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Modeling the spread of circulating vaccine-derived poliovirus type 2 outbreaks and interventions: A case study of Nigeria

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ABSTRACT

Background: Despite the successes of the Global Polio Eradication Initiative, substantial challenges remain in eradicating the poliovirus. The Sabin-strain (live-attenuated) virus in oral poliovirus vaccine (OPV) can revert to circulating vaccine-derived poliovirus (cVDPV) in under-vaccinated communities, regain neurovirulence and transmissibility, and cause paralysis outbreaks. Since the cessation of type 2-containing OPV (OPV2) in 2016, there have been cVDPV type 2 (cVDPV2) outbreaks in four out of six geographical World Health Organization regions, making these outbreaks a significant public health threat. Preparing for and responding to cVDPV2 outbreaks requires an updated understanding of how different factors, such as outbreak responses with the novel type of OPV2 (nOPV2) and the existence of under-vaccinated areas, affect the disease spread.

Methods: We built a differential-equation-based model to simulate the transmission of cVDPV2 following reversion of the Sabin-strain virus in prolonged circulation. The model incorporates vaccinations by essential (routine) immunization and supplementary immunization activities (SIAs), the immunity induced by different poliovirus vaccines, and the reversion process from Sabin-strain virus to cVDPV. The model's outcomes include weekly cVDPV2 paralytic case counts and the die-out date when cVDPV2 transmission stops. In a case study of Northwest and Northeast Nigeria, we fit the model to data on the weekly cVDPV2 case counts with onset in 2018–2021. We then used the model to test the impact of different outbreak response scenarios during a prediction period of 2022–2023. The response scenarios included no response, the planned response (based on Nigeria's SIA calendar), and a set of hypothetical responses that vary in the dates at which SIAs started. The planned response scenario included two rounds of SIAs that covered almost all areas of Northwest and Northeast Nigeria except some under-vaccinated areas (e.g., Sokoto). The hypothetical response scenarios involved two, three, and four rounds of SIAs that covered the whole Northwest and Northeast Nigeria. All SIAs in tested outbreak response scenarios used nOPV2. We compared the outcomes of tested outbreak response scenarios in the prediction period.

Results: Modeled cVDPV2 weekly case counts aligned spatiotemporally with the data. The prediction results indicated that implementing the planned response reduced total case counts by 79% compared to no response, but did not stop the transmission, especially in under-vaccinated areas. Implementing the hypothetical response scenarios involving two rounds of nOPV2 SIAs that covered all areas further reduced cVDPV2 case counts in under-vaccinated areas by 91–95% compared to the planned response, with greater impact from completing the two rounds at an earlier time, but it did not stop the transmission. When the first two rounds were completed in early April 2022, implementing two additional rounds stopped the transmission in late January 2023. When the first two rounds were completed six weeks earlier (i.e., in late February 2022), implementing one (two) additional round stopped the transmission in early February 2023 (late November 2022). The die out was always achieved last in the under-vaccinated areas of Northwest and Northeast Nigeria.

Conclusions: A differential-equation-based model of poliovirus transmission was developed and validated in a case study of Northwest and Northeast Nigeria. The results highlighted (i) the effectiveness of nOPV2 in reducing outbreak case counts; (ii) the need for more rounds of outbreak response SIAs that covered all of Northwest and Northeast Nigeria in 2022 to stop the cVDPV2 outbreaks; (iii) that persistent transmission in under-vaccinated

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areas delayed the progress towards stopping outbreaks; and (iv) that a quicker outbreak response would avert more paralytic cases and require fewer SIA rounds to stop the outbreaks.

Introduction

Since the resolution in 1988 to eradicate polio globally [1], the Global Polio Eradication Initiative (GPEI) and its partners have made significant progress towards a polio-free world. Wild poliovirus (WPV) types 2 and 3 have been eradicated in 2015 and 2019, respectively [2,3]. The cases of type 1 (WPV1) have decreased significantly, as of in 2023 there were 12 cases in the last two endemic countries (i.e., Pakistan and Afghanistan) [4].

However, there has been an increase in the outbreaks of circulating vaccine-derived poliovirus (cVDPV) infections, especially for poliovirus type 2 (cVDPV2). cVDPV emerges where children are under-vaccinated. In under-vaccinated population areas, the live-attenuated virus from the oral poliovirus vaccine (OPV) can circulate and accumulate enough mutations to revert to cVDPV, a WPV-like form infecting susceptible individuals and causing paralysis [5,6]. To avoid the cVDPV emergence, the GPEI has planned a phased cessation of OPV after global WPV eradication by serotype [7]. As a first step, after WPV type 2 was certified as eradicated in 2015, type 2-containing OPV (OPV2) cessation was achieved by a "switch" from trivalent OPV (tOPV; containing types 1, 2, and 3) to bivalent OPV (bOPV; containing types 1 and 3) in essential (routine) immunization (EI) in April 2016 [8]. However, cVDPV2 transmission persists, possibly because of insufficient and delayed pre- and post-switch vaccination campaigns (e.g., caused by insurgency), the emergence of cVDPV2 before the switch, and the use of Sabin-strain OPV2 after the switch [9]. Since May 2016, more than 30 countries have reported over 4000 global cVDPV2 paralytic cases, based on the World Health Organization (WHO) Polio Information System (POLIS) which summarizes polio information related to surveillance and vaccination campaigns.

There are many challenges in preventing and stopping cVDPV2 transmission. First, in the prevention of transmission, the first dose of (trivalent) inactivated poliovirus vaccine (IPV) was included in EI in 2015 to prepare for the switch and provide a level of protection against type 2. Some countries introduced the second IPV dose at a later date, e.g., in July 2021 in Nigeria [10]. Unlike OPV, IPV does not directly induce intestinal mucosal immunity which is required to stop person-to-person transmission in cVDPV2-affected countries. IPV induces humoral immunity and individual protection against paralysis, and it boosts mucosal immunity for those who have previously received OPV or been infected. However, the coverage of EI remains low in some areas of many countries, e.g., due to insurgency or in hard-to-reach areas or in where EI services are limited (as in many northern Nigeria states) [11,12]. As a result, there are birth cohorts with both low intestinal mucosal and humoral immunity who contribute to cVDPV2 outbreaks and the number of cases [13]. Second, in the response to outbreaks, supplementary immunization activities (SIAs) of Sabin-strain monovalent OPV2 (mOPV2) and tOPV have been used, but mOPV2/tOPV can seed new cVDPV2 emergences if the effective coverage of the SIA is limited [14,15]. Beginning in March 2021, although a novel type of OPV2 (nOPV2) with a lower risk of virus reversion was rolled out for outbreak response SIAs, the effectiveness (quality) of some of these SIAs was compromised. The incompletion of outbreak response plans led to households/communities being overlooked in house-to-house campaigns. Vaccines failed to reach children in the most critical transmission areas (e.g., due to insecurity). Consequently, despite the adoption of nOPV2, existing outbreaks persisted through multiple SIA rounds [16]. If transmission continues and is detected by the surveillance system after conducting SIAs in outbreak response, additional rounds of SIAs will be implemented [17]. However, with the current use of IPV in EI, there is an increasingly higher proportion of asymptomatic transmission of cVDPV2 [18]. The acute flaccid paralysis surveillance (AFP) does not detect asymptomatic transmission. In such situations, supplemental environmental surveillance can detect asymptomatic transmission by identifying cVDPV2 in sewage samples. However, the limits in establishing catchment areas for environmental surveillance [18] may cause delays in detection, which, in turn, might create a false impression that transmission has ceased and that no additional rounds are needed.

