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Modeling Poliovirus Transmission in Borno and Yobe, Northeast Nigeria

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Abstract

Beginning in 2013, multiple local government areas (LGAs) in Borno and Yobe in northeast Nigeria and other parts of the Lake Chad basin experienced a violent insurgency that resulted in substantial numbers of isolated and displaced people. Northeast Nigeria represents the last known reservoir country of wild poliovirus (WPV) transmission in Africa, with detection of paralytic cases caused by serotype 1 WPV in 2016 in Borno and serotype 3 WPV in late 2012. Parts of Borno and Yobe are also problematic areas for transmission of serotype 2 circulating vaccine-derived polioviruses, and they continue to face challenges associated with conflict and inadequate health services in security-compromised areas that limit both immunization and surveillance activities. We model poliovirus transmission of all 3 serotypes for Borno and Yobe using a deterministic differential-equation based model that includes four subpopulations to account for limitations in access to immunization services and dynamic restrictions in population mixing. We find that accessibility issues and insufficient immunization allow for prolonged poliovirus transmission and potential undetected paralytic cases, although as of the end of 2019, including responsive program activities in the modeling suggest die out of WPV1. Specifically, recent and current efforts to access isolated populations and provide oral poliovirus vaccine continue to reduce the risks of sustained and undetected transmission, although some uncertainty remains. Continued improvement in immunization and surveillance in the isolated subpopulations should minimize these risks. Stochastic modeling can build on this analysis to characterize the implications for undetected transmission and confidence about no circulation.

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Declaration of interest

None.

Keywords

polio; eradication; Nigeria

Introduction

As the polio endgame continues, the Global Polio Eradication Initiative (GPEI) must aggressively manage program weaknesses in immunization and surveillance and fully characterize the last remaining reservoirs of poliovirus transmission to prepare for global certification of eradication (Barrett, 2009). At the time of certification, the areas with the most recent cases will have the shortest times since the last reported case or detected signal of transmission from environmental surveillance. Delays in polio eradication, program fatigue, and other challenges can contribute to the identification of program weaknesses only after outbreaks occur (i.e., once prevention is too late). Following intensive efforts to stop poliovirus transmission in Nigeria after July 2014, the African continent experienced an extended period of no detections of any paralytic cases caused by wild polioviruses (WPVs) despite active surveillance in most areas.

At the same time, beginning in 2013 and peaking in 2015, large areas in Borno and Yobe states in northeast Nigeria came under the control of insurgents who disrupted health systems and polio eradication program activities. This limited polio program access and reduced performance in these areas, and consequently led to ongoing WPV serotype 1 (WPV1) transmission. Surveillance activities only identified and reported these cases in August 2016 after some previously inaccessible areas opened up. Prior to early-2016, monitoring studies reported over a million people as internally displaced from insurgent-held areas in Borno, primarily into other parts of Borno (United Nations Office for the Coordination of Humanitarian Affairs, 2016a), and notable displacement in affected parts of Yobe (United Nations Office for the Coordination of Humanitarian Affairs, 2016b), with some displacement occurring throughout the Lake Chad basin. Although health authorities initially estimated that relatively few children under 5 years of age remained in those areas in early 2016, satellite imagery that supported the assessment of the settlements that remained potentially inhabited suggested that 130,000–210,000 of the 468,000 children under 5 years of age who remained in isolated areas in 2016 remained unreached by vaccination in 2017 (Bolu et al., 2018).

In August 2016, Nigeria reported the detection of two polio cases caused by WPV1 in Borno with onset in July (Nnadi et al., 2017; World Health Organization, 2016a) and subsequently, two additional cases with onset in August (Nnadi et al., 2017). The unexpected detection of cases in 2016 after 2 years with no reported cases, dashed hopes that confidence would be high enough for the African Regional Certification Commission to certify the African region of the World Health Organization (WHO) in 2017 as the fifth of the 6 WHO regions to successfully eradicate WPVs (i.e., 3 years after the reported cases in 2014). Laboratory analyses estimated that the 2016 isolated polioviruses genetically split from the other 2013 Borno isolates sometime in 2012 and suggested undetected circulation for at least 4 years,

which implied quality and program access issues for both immunization and surveillance activities in inaccessible parts of Borno (Nnadi et al., 2017).

