prediction period.

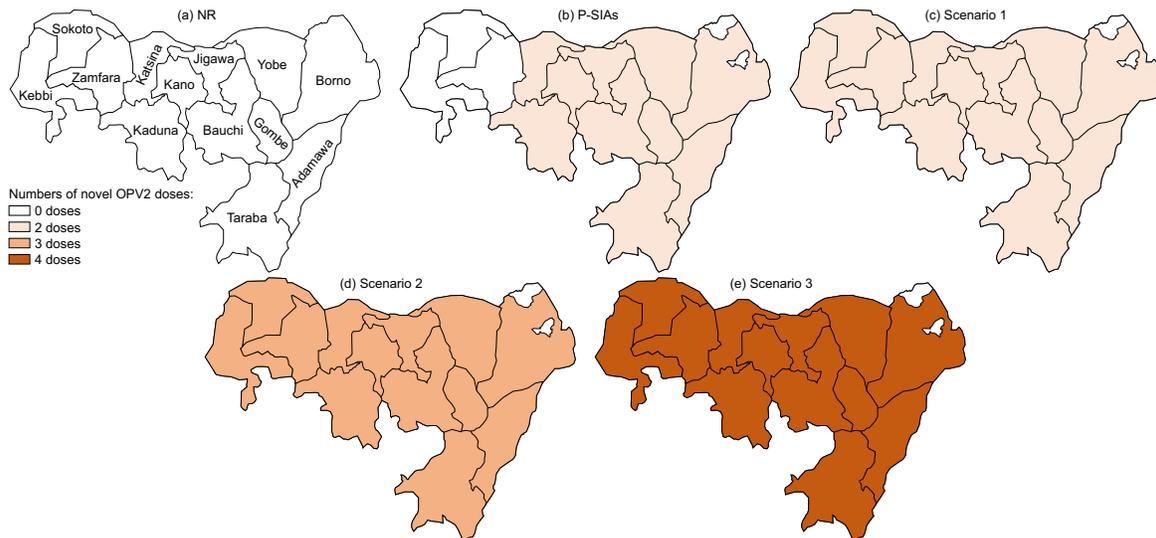


Figure 4: Numbers of novel OPV2 (serotype 2-containing oral polio vaccine) doses in the prediction period (January 1, 2022 to December 31, 2023) under (a) NR (No Response); (b) P-SIAs (Planned Supplementary Immunization Activities); (c) Scenario 1; (d) Scenario 2; and (e) Scenario 3.

3 RESULTS

Figure 5 shows that the simulated weekly case counts (from all subpopulations) closely match the reported weekly case counts during the calibration and validation periods. Table 2 demonstrates the distributions of simulated cases across age groups and subpopulations also align with that of the reported cases.

For the prediction period, Figure 5 shows the weekly case counts (from all subpopulations) under NR, P-SIAs, and Scenarios 1 and 3. Table 3 and Table 4 summarize the outbreak sizes and the die-out dates of

all tested scenarios, respectively. No cases were predicted in SPs 6 and 7. The trajectory of weekly case counts from all subpopulations in Scenario 2 were between that of Scenarios 1 and 3.