To quantify the impact of EI and SIAs on cVDPV2 transmission, we built a differential-equation-based (DEB) model [19–23] of live poliovirus (LPV) transmission. We calibrated and validated the model in a case study of Nigeria, using the data of cVDPV2 paralytic cases that occurred between 2018 and 2021 in Nigeria. This case study was performed in February 2022 to inform the outbreak response strategies to stop ongoing cVDPV2 outbreaks in Nigeria. We used the validated model to evaluate the effectiveness of various outbreak response scenarios by predicting the total number of confirmed cases during 2022–2023 under each scenario. The response scenarios included no response, planned outbreak response SIAs (based on Nigeria's SIA calendar as of January 21, 2022), and some hypothetical scenarios that varied in the number of SIA rounds, the extent of targeted areas, and the start dates of SIAs. We assumed constant coverage of IPV doses in EI in all tested scenarios. All SIAs in test scenarios used nOPV2 and targeted vaccination of children aged 0–4 years.

Material and methods

Live poliovirus transmission model

Model compartments

We adapted a deterministic DEB model to simulate the LPV transmission [19–23]. The model follows an extended susceptible (S), exposed (E), infectious (I) – susceptible (SEIS) compartmental framework, with the addition of an IPV-injected (H) compartment representing individuals who have recently received an IPV dose but have not acquired the corresponding immunity since their immune systems are still mounting a response to the vaccine. 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 (IG; $i = 0$) to represent unimmunized individuals and seven IGs ($i = 1, \ldots, 7$) depending on the source of immunity (from LPV or IPV), the timing of the most recently acquired immunity (to incorporate waning of humoral and intestinal mucosal immunity), and the number of exposures to LPV or the number of IPV doses received by an individual [20].

- IG 0 (Unimmunized): Individuals who have no immunity.
- IGs 1–4 (IPV-immunized): Individuals who only have humoral immunity induced by IPV, including those who
  a. received their most recent IPV doses more than two years ago (IG 1);
  b. received their most recent IPV doses within the last two years and had one, or two, or $\geq$ three IPV doses (IGs 2, 3, 4 respectively).
- IGs 5–7 (LPV-immunized): Individuals who have intestinal mucosal immunity induced by LPV, including those who
  a. acquired immunity more than two years ago (IG 5);
  b. acquired immunity within the last two years and had only one exposure to LPV (IG 6);
  c. acquired immunity within the last two years and had $\geq$ two exposures to LPV or had both LPV exposures and IPV doses (IG 7).

The individuals in IG i are distinguished by their relative susceptibility (σ_i) and infectiousness (π_i) (compared to that of individuals in IG 0) and their duration of being infectious (γ_i) [20].

Virus strains: Different forms of LPV have different virological properties; hence, the model includes 21 hypothetical virus strains LPV_j ($j = 0,\ldots,20$) [24], with strain 0 representing the genetically stabilized virus in nOPV2 (assuming no reversion and no vaccine-associated paralytic poliomyelitis [25]); strain 1 represents the live-attenuated Sabin-strain OPV virus (i.e., virus in tOPV, bOPV, or mOPV); strains 2–19 represent the partially and progressively reverted forms from the Sabin-strain OPV virus during community circulation; and strain 20 represents cVDPV. The model simulates the transmission of one LPV serotype at a time, and thus, it does not include strain 0 when simulating LPV type 1 or 3 transmission and does not consider strain 1 from bOPV when simulating LPV type 2 transmission.

Age groups and subpopulations: The studied population is stratified by non-overlapping age groups (AGs; $a = 1, \ldots, n_a$) and subpopulations (SPs; $s = 1, \ldots, n_s$) based on geography, vaccination coverage, and accessibility. The vaccination coverage is the estimated percentage of individuals who have received poliovirus vaccines from EI and/or SIAs. The accessibility is evaluated by the probability that the poliovirus vaccines can be delivered and administered. Both n_a and n_s depend on the studied population. For instance, the age-dependent schedule of EI impacts the value of n_a.

Compartments: $S_{i,a,s}$ and $H_{i,a,s}$ correspond to (partially) susceptible and IPV-injected individuals, respectively, in IG i, AG a, and 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 IG i, infected by LPV_j, and in AG a and SP s. D corresponds to dead individuals.

Transitions between compartments

Transitions between compartments happen due to infection, vaccination through EI or SIAs, disease dynamics (e.g., recovery from infection), virus reversion, waning of immunity (see Fig. 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 AG a and SP s ($\lambda_{j,a,s}$) and the relative susceptibility of individuals in IG i (σ_i).

The $\lambda_{j,a,s}$ depends on the basic reproductive number of LPV_j (R_{0_j}) and the proportion of infectious individuals who can spread LPV_j to susceptible individuals in AG a and SP s, denoted by $EIP_{j,a,s} = \frac{\sum_{s'=1}^{n_s}\left\{\sum_{a'=1}^{n_a}\left[\sum_{i=0}^{7}\left(I_{i,j,a',s'}\times\pi_i\times\theta_{a'}\right)\times\beta^{A}_{a'a}\times\beta^{S}_{s's}\right]\right\}}{N^{s}_{a}}$. In the equation of $EIP_{j,a,s}$, π_i refers to the relative infectiousness of individuals in IG i; N^{s}_{a} refers to the number of individuals in AG a and SP s; $\theta_{a'}$ refers to the relative ability to transmit viruses (i.e., the age-based transmissibility) by individuals in AG a' (compared to that of individuals in age groups <5 years) [26]; $\beta^{A}_{a'a}$ refers to the proportion of mixing from AG a' to AG a (see Supplemental Materials A1); $\beta^{S}_{s's}$ refers to the proportion of mixing from SP s' to SP s, which is specified by the mixing matrix among subpopulations.