With respect to serotypes 2 and 3, Borno and Yobe also represent important areas. Notably, Borno and Yobe reported the last polio cases caused by WPV serotype 3 (WPV3) in Nigeria and in the WHO African Region, with onset of paralysis of the last case on November 10, 2012 (Kew et al., 2014). Ongoing issues with the poor quality of immunization and surveillance activities in inaccessible areas in Borno and Yobe raised some concerns related to the global certification of the eradication of WPV3, despite 3 years with no reported cases as of November 2015 (World Health Organization, 2016b). However, nearly 7 years after the latest reported WPV3 case in Borno, the Global Certification Commission certified the eradication of global transmission of indigenous WPV3 in October 2019 (World Health Organization, 2019a).

The conditions in parts of Nigeria, specifically insurgency and inaccessibility in some areas, also made Nigeria one of the most challenging areas for successful globally-coordinated cessation of the use of oral poliovirus vaccine (OPV) serotype 2 (OPV2), and thus, a high-risk area for circulating vaccine-derived polioviruses (cVDPVs) caused by serotype 2 (cVDPV2s). Nigeria introduced monovalent OPV (mOPV) containing only serotype 1 (mOPV1) or serotype 3 (mOPV3) for some of its supplemental immunization activities (SIAs) after 2005, then bivalent OPV (bOPV, containing both serotypes 1 and 3) in 2010. The immunity gap created by SIAs that predominantly used OPV formulations that did not contain serotype 2 and very low routine immunization coverage with trivalent OPV (tOPV) in northern states led to widespread transmission of cVDPV2s starting in 2005 (Burns et al., 2013; Wassilak et al., 2011), which continued through 2015 (Diop et al., 2015). Nigeria performed tOPV SIAs throughout the country prior to OPV2 cessation to boost population immunity to transmission in all communities and to try to stop and prevent cVDPV2s (Thompson & Duintjer Tebbens, 2014). However, Nigeria faced challenges in raising population immunity to transmission for serotype 2 polioviruses in all areas sufficiently to stop transmission of persistent cVDPV2s prior to OPV2 cessation (Wassilak et al., 2011). Just days after globally-coordinated cessation of OPV2, Nigeria reported the detection of cVDPV2 by environmental surveillance of a sewage specimen collected in March 2016 in Borno that genetically was most closely linked to a May 2014 Borno cVDPV2 virus lineage that originally emerged in Chad in 2012 (Etsano et al., 2016). A few months later, Nigeria reported an unrelated cVDPV2 in Sokoto (a state in northwest Nigeria), which signaled the failure of efforts by Nigeria to perform effective tOPV campaigns prior to OPV2 cessation to sufficiently boost population immunity to transmission in all communities (Blake et al., 2018; Duintjer Tebbens & Thompson, 2017). Stopping the cVDPV2s remains a challenge to date in Nigeria. Successfully stopping cVDPV2 transmission requires the use of serotype 2 monovalent OPV (mOPV2) in high quality immunization activities that achieve high coverage and rapidly raise population immunity to transmission to high levels, and then again stopping its use (Duintjer Tebbens, Pallansch, Wassilak, Cochi, & Thompson, 2016). Nigeria conducted 33 subnational SIAs in various states using mOPV2 with variable quality and scope between mid-2016 and September 2019, which did not stop transmission of cVDPV2 or onward geographic spread (i.e., the cVDPV2 outbreak originating in Jigawa and its spread across Nigeria and subsequently Central and West Africa (Adamu et al., 2019)).

The transmission of OPV2-related viruses thus continued in a population with increasing vulnerability to sustaining serotype 2 live poliovirus transmission (Duintjer Tebbens, Hampton, & Thompson, 2016). The recent global experience with continuing transmission of new, post-switch cVDPV2s raises significant concerns about the success of the April-May 2016 globally-coordinated cessation of OPV2 use.