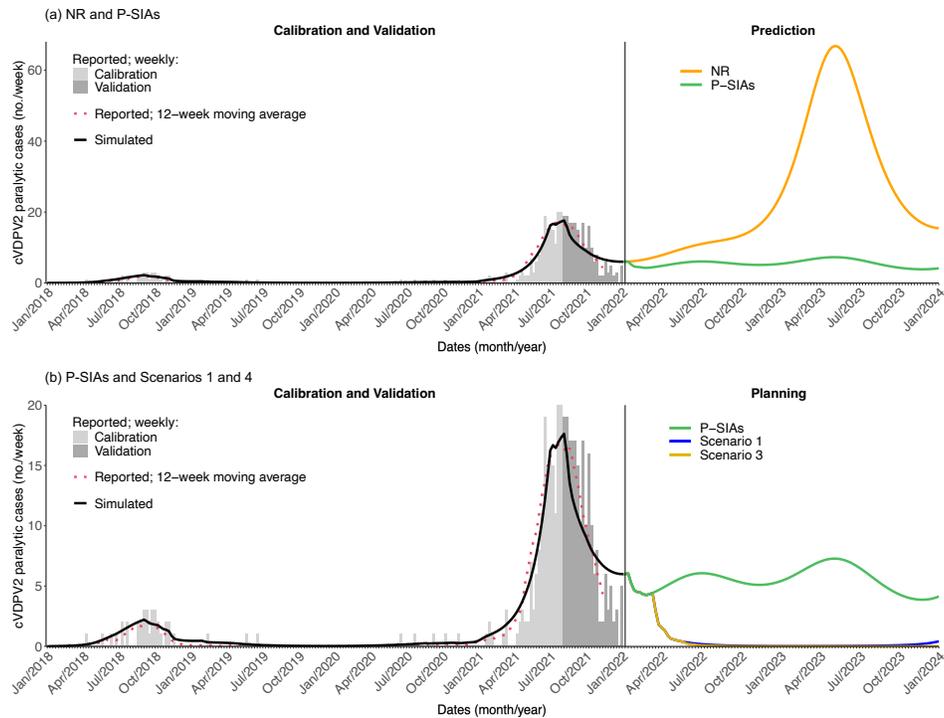


Figure 5: The weekly case counts from all subpopulations in the calibration period (January 1, 2018 to August 1, 2021) and the validation period (August 2 to December 31, 2021), and in the prediction period (January 1, 2022 to December 31, 2023) under (a) NR (No Response) and P-SIAs (Planned Supplementary Immunization Activities); and (b) P-SIAs and Scenarios 1 and 4.

During the prediction period, the NR scenario resulted in a cumulative 2641 cases among all subpopulations and cVDPV2 continued to spread in SPs 1-5. The most severe outbreaks happened in SPs 1 and 2, and then in SPs 4, 3, and 5, with outbreak sizes of 1208 cases, 551 cases, 376 cases, 329 cases, and 177 cases, respectively (see Table 3).

Implementing the two rounds of 90%-coverage SIAs that targeted SPs 1, 3, 4, and 5 (as in P-SIAs) resulted in 567 cases from all subpopulations in the prediction period. In comparison to NR, the reduction in the case burden was due to fewer cases in SPs 1, 3, 4, and 5. In P-SIAs, the outbreak size in SP 1 was 10 cases and the outbreak size in each one of SPs 3, 4, and 5 was 2 cases. P-SIAs did not change the outbreak size in SP 2 and only achieved die-out of cVDPV2 in SPs 3 and 4.

Compared to NR and P-SIAs, including SP 2 in the two rounds of SIAs but starting SIAs in SP 2 in a separate Phase 3 (as in Scenario 1) decreased the outbreak size in SP 2 (i.e., 49 cases in Scenario 1 compared to 551 cases in NR and P-SIAs). Compared to P-SIAs, Scenario 1 barely changed the outbreak sizes in SPs 1, 3, 4, and 5. Scenario 1 only achieved die-out of cVDPV2 in SPs 1, 3, and 4.

Compared to Scenario 1, adding two additional rounds (i.e., SIAs 3 and 4) after the first two rounds with all rounds targeting SPs 1-5 (as in Scenario 3) achieved die-out of cVDPV2 in all subpopulations in the week of January 23, 2023, even if it did not significantly change the outbreak sizes in SPs 1-5. In Scenario 3, the last die-out happened in SP 2. In addition to that die out happened in SPs 1, 3, and 4 as in Scenario 1, adding only one additional round (i.e., SIA 3) after the first two rounds (as in Scenario 2) further achieved die-out in SP 5 but not SP 2. Results for the prediction period also indicated that, in scenarios and subpopulations where die-out was not achieved, the weekly case counts oscillated over time.

Table 2: Distributions of reported and simulated serotype 2 circulating vaccine-derived poliovirus paralytic cases from 2018 to 2021 across subpopulations and age groups 0-4 years and ≥ 5 years.