Since differential-equation-based models maintain very small fractional numbers of infectious individuals (and therefore very small fractional numbers of infections) when in fact the virus dies out [20], our model includes a die-out threshold (EIP^{*}) to force die-out of transmission [27]. When $EIP_{j,a,s} < EIP^{*}$, the model sets $\lambda_{j,a,s}$ to 0, which indicates die-out of currently spreading LPV_j in AG a and SP s.

The model also considers seasonal changes of R_{0_j} that depend on the studied population (e.g., through the income level and the temperate/nontemperate climate [20,28]; see Supplemental Materials A1).

Vaccination through SIAs: Individuals in $S_{i,a,s}$ transition to $E_{i,0,a,s}$, $E_{i,1,a,s}$, and $H_{i,a,s}$, based on the effective vaccination coverage of nOPV2, Sabin-strain OPV, and IPV through SIAs in AG a and SP s, respectively.

The model uses $f^{v}_{a,s}$ to denote the effective coverage of vaccine v through SIAs in AG a and SP s with $v = 0$ (nOPV2), 1 (Sabin-strain OPV), and 2 (IPV). The $f^{v}_{a,s}$ depends on the implementation period and the coverage of SIAs using vaccine v in AG a and SP s, and the efficacy of vaccine v (see Supplemental Materials A1).

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

Virus reversion: For $j = 1,\ldots,19$, 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, based on $1/\varepsilon$ where ε denotes the average time for virus strain LPV_j reverting to LPV_{j+1}.

Aging and vaccination through EI: For $a = 1,\ldots,n_a - 1$, 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, based on $1/w_a$. The w_a denotes the "width" of AG a, which is defined as the number of days contained by AG a [19,20]. For

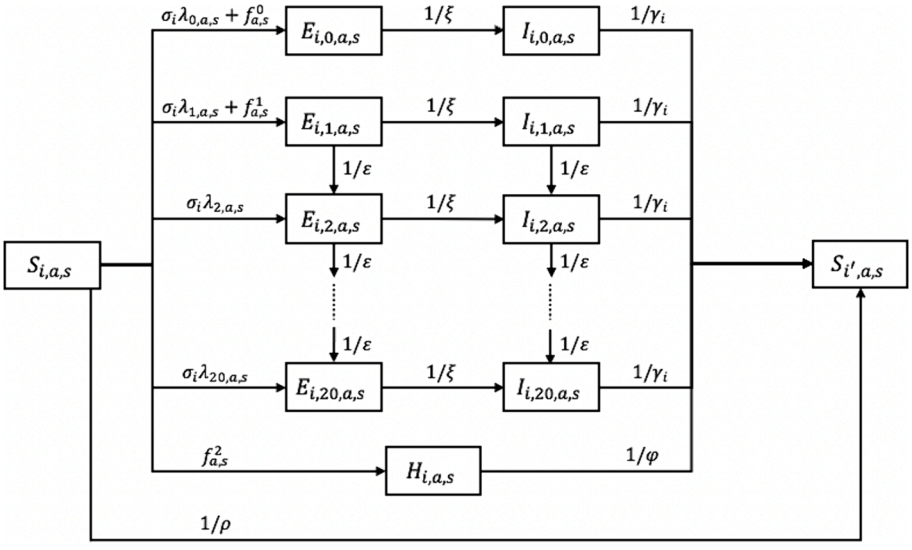

Fig. 1. Transitions among the susceptible (S), exposed (E), infectious (I), and inactivated poliovirus vaccine (IPV)-injected (H) compartments due to infection, vaccination through supplementary immunization activities, disease dynamics, virus reversion (through strains $j = 1, \ldots, 20$), and waning immunity for immunity group i. Transitions due to vaccination through essential immunization, aging, birth, and death are not shown.

example, if $a = 1$ includes children aged 1 year, then the value of $w_{a=1}$ is 365 days.

The model uses $e^{v}_{a,s}$ to denote the effective vaccination percentage of the EI (in SP s) that uses vaccine v ($v = 0, 1, 2$) to vaccinate susceptible individuals when they reach AG a [20]. Therefore, among individuals in $S_{i,a,s}$ that transition to AG $a+1$ (based on $1/w_a$), the proportions $e^{0}_{a+1,s}$, $e^{1}_{a+1,s}$, and $e^{2}_{a+1,s}$ 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 $1-\sum_{v=0}^{2} e^{v}_{a+1,s}$ of them transition to $S_{i,a+1,s}$. The $e^{v}_{a,s}$ depends on coverage and efficacy of the vaccine v in EI (see Supplemental Materials A1). The coverage of vaccine v in EI is estimated based on the available data on EI vaccination rates (e.g., the Demographic and Health Surveys [29]) in the studied population.

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

Disease dynamics: Individuals in $I_{i,j,a,s}$ transition to $S_{i',a,s}$ based on $1/\gamma_i$ where γ_i denotes the duration of being infectious for individuals in IG i.

Individuals in $H_{i,a,s}$ transition to $S_{i',a,s}$ based on $1/\varphi$ where φ denotes the duration of IPV immunity delay. The duration of IPV immunity delay represents the brief period following receipt of one dose of IPV to the acquisition of the immunity induced by this dose of IPV [20].

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

(3) Transitions due to birth and death:

Among newborns of SP s that enter the model based on the birth rate b, the proportions $e^{0}_{1,s}$, $e^{1}_{1,s}$, and $e^{2}_{1,s}$ of them transition to $E_{0,0,1,s}$, $E_{0,1,1,s}$, and $H_{0,1,s}$, respectively, and the proportion $1-\sum_{v=0}^{2} e^{v}_{1,s}$ 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 based on the death rate μ.

Other dynamics

The model allows for the importation of LPV_j into AG 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 [30,31], by specifying the percentage decrease in population mixing and the start and end days of the decrease (see equations in Supplemental Materials A1). Each model run begins with an *initial condition*, which specifies the number of individuals in each compartment.

Outcome measures

Outcome measures from the model include:

- **Weekly case counts:** the number of weekly new cVDPV paralytic cases.
- **Outbreak size**: the total number of cVDPV paralytic cases.
- **Die-out date**: the first week when the weekly case counts become 0.

The cVDPV paralytic cases in AG a and SP s (see Supplemental Materials A1) 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 type 2). The model generates no cases from LPV_{20} infections of (partially) susceptible individuals in IGs 1–7 since we assume the immunity provides protection against paralysis [20,31].

In AG a and SP s, the simulated weekly case counts become 0 only after the proportion of infectious individuals who can spread LPV_{20} to susceptible individuals in AG a and SP s ($EIP_{20,a,s}$) becomes less than the die-out threshold (EIP^{*}). Therefore, when the simulated weekly case counts become 0 in AG a and SP s, die-out of cVDPV happens (and the transmission of cVDPV stops) in AG a and SP s. Similarly, when the simulated weekly case counts become 0 across all age groups in SP s, die-out of cVDPV happens in SP s.