Recognizing Nigeria as one of the last three remaining polio endemic countries, and the specific challenges in northwest Nigeria (i.e., Jigawa, Kaduna, Kano, Katsina, Kebbi, Sokoto, Zamfara states) related to immunization and surveillance activities, we previously developed a model to characterize poliovirus transmission in northwest Nigeria (Duintjer Tebbens et al., 2014; Duintjer Tebbens et al., 2013; Kalkowska, Duintjer Tebbens, & Thompson, 2014). We identified the need for northwest Nigeria to intensify its immunization efforts, and particularly to increase immunization coverage in under-vaccinated subpopulations (Kalkowska et al., 2014) given the important role of these subpopulations in sustaining transmission (Thompson & Duintjer Tebbens, 2017). The need to better understand the global risks and costs of the polio endgame and to support deliberations about the certification of eradication of WPV1, led to this analysis of transmission modeling focused on northeast Nigeria, and specifically Borno and Yobe.

Methods

We started with a deterministic, differential equation-based (DEB) poliovirus transmission and OPV evolution model developed previously (Duintjer Tebbens et al., 2014; Duintjer Tebbens et al., 2013; Kalkowska et al., 2014), and considered the Nigeria-specific model inputs. Within the northeast Nigeria zone, we focused on only Borno and Yobe states (omitting Bauchi, Gombe, Adamawa, and Taraba states also affected by insurgency in limited areas) and did not consider the neighboring countries in the Lake Chad region. The model divides the population into 8 immunity states (fully susceptible, maternally immune, and six partially immune states resulting from live poliovirus infections and/or successful IPV vaccinations). We model waning of immunity as a 5-stage process, infection as a 6-stage process (i.e., 2 latent and 4 infectious stages) for both fecal-oral and oropharyngeal transmission, and OPV evolution as a 20-stage process (i.e., starting with stage 0 for fully attenuated Sabin strains and progressing to stage 19 for fully reverted cVDPV strains that behave like homotypic WPV) (Kalkowska, Wassilak, Cochi, Pallansch, & Thompson, 2020). We use a model time horizon that extends through the end of 2020.

We reconstructed the history of polio immunization in Borno and Yobe. Prior to 2014, Nigeria relied on OPV exclusively, which included tOPV for routine immunization (RI) and all SIAs before 2006. In 2006, Nigeria began using mOPV1 for some SIAs, which resulted in some immunity gaps for serotypes 2 and 3. Following the observation of WPV3 outbreaks, in 2007 Nigeria began using mOPV3 in some SIAs, which resulted in continued immunity gaps for serotype 2. In 2010, Nigeria began using bivalent OPV (bOPV, containing OPV for serotypes 1 and 3) for most SIAs, but continued to conduct some SIAs with tOPV. In 2015, Nigeria introduced a single dose of IPV into RI, delivered at the same time as the third OPV dose. Nigeria also conducted some SIAs with IPV starting in 2014 and using fractional (one-fifth) dose IPV delivered intradermally starting in 2018.

Table 1 summarizes inputs for Borno and Yobe that remained constant in all model runs. We assumed constant model inputs related to the population structure, poliovirus transmission, and vaccination take rates, and used the same best estimate values for Borno and Yobe (in northeast Nigeria) as we used in an earlier northwest Nigeria model (Kalkowska et al., 2014). Specifically, we adopted the same age group structure and preferential mixing between broad age groups, average WPV1 R_0 with low seasonal variation and small contribution of oropharyngeal transmission to overall poliovirus transmission, average per-dose take rates, IPV introduction time, and the time of the national switch from tOPV to bOPV.

To model poliovirus transmission specifically in Borno and Yobe, first we estimated the population size based on the most recent available census information (Nigeria/Africa Masterweb, 2013), and we scale down Nigerian demographic information (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2019) proportionally to the size of Borno and Yobe. We divided the total population of Borno and Yobe into four subpopulations: a general population, two isolated subpopulations, and an under-vaccinated subpopulation. We based the sizes of the subpopulations on satellite imagery, with inhabitance assessed and population estimated based on intensive, settlement-by-settlement review performed by one author (JH). The general population represented the fraction of the population with constant accessibility levels over time and vaccination consistent with general levels reported for the whole country. The isolated subpopulations represented the fraction of the population characterized by the persistent lack of access (i.e., limited to no outside contact or direct vaccination) since 2013 due to security issues, which we split into two zones that we designated generically as north (N) and central (C). The under-vaccinated subpopulation represented the remainder of population in Borno and Yobe, and it consisted of historically under-vaccinated communities with variable accessibility levels over time, which included the populations that became increasingly isolated starting in 2013 and completely isolated in 2015. The structure we chose provided a conceptual rather than geographical representation of the population that grouped people by their levels of accessibility and therefore levels of vaccination.