Subpopulations and age groups	Paralytic cases							
	2018		2019		2020		2021	
	R*	S*	R	S	R	S	R	S
SP 1: 0-4 years	21	20	0	1	0	0	147	148
≥ 5 years	0	3	0	1	0	0	20	19
SP 2: 0-4 years	0	0	1	1	5	6	100	94
≥ 5 years	0	0	0	1	0	0	5	5
SP 3: 0-4 years	0	1	0	0	0	0	26	30
≥ 5 years	1	0	0	0	0	0	6	4
SP 4: 0-4 years	0	1	0	0	0	0	38	36
≥ 5 years	0	1	0	0	0	0	1	3
SP 5: 0-4 years	10	11	1	1	0	0	32	32
≥ 5 years	1	1	1	1	0	0	2	3
SP 6: 0-4 years	0	0	0	0	0	0	0	0
≥ 5 years	0	0	0	0	0	0	0	0
SP 7: 0-4 years	0	0	0	0	0	0	0	0
≥ 5 years	0	0	0	0	0	0	0	0

* R = reported; S = simulated; reported cases are from the AFP surveillance data as of February 10, 2022.

Table 3: The outbreak sizes from all subpopulations (SPs) and each one of the SPs 1-5 under all scenarios during the prediction period from January 1, 2022 to December 31, 2023.

Scenarios	Outbreak sizes					
	SP 1	SP 2	SP 3	SP 4	SP 5	All SPs
No Response	1,208	551	329	376	177	2,641
Planned SIAs	10	551	2	2	2	567
Scenario 1	8	49	2	2	2	63
Scenario 2	8	45	2	2	1	58
Scenario 3*	8	45	2	2	1	58

*Scenarios achieved die-out of serotype 2 circulating vaccine-derived poliovirus in all subpopulations

Table 4: The die-out dates from all subpopulations (SPs) and each one of the SPs 1-5 under all scenarios during the prediction period from January 1, 2022 to December 31, 2023.

Scenarios	Die-out dates					
	SP 1	SP 2	SP 3	SP 4	SP 5	All SPs
No Response	¹	–	–	–	–	–
Planned SIAs	–	–	Dec-26, 22	Dec-05, 22	–	–
Scenario 1	Dec-05, 22	–	Dec-19, 22	Nov-28, 22	–	–
Scenario 2	Sep-19, 22	–	Sep-19, 22	Sep-12, 22	Nov-07, 22	–
Scenario 3*	Sep-05, 22	Jan-23, 23	Sep-05, 22	Aug-29, 22	Oct-10, 22	Jan-23, 23

*Scenarios achieved die-out of serotype 2 circulating vaccine-derived poliovirus in all subpopulations

¹ Not applicable

4 DISCUSSION

We developed a differential equation-based model of live poliovirus transmission, validated it using data from northern Nigeria, and evaluated the effectiveness of a wide range of outbreak response vaccination scenarios during the prediction period of 2022-2023. When there was only preventive vaccination (i.e., EI) and no outbreak response vaccination (i.e., SIAs), the results indicated substantial cVDPV2 transmission during the prediction period in all states of northern Nigeria, due to the limited coverage and efficacy of the one IPV dose. Implementing planned novel OPV2 SIAs (i.e., P-SIAs) reduced case counts by 79% but did not stop the outbreaks, partly because they did not target SP 2 and the model predicted continued transmission in SP 2. The implementation of four rounds of 90%-coverage novel OPV2 SIAs (targeting all non-isolated areas with an interval of 4-6 weeks between two successive rounds) stopped cVDPV2 outbreaks, as in Scenario 3.

Persistent transmission in under-vaccinated areas, especially in SP 2 (i.e., Kebbi, Sokoto, and Zamfara), largely delayed the progression towards stopping outbreaks. This finding corroborates previous findings regarding the role of under-vaccinated subpopulations in sustaining polio transmission (Duintjer Tebbens et al. 2014; Kalkowska et al. 2014; Thompson and Kalkowska 2020). Compared to SPs 1, 3, 4, and 5, SP 2 required 1-2 more rounds of novel OPV2 SIAs to stop the transmission and achieved die-out of cVDPV2 15-21 weeks later. Our results also highlighted the need for additional rounds of SIAs to guarantee die-out in under-vaccinated subpopulations even though these rounds didn't further largely decrease the outbreak sizes after the two initial rounds, as comparing Scenarios 2 and 3 to Scenario 1.