Supplemental Materials A1 provides more details of the model, including all mathematical indices, notations, and equations.

Case study: Post-switch cVDPV2 outbreaks in Nigeria

Our case study focused on Nigeria which had multiple large cVDPV2 outbreaks after OPV2 cessation. From May 2016 to December 2023, there were 609 cVDPV2 paralytic cases, accounting for around 18% of global cVDPV2 paralytic cases during the same time period.

We selected the Northwest and Northeast geopolitical zones of Nigeria (see Fig. 2) for model development and validation due to the high level of cVDPV2 transmission and the related challenges in these zones [23], including the historically dominant use of vaccines containing no type 2 viruses [32,33], low-coverage EI (which comprises of two IPV doses against type 2 as of July 2021) and SIAs [10,14,23,32], insurgency [12,34], and vaccine hesitancy [35]. The COVID-19 pandemic had mixed effects on Northwest and Northeast Nigeria's cVDPV2 outbreaks by delaying SIAs and decreasing surveillance sensitivity, but also reducing population mixing (especially in 2020) by some lockdown measures [36–38]. Aside from internal transmission, cVDPV2 was also potentially transmitted from other regions in Nigeria (e.g., Niger or Plateau states) to Northwest and Northeast Nigeria, mostly likely in late 2020/early 2021, based on experts' interpretations of the genomic sequencing of reported cVDPV2 isolates [Jaume Jorba; personal communication].

cVDPV2 paralytic case data

Data in the case study of Northwest and Northeast Nigeria include confirmed paralytic poliomyelitis cases caused by cVDPV2 infections as detected through acute flaccid paralysis (AFP) surveillance after OPV2 cessation (through the WHO POLIS database available to GPEI partner agencies and modeling collaborators). We focused on reported cVDPV2 paralytic cases with onset between January 1, 2018, and December 31,

Table 1
Feasible transitions from the immunity group i to the 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

Compartments: S = susceptible; I= infectious; H= inactivated poliovirus vaccine (IPV)-injected.

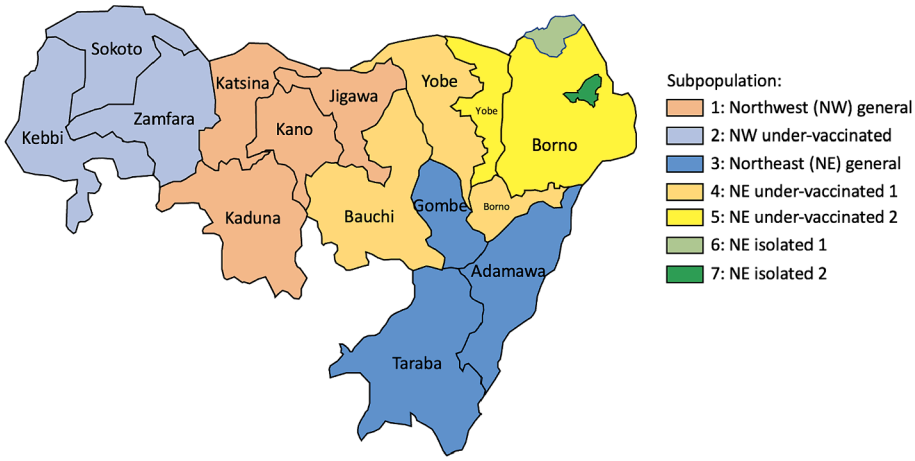

Fig. 2. The model's seven subpopulations of Northwest and Northeast Nigeria.

2021 (as of February 10, 2022), with data from January 1, 2018, to August 1, 2021 for model calibration (i.e., calibration period), and data from August 2 to December 31, 2021 for model validation (i.e., validation period).

Model setup

The model inputs for Northwest and Northeast Nigeria were estimated based on prior polio reports on cVPDV2 epidemiology and modeling studies [15,19,20,22,23,39–45], demographic data [46–54], and data on AFP cases and SIAs available in POLIS. We defined 7 subpopulations (see Fig. 2) with SPs 1–2 in Northwest Nigeria and SPs 3–7 in Northeast Nigeria. Given the historic estimated coverage of EI [46,52–54] and SIAs, and accessibility [unpublished data; personal communication], SPs 1 and 3 are "general" (i.e., higher 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. Eleven 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 $\geq$ 40 years) based on prior modeling studies of polio in Nigeria [22,23]. The values of these and other model inputs are in Tables A2.1 and A2.2 in Supplemental Materials A2, including estimates of coverage and efficacy of IPV doses in EI.

Model calibration and validation

We calibrated the model to the weekly incidence data of the calibration period stratified by subpopulations and the age groups 0–4 years and $\geq$ 5 years. The calibrated parameters include: (i) mixing matrix among subpopulations; (ii) age-based transmissibility; (iii) percentage decrease in population mixing (due to COVID-19) and start and end days of the percentage decrease in population mixing; (iv) cVDPV2 importation; (v) die-out threshold; and (vi) 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, of which 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 $\geq$ 5 years to that of the data of the validation period.

Supplemental Materials A2 provides additional details on model calibration and validation, including estimates of the calibrated parameters and the coverage of SIAs implemented in the validation period.

Simulating the cVDPV2 outbreaks in 2022–2023

Using the validated model, we evaluated the impact of various outbreak response scenarios, by simulating cVDPV2 transmission in the prediction period from January 1, 2022 to December 31, 2023 under each scenario.

The outbreak response scenarios include (see Fig. 3):

- **No response (NR)**: No SIAs since January 1, 2022.
- **Planned SIAs (P-SIAs)**: Two rounds of outbreak response SIAs (oSIAs) target SPs 1, 3, 4, and 5 in 2022 with a 4-week interval between the two rounds, according to the SIA calendar of Nigeria as of January 21, 2022. Both rounds 1 and 2 include two phases. Phase 1 includes two *planned* oSIAs (SIAs 1a and 2a) that target SPs 1, 3 (Gombe), 4, and 5. Phase 2 includes two *planned* oSIAs (SIAs 1b and 2b) that target SP 3 (Adamawa and Taraba).
- **Scenario 1:** Two rounds of oSIAs target SPs 1–5 in 2022 with a 4-week interval between the two rounds. Both rounds 1 and 2 include three phases. Phases 1 and 2 are the same as P-SIAs. Phase 3 includes two *hypothetical* oSIAs (i.e., not in Nigeria's SIA calendar; SIAs 1c and 2c) that target SP 2.
- **Scenario 2**: Three rounds of oSIAs target SPs 1–5 in 2022. Rounds 1 and 2 are the same as in Scenario 1. Round 3 includes one *hypothetical* oSIA (SIA 3) that targets SPs 1–5. There is a 6-week interval between Rounds 2 and 3.
- **Scenario 3**: Four rounds of oSIAs target SPs 1–5 in 2022. Rounds 1–3 are the same as in Scenario 2. Round 4 includes one *hypothetical* oSIA (SIA 4) that targets SPs 1–5. There is a 4-week interval between Rounds 3 and 4.
- **Scenario 4**: Similar to Scenario 1 but the start days of SIAs 1c and 2c are 6 weeks earlier than in Scenario 1.
- **Scenario 5**: Similar to Scenario 2 but the start days of SIAs 1c, 2c, and 3 are 6 weeks earlier than in Scenario 2.
- **Scenario 6**: Similar to Scenario 3 but the start days of SIAs 1c, 2c, 3, and 4 are 6 weeks earlier than in Scenario 3.