We modified the level of mixing between subpopulations and the amount of vaccination in the subpopulations for different years to produce model behavior consistent with program experience in the region and observed WPV and cVDPV2 cases. The mixing structure assumed that under-vaccinated and isolated subpopulations behave as one homogeneously-mixing subpopulation (with 12% of contacts occurring with individuals in the general population) until the isolation time (see Table 2a). Once the isolation started to affect population movements and access (and therefore vaccination), the isolated subpopulations gradually lost contact with other subpopulations (see Table 2b and Table 2c for assumed mixing levels in 2013 and 2014). Once the isolation reached its peak in 2015, the isolated subpopulations lost all contact with other subpopulations as well as all access to direct vaccination (i.e., no RI and no SIAs). At that time, all external contacts for the under-vaccinated subpopulation switched to only those with individuals in the general population (see Table 2d). We assumed that starting from mid-2016 the isolation levels started to change, allowing for minimal contact between isolated and under-vaccinated subpopulations

(initially 0.5% of contacts, then 1% as of early 2018, occurring with individuals from the under-vaccinated subpopulation, see Tables 2e and Table 2f).

Fig. 1 shows assumed RI coverage by dose over time based on 3 doses of diphtheria-tetanus-pertussis vaccine (DTP3) (DTP3) coverage estimates (World Health Organization, 2019b), Nigeria Demographic and Health Study (DHS) point estimates of Polio vaccine birth dose (POL0) and doses 1, 2, and 3 (POL1, POL2, and POL3) for the northeast Nigeria zone covering years 1989, 1998, 2002, 2007, 2012, and 2018, and Borno- and Yobe-specific estimates for 2012 (The DHS Program US AID, 2019). We used DHS point estimates for the northeast Nigeria zone and we linearly interpolated between those estimates. For all years from 1984 to 1988 (i.e., from the assumed beginning of RI to the last birth year not covered by DHS surveys), we calculated the coverage of 3 or more non-birth doses (COV3) using DTP3 coverage (World Health Organization, 2019b) scaled by the first known POL3 estimate. We assumed that the birth dose (COV0) and partial (i.e., 1- or 2-dose) coverages (COV1, COV2) increased proportionally to the COV3 during this period. . We assumed constant POL0, POL1, POL2 and POL3 coverages at the 2012 DHS estimates from 2012 on. Finally, we scaled all coverage estimates using the dose-specific 2012 relative coverages for Borno and Yobe compared to dose-specific 2012 relative coverages for the northeast Nigeria zone. Although the data from the 2018 DHS became available after this manuscript went into review, we did not update our assumptions to use the 2018 data, because as noted in the DHS report (page 3) “In the case of Borno, 11 of the 27 LGAs were dropped due to high insecurity, and therefore the results might not represent the entire state” (National Population Commission and ICF, 2019).

We assumed relative RI coverage (*relRI*) of 30% for the under-vaccinated subpopulation (relative to the general population) for all years that RI vaccination was available (starting from 1984). We assumed the same relative RI coverage in the isolated subpopulations prior to 2013, while they effectively mix homogeneously as part of the under-vaccinated subpopulation. However, given the increasingly limited access from 2013, for the isolated subpopulations we assumed a decrease in relative coverage by 10% per year (i.e., 20% in 2013, 10% in 2014), followed by 0% relative RI coverage from 2015 onwards (i.e., when the population becomes almost completely isolated). To maintain the overall average RI coverage values presented in Fig. 1, we multiplied all coverage values by the corresponding relative RI coverage of isolated and under-vaccinated subpopulations, while the general population receives relative RI coverage weighted according to the subpopulation sizes: $relRI_G = (1 - n_{IN} \times relRI_{IN} - n_{IC} \times relRI_{IC} - n_U \times relRI_U) / n_G$, where n_x represents the fraction of the population residing in subpopulation x (x = IN, isolated north; IC, isolated central; U, under-vaccinated; G, general).