There are several limitations. Calibration has been challenging due to the large range of possible values and interdependence among model parameters; hence, we found one set of parameter values from values we tested to generally match the dynamics of the cVDPV2 transmission in northern Nigeria. It is possible that there is more than one set of parameters that results in a well calibrated model. In future works, will investigate the sensitivity of the vaccination strategies to the calibrated parameters. We will also try a more systematic calibration process to find the set of parameter values that empirically optimize some goodness-of-fit measures (e.g., the sum of squared errors between simulated and reported polio paralytic cases). The model only considers AFP surveillance but not environmental surveillance which tests poliovirus in sewage samples. Environmental surveillance is limited in geographic scope, generally covering populations living in urban areas, but can be informative, especially in detecting asymptomatic transmission. For example, in Scenario 1, after the two rounds of SIAs, weekly case counts were close to 0 and cVDPV2 died out in SPs 1, 3, and 4 but not in SPs 2 and 5, which was not detectable by AFP surveillance. If the environmental surveillance further found no cVDPV2 in SPs 1, 3, and 4, then the two additional rounds of SIAs (i.e., SIAs 3 and 4) might only cover SPs 2 and 5 to save limited resources like vaccines. Future works could incorporate environmental surveillance and its impact on planning outbreak response vaccination. The model assumes constant access to all subpopulations in interventions; in reality, access might change over time, but current data on access is very limited (Adamu et al. 2019; Bolu et al. 2018). In the scenarios tested, we assumed a 90% coverage for all SIAs, whereas in practice, coverage can be lower or vary over time (Duintjer Tebbens et al. 2013). However, the results are still informative as they show that the interruption of cVDPV2 outbreaks might be achievable by increasing vaccination coverage levels and they highlight the gap in northern Nigeria's population immunity against serotype 2, especially in under-vaccinated areas such as Kebbi, Sokoto, and Zamfara. Given the number of model compartments and the population size (e.g., 27,104 compartments and 77,303,930 individuals (at the start of 2018) in the case study), we used a deterministic model to validate the dynamics of vaccination, reversion, and waning immunity by comparing modeled cases to observed cases. In practice, policymakers plan for a wide range of scenarios involving stochasticity, and decisions on outbreak control can be different in stochastic settings (Brennan et al. 2006; Koopman et al. 2002). Future works could expand the compartmental framework to a stochastic model and then use it to test various outbreak response scenarios.

5 CONCLUSIONS

With the goal to “stop cVDPV transmission and prevent outbreaks in non-endemic countries” in the Polio Eradication Strategy 2022 – 2026 (Global Polio Eradication Initiative 2022), stakeholders need to revisit the guidance in the standard operating procedures in terms of the number of outbreak response vaccination rounds initially planned, and endeavor to reach suggested timeline targets. Using novel OPV2 provides a chance for effective vaccinations with markedly reduced risks of seeding new cVDPV2 emergence. However, as evidenced by persistent outbreaks in 2021 and 2022, an improved vaccine does not compensate for low-quality outbreak response vaccination campaigns that fail to quickly immunize all target children. All cVDPV2-affected countries also need to keep identifying under-vaccinated population areas and conduct effective vaccination campaigns to boost population immunity and prevent possibly prolonged transmission in these areas.

In the future, our model can be used to assess the interaction between preventive vaccination and outbreak response vaccination, evaluate the tradeoffs between factors of outbreak response vaccination (e.g., timeliness and coverage), study the impact of surveillance systems on planning vaccinations (e.g., the decisions on additional rounds after the first two high-quality large-scale rounds), and identify feasible and effective intervention strategies in a context-specific manner for countries affected by one polio serotype. Further, for countries with co-circulation of more than one serotype (e.g., serotypes 1 and 2 in Malawi and Mozambique), our modeling framework can be extended and used to guide the decision-making on vaccination strategies to balance the priorities of eradicating different serotypes.