Based on the guidance in the standard operating procedures (SOPs) [17], we assumed that all oSIAs used nOPV2, targeted individuals aged 0–4 years, had a duration of 4 days, and achieved 90% coverage in target areas. We set up at least a 4-week interval between each two successive rounds of oSIAs, being consistent with the SOPs and the Emergency Use Listing requirements for the use of nOPV2 [17]. Fig. 3 summarizes the start dates of all oSIAs. Fig. 4 summarizes the number of nOPV2 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 oSIAs did not target SP 2 while SP 2 experienced cVDPV2

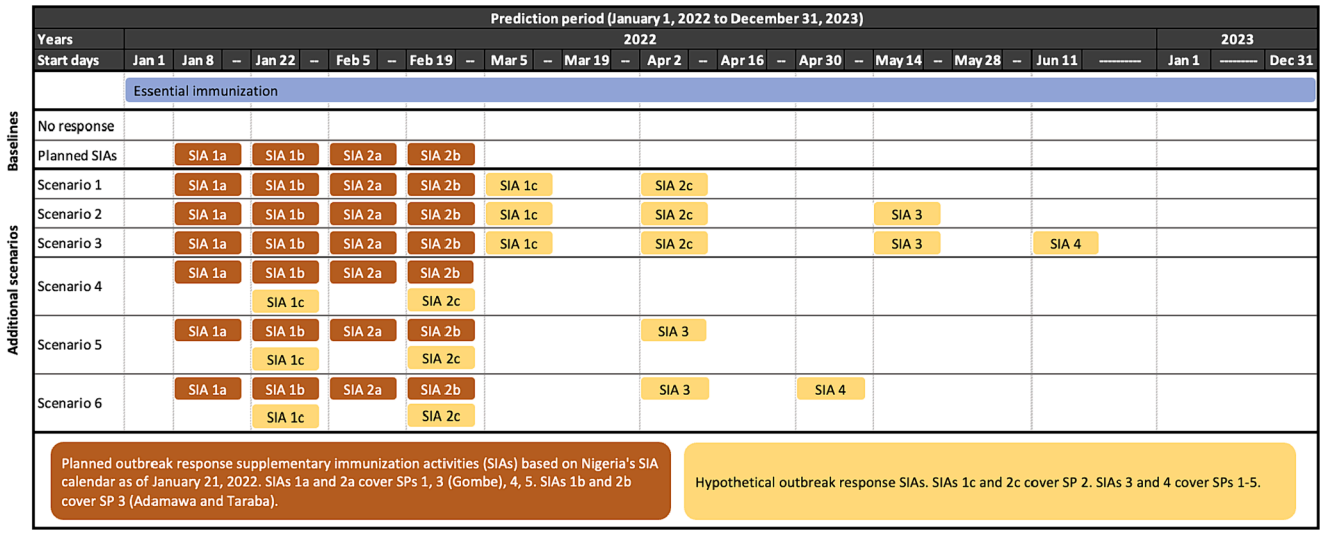

Fig. 3. Outbreak response scenarios tested in the prediction period (January 1, 2022 to December 31, 2023).

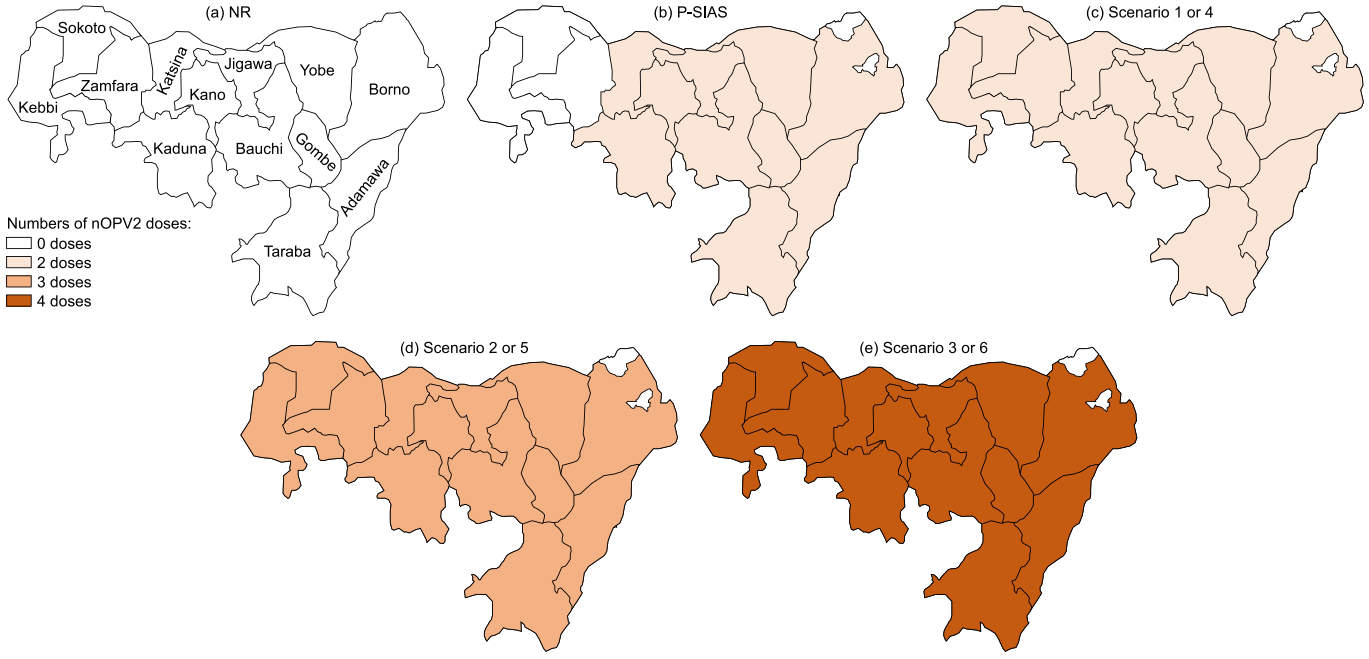

Fig. 4. Numbers of nOPV2 (novel type 2-containing oral poliovirus vaccine) doses in the prediction period (January 1, 2022 to December 31, 2023) under (a) NR (no response); (b) P-SIAs (planned SIAs); (c) Scenario 1 or 4; (d) Scenario 2 or 5; and (e) Scenario 3 or 6.