Fig. 2 shows the historical SIAs for Borno and Yobe by type of vaccine used and fraction of the population targeted (see appendix for subpopulation-specific assumptions, which include assumptions about the fraction targeted multiplied by assumed true coverage and the round-to-round probability of repeatedly missing the same children). All SIAs targeted children under 5 years old (i.e., <60 months), except for IPV SIAs, which targeted 3- through 59-month-olds. For the general population, we assumed constant 45% true coverage for all SIAs through 2007, fluctuating 40–50% true coverage for all SIAs from 2008 through 2012, and

5% step increases from 2013 until true coverage reaches 80% in 2019. For the under-vaccinated subpopulation, we adjusted the true coverage relative to the general population (i.e., 50% relative coverage for all SIAs through 2004, fluctuating 10–60% relative coverage for all SIAs from 2005 through 2012, and 5% step increases from 2013 until mid-2016, when relative coverage reaches 65%). We assumed that relative coverage in the isolated subpopulations began to diverge from the relative coverage in the under-vaccinated subpopulation due to the partial loss of access in 2013 and 2014, followed by no direct SIAs in the isolated subpopulations from 2015. For the mid-2016–2019 period, we based our estimates on accessibility data derived from geographic tracking of vaccination teams that one authors used to estimate relative coverage in the under-vaccinated subpopulation (Higgins et al., 2019). These estimates included explicit consideration of immunization doses delivered via special interventions (e.g. vaccination strategies supported by security personnel). Recognizing that SIAs preferentially miss the same children in repeated rounds, we defined the concept of repeated-missed probability as “the conditional probability that a targeted individual does not receive a dose in a round, conditional on the individual not receiving a dose in the previous round despite falling into the targeted population for that round” (Kalkowska et al., 2020). We varied those probabilities only for SIAs in the general population, whereas in the under-vaccinated subpopulations the repeated-missed probabilities adjust automatically after applying relative coverage. We fit the true coverage and the repeated-missed probability of the general population to minimize the difference between the series of modeled and reported proportions of children with 0 doses.

From the time of complete isolation of the isolated populations (i.e., 2015), we accounted for some vaccine taken into the isolated subpopulations by the small number of people who receive vaccination while temporarily exiting the isolation zones before returning to their settlements. After the first quarter of 2018, we also added more vaccine taken in by community volunteers, recruited from 2018 onward, who conducted surveillance and performed very limited vaccination in some areas inaccessible to the polio program. Discussions with subject matter experts revealed that movement of small numbers of people (e.g., migrants, insurgents, etc.) could transport vaccine virus in and out of the isolated areas by these routes. We captured this by introducing OPV vaccine of the serotype given at the time of an SIA in areas surrounding the isolated populations (with an assumed 1-day delay relative to the start day of the related SIA) to a small number of children ages 3 months to 4 years residing in the isolated subpopulations. For these introductions, we assumed a frequency of 2 fully susceptible children per age group per day receiving the OPV for the duration of 4–7 days from 2015 on (see Table 3). From mid-2018, we also introduced OPV vaccine to children ages 3 months to 9 years with the frequency of 1–2 fully susceptible children per age group per day (see Table 3). The structure of the differential equation-based model can maintain a fractional infectious individual, which allows for continuous transmission in situations in which viral transmission would die out in nature; we therefore applied a transmission threshold for die-off (Kalkowska et al., 2020) (see Table 1).

To account for gaps in AFP surveillance caused by insecurity and isolation, we applied yearly accessibility factors from 2013 onwards to estimate the proportion of paralytic poliovirus cases in the model detectable by the program under the challenging conditions in the under-vaccinated and isolated subpopulations. We assumed perfect AFP surveillance

(accessibility factor equal 1.0) for the general population from 2013, no AFP surveillance in isolated subpopulations (accessibility factor = 0.0) from 2015 on, and varied AFP surveillance quality in the under-vaccinated subpopulation from 2013 on and in the isolated subpopulations in 2013 and 2014 (see Table 4). We varied the accessibility factors in the under-vaccinated subpopulation (and isolated subpopulations before 2015) based on personal communications with Borno and Yobe subject matter experts via an accessibility survey.