ACKNOWLEDGMENTS

We acknowledge the support from Cara Burns and Jaume Jorba on behalf of the US Centers for Disease Control and Prevention (CDC) laboratory on providing data tracking poliovirus lineages in African countries. We appreciate Walter Orenstein for his generous comments and suggestions on this study. We thank the Nigeria National Primary Health Care Development Agency for sharing the polio data. This study was funded by a cooperative agreement between Georgia Tech and the CDC (1 NU2RGH001919-01-00). This research was also supported in part by the William W. George endowment and the following benefactors at Georgia Tech: Andrea Laliberte, Richard Rick E. and Charlene Zalesky, and Claudia and Paul Raines. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

REFERENCES

- Adamu, U. S., W. R. Archer, F. Braka, E. Damisa, A. Siddique, S. Baig, J. Higgins, G. E. Sume, R. Banda, C. K. Korir, N. Waziri, S. Gidado, P. Bammeke, A. Edukugo, G. W. Nganda, J. C. Forbi, C. C. Burns, H. Liu, J. Jorba, A. Asekun, R. Franka, S. G. F. Wassilak, and O. Bolu. 2019. "Progress toward Poliomyelitis Eradication - Nigeria, January 2018-May 2019". *MMWR. Morbidity and Mortality Weekly Report* 68(29): 642-646.
- Bolu, O., C. Nnadi, E. Damisa, F. Braka, A. Siddique, W. R. Archer, P. Bammeke, R. Banda, J. Higgins, A. Edukugo, G. W. Nganda, J. C. Forbi, H. Liu, S. Gidado, M. Soghaier, R. Franka, N. Waziri, C. C. Burns, J. Vertefeuille, E. Wiesen, and U. Adamu. 2018. "Progress toward Poliomyelitis Eradication - Nigeria, January-December 2017". *MMWR. Morbidity and Mortality Weekly Report* 67(8): 253-256.
- Brennan, A., S. E. Chick, and R. Davies. 2006. "A Taxonomy of Model Structures for Economic Evaluation of Health Technologies". *Health Economics* 15(12): 1295-1310.
- Duintjer Tebbens, R. J., D. A. Kalkowska, S. G. F. Wassilak, M. A. Pallansch, S. L. Cochi, and K. M. Thompson. 2014. "The Potential Impact of Expanding Target Age Groups for Polio Immunization Campaigns". *BMC Infectious Diseases* 14(1): 45.
- Duintjer Tebbens, R. J., M. A. Pallansch, D. A. Kalkowska, S. G. F. Wassilak, S. L. Cochi, and K. M. Thompson. 2013. "Characterizing Poliovirus Transmission and Evolution: Insights from Modeling Experiences with Wild and Vaccine-related Polioviruses". *Risk Analysis* 33(4): 703-749.
- Global Polio Eradication Initiative. 2013. Polio Eradication and Endgame Strategic Plan 2013-2018. https://polioeradication.org/wp-content/uploads/2016/07/PEESP_EN_A4.pdf, accessed 2nd April 2022.
- Global Polio Eradication Initiative. 2015. Global Eradication of Wild Poliovirus Type 2 Declared. <https://polioeradication.org/news-post/global-eradication-of-wild-poliovirus-type-2-declared/>, accessed 18th June 2022.