outbreaks in 2021. Scenario 1 complies with the requirement in SOPs that at least two rounds of high-quality large-scale oSIAs (≥ 90% of children vaccinated) are conducted in outbreak-affected areas. We simulated Scenarios 2 and 3 to study the need for additional oSIA rounds (i.e., SIAs 3 and 4) to ensure die-out of cVDPV2 in Northwest and Northeast Nigeria after the first two rounds of high-quality large-scale oSIAs (i.e., the SIAs 1 and 2). We included Scenarios 4–6 to examine the impact on cVDPV2 transmission of completing the first two rounds of oSIAs at an earlier time point and to assess the need for additional rounds. We compared the outcomes (i.e., weekly case counts, outbreak size, and die-out date) of NR, P-SIAs, and Scenarios 1–6 in the prediction period. Supplemental Materials A2 provides additional details of tested scenarios.

Through the prediction period, we assumed that EI remained constant as in the model setup (see Section Model setup). More specifically, for immunity against type 2 poliovirus in Nigeria's EI, the model included two IPV doses targeted for individuals transitioning from age group 0–2 months to age group 3–11 months [20]. See Section A2.1 in Supplemental Materials A2 for more details on how the model incorporates Nigeria's EI against type 2 poliovirus.

Results

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

For the results of the prediction period, Fig. 5 shows the weekly case counts (from all subpopulations) under NR, P-SIAs, and Scenarios 1 and 4. Table 3 and Table 4 summarize the outbreak sizes and the die-out dates of all tested scenarios, respectively. Supplemental Materials A3

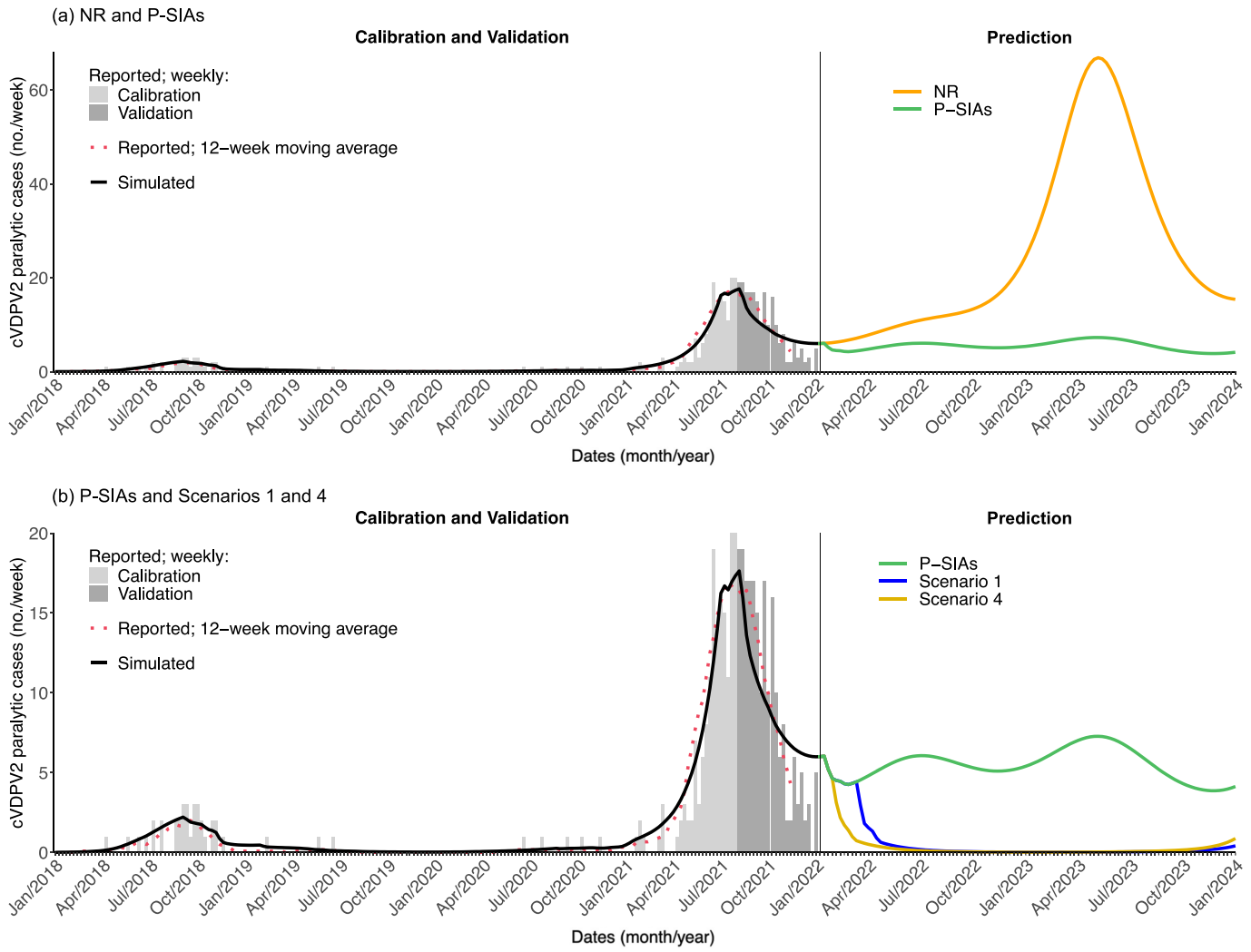

Fig. 5. The weekly case counts from all subpopulations in the calibration period (January 1, 2018 to August 1, 2021) and the validation period (August 2 to December 31, 2021), and in the prediction period (January 1, 2022 to December 31, 2023) under (a) NR (no response) and P-SIAs (planned supplementary immunization activities); and (b) P-SIAs and Scenarios 1 and 4.

provides subpopulation-level weekly case counts for all tested scenarios. No cases were predicted in SPs 6 and 7 in the prediction period. The weekly case counts from all subpopulations in Scenarios 2 and 3 (Scenarios 5 and 6) were similar to that in Scenario 1 (Scenario 4).

During the prediction period, the NR scenario resulted in a cumulative 2,641 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 1,208 cases, 551 cases, 376 cases, 329 cases, and 177 cases, respectively (see Table 3).

Implementing the two rounds of 90%-coverage oSIAs 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 3–5 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 oSIAs but starting oSIAs 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) did not significantly change the outbreak sizes in SPs 1–5, but it achieved die-out of cVDPV2 in all SPs (and therefore stopped the transmission in Northwest and Northeast Nigeria) in the week of January 23, 2023. Adding only one additional round (i.e., SIA 3) after the first two rounds (as in Scenario 2) did not achieve die-out in SP 2.

Compared to Scenario 1, completing the two rounds that targeted SPs 1–5 6 weeks earlier by starting oSIAs in SP 2 at the same time with SIAs 1b and 2b in Phase 2 (as in Scenario 4) further decreased the outbreak size in SP 2 (i.e., 29 cases in Scenario 4 compared to 49 cases in Scenario 1). Adding one and two additional rounds based on Scenario 4, respectively, Scenarios 5 and 6 did not significantly change the outbreak sizes in SPs 1–5 compared to Scenario 4. However, compared to Scenario 2, Scenario 5 stopped the transmission in Northwest and Northeast Nigeria in the week of February 6, 2023. Compared to Scenario 3, Scenario 6 stopped the transmission 8 weeks earlier (i.e., in the week of November 28, 2022). In Scenarios 3, 5, and 6 where die-out of cVDPV2 happened in all SPs, the last die-out happened in SP 2. Overall, additional rounds of oSIAs aside from the initial two rounds and/or earlier start dates of the initial two rounds were needed to reach die-out of cVDPV2 transmission.

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

Subpopulations[1] 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
All	21	23	0	2	0	0	167	167
SP 2:								
0–4 years	0	0	1	1	5	6	100	94
≥ 5 years	0	0	0	1	0	0	5	5
All	0	0	1	2	5	6	105	99
SP 3:								
0–4 years	0	1	0	0	0	0	26	30
≥ 5 years	1	0	0	0	0	0	6	4
All	1	1	0	0	0	0	32	34
SP 4:								
0–4 years	0	1	0	0	0	0	38	36
≥ 5 years	0	1	0	0	0	0	1	3
All	0	2	0	0	0	0	39	39
SP 5:								
0–4 years	10	11	1	1	0	0	32	32
≥ 5 years	1	1	1	1	0	0	2	3
All	11	12	2	2	0	0	34	35
SP 6:								
0–4 years	0	0	0	0	0	0	0	0
≥ 5 years	0	0	0	0	0	0	0	0
All	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
All	0	0	0	0	0	0	0	0
All SPs								
0–4 years	31	33	2	3	5	6	343	335
≥ 5 years	2	5	1	3	0	0	34	39
All	33	38	3	6	5	6	377	374

* R = reported; S = simulated; reported cases are from the AFP surveillance data as of February 10, 2022 (available through POLIS).
[1] See Fig. 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 (see Figure A3.2 in Supplemental Materials A3).

Discussion

The cVDPV2 outbreaks reported in more than 30 countries since May 2016 indicated not only the failure of pre-switch SIAs in substantially increasing population immunity against type 2 in all communities [14] but also the persistent challenges including low-coverage EI and SIAs in the post-switch era. Mitigating future risks of cVDPV2 transmission necessitates a careful evaluation of how vaccinations through EI and SIAs influence the outbreaks. Given that many African countries have had persistent cVDPV2 transmission and have borne substantially higher case burdens compared to countries of other regions, there is a need to fully characterize these areas and recognize context-specific interventions [55].

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

Scenarios[1]	Outbreak sizes					
	SP 1	SP 2	SP 3	SP 4	SP 5	All SPs[2]
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
Scenario 4	8	29	2	2	2	43
Scenario 5*	8	21	2	2	1	34
Scenario 6*	8	21	2	2	1	34

* Scenarios that achieved die-out of circulating vaccine-derived poliovirus type 2 in all SPs.
[1] See Fig. 3 and Fig. 4.
[2] See Fig. 2.

In this study, we developed a differential equation-based model of live poliovirus transmission. We validated the model using data from a representative African area, Northwest and Northeast Nigeria. We demonstrated the model's ability to simulate cases that were consistent with reported cases in terms of case counts, spatiotemporal distribution, and age distribution. Our prediction of cVDPV2 outbreaks in 2022 and 2023 under various outbreak response scenarios showed that: (i) substantial cVDPV2 transmission would occur if there was only EI (with limited coverage of the two IPV doses) but no oSIAs (i.e., no response), and (ii) implementing the oSIAs as planned in Nigeria's SIA calendar would reduce case counts by 79% compared to no response. With four rounds of 90%-coverage nOPV2 oSIAs that targeted all non-isolated areas and an interval of 4–6 weeks between two successive rounds, there would be a chance of apparently stopping cVDPV2 outbreaks in Northwest and Northeast Nigeria by November 2022 (as in Scenario 6) or by January 2023 (as in Scenario 3).

When no SIAs were implemented in the prediction period (i.e., no response), although there was a decrease in weekly case counts in late 2023 after depletion in the number of unimmunized susceptible individuals, case counts subsequently increased after the accumulation of unimmunized newborns. The planned nOPV2 oSIAs did not stop the outbreaks since i) they did not target SP 2 (i.e., Kebbi, Sokoto, and Zamfara) while the model predicted continued transmission in SP 2 and ii) they barely impacted the outbreaks in SP 2 given the limited mixing between SP 2 and SPs 1, 3, 4, and 5 (decided by model calibration).

Persistent transmission in under-vaccinated areas, especially in SP 2, largely delayed the progression towards stopping outbreaks. This finding corroborates previous findings that the role of under-vaccinated subpopulations in sustaining polio transmission [21,22,27,56–59]. Compared to SPs 1, 3, 4, and 5, SP 2 required 1–2 more rounds of nOPV2 oSIAs to stop the transmission and achieved die-out of cVDPV2 transmission 7–21 weeks later (see results of Scenarios 3, 5, and 6 in Table 4).

Consistent with previous studies which pointed out the great impact of quickly responding to outbreaks [21,26,31,42,43,60], completing the first two rounds of oSIAs at an earlier time greatly reduced outbreak size (especially in SP 2) and stopped outbreaks earlier in Northwest and Northeast Nigeria with fewer rounds of oSIAs. We also highlighted the importance of additional rounds of oSIAs in ensuring die-out in Northwest and Northeast Nigeria, even though these additional rounds did not further decrease the outbreak size after the first two rounds. When the first two rounds were completed in late February 2022, adding one additional round stopped cVDPV2 transmission in Northwest and Northeast Nigeria. However, when the first two rounds were completed in early April 2022, it took two additional rounds to achieve die-out in all SPs.