- Global Polio Eradication Initiative. 2022. Polio Eradication Strategy 2022-2026: Executive Summary. <https://apps.who.int/iris/bitstream/handle/10665/341938/9789240024830-eng.pdf>, accessed 28th May 2022.
- Hyndman, R. J. , and G. Athanasopoulos. 2018. Forecasting: Principles and Practice, 2nd Edition, OTexts: Melbourne, Australia. [OTexts.com/fpp2](https://www.otexts.com/fpp2), accessed 28th February 2022.
- Kalkowska, D. A., R. J. Duintjer Tebbens , and K. M. Thompson. 2014. "Modeling Strategies to Increase Population Immunity and Prevent Poliovirus Transmission in the High-risk Area of Northwest Nigeria". *The Journal of Infectious Diseases* 210(suppl_1): S412-S423.
- Kalkowska, D. A., R. Franka, J. Higgins, S. D. Kovacs, J. C. Forbi, S. G. F. Wassilak, M. A. Pallansch , and K. M. Thompson. 2020. "Modeling Poliovirus Transmission in Borno and Yobe, Northeast Nigeria". *Risk Analysis* 41(2): 289-302.
- Koopman, J. S., S. E. Chick, C. P. Simon, C. S. Riolo , and G. Jacquez. 2002. "Stochastic Effects on Endemic Infection Levels of Disseminating versus Local Contacts". *Mathematical Biosciences* 180: 49-71.
- Molodecky, N. A., H. Jafari, R. M. Safdar, J. A. Ahmed, A. Mahamud, A. S. Bandyopadhyay, H. Shukla, A. Quddus, M. Zaffran, R. W. Sutter, N. C. Grassly , and I. M. Blake. 2023. "Modelling the Spread of Serotype-2 Vaccine Derived-poliovirus Outbreak in Pakistan and Afghanistan to Inform Outbreak Control Strategies in the Context of the COVID-19 Pandemic". *Vaccine* 41: A93-A104.
- Roberts, L. 2022. Africa Battles Out-of-control Polio Outbreaks. <https://www.science.org/content/article/africa-battles-out-of-control-polio-outbreaks>, accessed 27th May 2022.
- Thompson, K. M. , and D. A. Kalkowska. 2020. "Review of Poliovirus Modeling Performed from 2000 to 2019 to Support Global Polio Eradication". *Expert Review of Vaccines* 19(7): 661-686.
- World Health Organization. 2019. Report from the Twentieth Meeting of the Global Commission for Certification of Poliomyelitis Eradication, Geneva, Switzerland, 17-18 October 2019. <https://polioeradication.org/wp-content/uploads/2016/07/20th-meeting-of-the-Global-Commission-for-the-Certification-of-Eradication-of-Poliomyelitis-17-18-October-2019.pdf>, accessed 31st August 2021.
- World Health Organization. 2022. Standard Operating Procedures: Responding to a Poliovirus Event or Outbreak Version 4. <https://polioeradication.org/wp-content/uploads/2022/07/Standard-Operating-Procedures-For-Responding-to-a-Poliovirus-Event-Or-Outbreak-20220807-EN-Final.pdf>, accessed 2nd April 2022.

AUTHOR BIOGRAPHIES

YUMING SUN is a Ph.D. in Operations Research (OR) student in the H. Milton Stewart School of Industrial and Systems Engineering at Georgia Institute of Technology (Georgia Tech). His research interests lie in the application of OR methodologies to healthcare delivery and optimization, vaccine-preventable disease modeling, evaluation of intervention strategies, and resource allocation. His email address is ysun608@gatech.edu and his homepage is <https://www.isye.gatech.edu/users/yuming-sun>.

PINAR KESKINOC AK is the William W. George Chair and Professor in the H. Milton Stewart School of Industrial and Systems Engineering at Georgia Tech. Her research focuses on the applications of operations research and management science with societal impact, particularly health and humanitarian applications, supply chain management, and logistics/transportation. Her email address is pinar@isye.gatech.edu, and her website is https://www2.isye.gatech.edu/people/faculty/Pinar_Keskinocak/.

LAUREN N. STEIMLE is the Harold R. and Mary Anne Nash Early Career Professor and an Assistant Professor in the H. Milton Stewart School of Industrial and Systems Engineering at Georgia Tech. Her research interests include data analytics, optimization, and stochastic modeling with applications in public health and medical decision-making. Her email address is steimle@gatech.edu, and her website is <https://sites.gatech.edu/steimle/>.

STEPHANIE D. KOVACS is an Epidemiologist working on Polio eradication at the Centers for Disease Control and Prevention (CDC). She earned her Ph.D. and MPH degrees in Epidemiology from the University of Washington and Tulane University, respectively. Her email address is uvx4@cdc.gov.

STEVEN G. WASSILAK is a Medical Epidemiologist at the CDC. Previously he served as a Medical Officer at the World Health Organization Regional Office for Europe and focused on vaccine-preventable diseases and immunization, surveillance, and polio eradication activities. His email address is sgw1@cdc.gov.