There are several limitations of our modeling approaches. First, given the large space of possible values and interdependence among

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

Scenarios[1]	Die-out dates					
	SP 1	SP 2	SP 3	SP 4	SP 5	All SPs[2]
No response	–[3]	–	–	–	–	–
Planned SIAs	–	–	Dec-26–2022	Dec-05–2022	–	–
Scenario 1	Dec-05–2022	–	Dec-19–2022	Nov-28–2022	–	–
Scenario 2	Sep-19–2022	–	Sep-19–2022	Sep-12–2022	Nov-07–2022	–
Scenario 3*	Sep-05–2022	Jan-23–2023	Sep-05–2022	Aug-29–2022	Oct-10–2022	Jan-23–2023
Scenario 4	Dec-05–2022	–	Dec-19–2022	Nov-28–2022	–	–
Scenario 5*	Sep-19–2022	Feb-06–2023	Sep-19–2022	Sep-12–2022	Nov-07–2022	Feb-06–2023
Scenario 6*	Sep-05–2022	Nov-28–2022	Sep-05–2022	Aug-29–2022	Oct-10–2022	Nov-28–2022

* Scenarios that achieved die-out of circulating vaccine-derived poliovirus type 2 in all SPs.
[1] See Fig. 3 and Fig. 4.
[2] See Fig. 2.
[3] Not applicable.

model parameters, we did not expect our iterative calibration process to yield the optimal set of estimates. However, we generated a set of values that could reproduce the cVDPV2 transmission in Northwest and Northeast Nigeria. Second, the current model only considers AFP surveillance (i.e., the simulated weekly case counts) but not environmental surveillance (ES) which tests poliovirus in sewage samples. ES is limited in geographic scope, generally covering populations living in urban areas, but is informative, especially in detecting asymptomatic transmission. For example, in Scenarios 1 and 4, after the two rounds of oSIAs 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 ES further found no cVDPV2 in SPs 1, 3, and 4, then the two additional rounds of oSIAs (i.e., SIAs 3 and 4) might only need to cover SPs 2 and 5 to save limited resources (e.g., vaccines). Future modeling work could incorporate ES and its impact on planning outbreak response efforts. Third, the model does not automatically simulate poliovirus importation unless an importation is specified. When the local transmission has been largely mitigated but the areas remain at a low-level population immunity, an importation could elicit another outbreak, require additional vaccination efforts, and therefore delay the progress towards polio eradication in these areas. Future works could parameterize automatic importation if certain patterns of importation are observed in practice. Fourth, with a simplified population mixing, our model does not capture some micro-dynamics influencing die-out of viruses [23,61] or differentiate household and community transmission [20]. An agent-based model could overcome this limitation. However, using such a model may lead to challenges during calibration, since it will require a large number of parameters to characterize the network structure of the studied population [62].

There are also some limitations of our case study. First, we assumed constant accessibility of the subpopulations for immunization activities, when, in reality, the accessibility of some local government areas (LGAs) in a subpopulation can change over time based on the security situation [12,63]. This change in accessibility potentially influences both vaccination efforts and population mixing and thus local cVDPV2 transmission. However, limited data exist to assess LGAs' changing accessibility, and using constant accessibility at the subpopulation level still provides a reasonable model fit. Second, we stratified subpopulations by grouping Northwest and Northeast Nigeria's states. This is a simplification of the actual situation given the heterogeneities within states, like the different vaccination rates of an SIA across LGAs. Further research could model the population of Northwest and Northeast Nigeria with greater granularity when corresponding data (e.g., LGA-level vaccination rates and population sizes) are available. Third, we assumed a 90% coverage for all oSIAs implemented in the prediction period. In real life, achieving a 90%-coverage oSIA could be difficult in Northwest and Northeast Nigeria, given limitations like children chronically missed by vaccinations [20], vaccine hesitancy [35,64], and inaccessibility/insecurity [12,63,65]. However, modeling with this assumption was still informative, because we were able to investigate whether the interruption of cVDPV2 outbreaks was achievable in an optimistic scenario in which at least 90% of children aged 0–4 years were vaccinated. It also highlighted the gap in Northwest and Northeast Nigeria's population immunity against type 2, especially in greatly under-vaccinated areas like Kebbi, Sokoto, and Zamfara. Fourth, we assumed that there were cVDPV2 transmissions from outside of Northwest and Northeast Nigeria to some of our studied subpopulations in late 2020/early 2021, based on experts' interpretations of the genomic sequencing of cVDPV2 isolates. This assumption led to a model fit that was consistent with the reported cases. If the observed cases in those subpopulations were due to internal transmission within Northwest and Northeast Nigeria, the model might need to be recalibrated.

With the goal to "stop cVDPV transmission and prevent outbreaks in non-endemic countries" in the Polio Eradication Strategy 2022 – 2026 [66], stakeholders need to revisit the guidance in SOPs in terms of the number of oSIAs initially planned and the endeavor to reach SOP timeline targets. Using nOPV2 provides a chance for effective vaccinations with markedly reduced risk of seeding new cVDPV2 emergence. However, as evidenced by persistent outbreaks in 2021 and 2022 to date [67], a safer vaccine does not compensate for low-quality outbreak response vaccination campaigns which 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 to prevent possibly prolonged transmission in these areas.

In the future, our model can be used to assess the interaction between EI and SIAs, evaluate the tradeoffs between factors of SIAs (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., types 1 and 2 in Malawi and Mozambique [67]), our modeling framework can be adapted and then used to guide the decision-making on vaccination strategies to balance the priorities of eliminating the transmission of different serotypes.

Declarations

Consent for publication

All authors have approved the final article for publication.

Availability of data and material

All of the data that the authors can share is available in the public domain and appropriate citations are provided. Data available in the Polio Information System are owned by the World Health Organization

and shared among primary partners of Global Polio Eradication Initiative including the US Centers for Disease Control and Prevention and modeling collaborators.

Code availability

Upon request.

CRediT authorship contribution statement

Yuming Sun: Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Pinar Keskinocak:** Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Lauren N. Steimle:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Stephanie D. Kovacs:** Conceptualization, Data curation, Supervision, Validation, Writing – review & editing. **Steven G. Wassilak:** Conceptualization, Data curation, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Pinar Keskinocak reports financial support was provided by Centers for Disease Control and Prevention. Lauren N. Steimle reports financial support was provided by Centers for Disease Control and Prevention. Yuming Sun reports financial support was provided by Centers for Disease Control and Prevention. Pinar Keskinocak reports a relationship with Merck & Co Inc that includes: funding grants.

Data availability

All of the data that the authors can share is available in the public domain and appropriate citations are provided. Data available in the Polio Information System are owned by the World Health Organization and shared among primary partners of the Global Polio Eradication Initiative including the US Centers for Disease Control and Prevention and modeling collaborators.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2024.100476.

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