Considering variability in surveillance quality in the inaccessible areas in Borno and Yobe and the inability to detect poliovirus transmission in inaccessible areas, we explored multiple possibilities. For example, building on prior experience modeling completely isolated populations (Duintjer Tebbens, Kalkowska, & Thompson, 2019; Kalkowska, Duintjer Tebbens, & Thompson, 2018), we considered the possibility of completely cutting off the isolated subpopulations (i.e., making them unable to mix at all with either the under-vaccinated or the general population). However, this situation did not correspond with anecdotal information that suggests some movement and mixing (e.g., ad hoc stool sampling of healthy children leaving inaccessible areas showing exposure to OPV). In addition, the role of migrant populations that move among the settlements that comprise the isolated subpopulations and also mix with the under-vaccinated subpopulation remain incompletely characterized, although some mixing of this nature is known to occur. We also recognized based on our prior experience modeling confidence about no circulation (in the absence of the detections suggesting transmission from surveillance) (Duintjer Tebbens et al., 2019; Kalkowska et al., 2015; Kalkowska, Duintjer Tebbens, Pallansch, & Thompson, 2019; Kalkowska, Duintjer Tebbens, & Thompson, 2012) that immunization levels that led to population immunity to transmission near the threshold for die out led to the longest times required to achieve high confidence (i.e., when the expected time between cases is the longest if transmission continues). We developed this model as part of a larger effort to explore the confidence about no undetected transmission, and thus focused on characterization of the available evidence with this motivation in mind.

Integrating the information available about the types of activities that occurred in Borno and Yobe, we identified two possible scenarios that could describe the current situation and that provided bounds around the transmission threshold: (1) indirect vaccination introductions into isolated subpopulations sufficient to eliminate undetected WPV1 transmission after the latest case detected in 2016, and (2) indirect vaccination introductions into isolated subpopulations insufficient to eliminate undetected WPV1 transmission, but with sufficiently low WPV1 transmission consistent with the current lack of reported detection of WPV1 through 2019. Thus, we focused on selecting scenarios very close to the transmission threshold that appear consistent with the available data and experience. As shown in Table 3, a relatively small difference between the assumed number of days of OPV introduced secondarily for each SIA conducted from August 2016 on (i.e., 7 days for scenario 1 and 6 days for scenario 2) changes the transmission dynamics around the die out threshold..

Epidemiological experience and virological evidence suggested that Borno and Yobe experienced some importations from and exportations to other areas within Nigeria and nearby countries in the Lake Chad region. Consequently, although we modeled transmission

and OPV evolution endogenously for Borno and Yobe, we included the importation of some viruses exogenously to match the epidemiological and virological evidence.

Finally, although Nigeria introduced some environmental surveillance activities in Borno and Yobe during the analytical time horizon of the model and reported some results in the literature (Hamisu et al., 2019), we could not obtain sufficient information to characterize these activities with respect to the different subpopulations or the quality of the information. Consequently, our analysis focuses quantitatively only on AFP surveillance.

Results

The black squares connected by dashed lines in Fig. 3 show the reported incidence of (a) WPV1, (b) cVDPV2, and (c) WPV3 for Borno and Yobe for 2001–2019. Fig. 3 also shows the behavior of modeled transmission of all three serotypes in the model for both scenarios 1 and 2. The solid red, green, and blue lines represent the total modeled paralytic incidence of WPV1 in Fig. 3(a), cVDPV2 in Fig. 3(b), and WPV3 in Fig. 3(c), respectively, and the dashed lines of the same colors show the modeled detectable paralytic incidence. As described in the methods, the modeled detectable cases account for gaps in programmatic access for surveillance from 2013 on in the inaccessible parts of Borno and Yobe. The difference between the solid and dashed lines provide an indication of the incidence occurring in the model in areas not accessed by surveillance. Comparison of the lines to the reported incidence suggests that the overall level of incidence in the model appears consistent with the reported number of cases. The model also generally reproduces the kinetics of the year-to-year peaks in cases, and WPV2 elimination in the middle of 1998 followed by the importation of cVDPV2 and resultant cases in 2010.

Fig. 3(c) reports no differences in the model results between scenarios 1 and 2 for WPV3, which reflects the situation that WPV3 died out before the mid-2016 time in the model at which the input assumptions began to differ for the scenarios. Similarly, for Fig. 3(b), the very small differences between the cVDPV2 modeled results for scenarios 1 and 2 cannot be discerned at the scale of the figure, and thus Fig. 3(b) shows the model results for both scenarios with a single set of curves. Fig. 3(a) also shows the results for both scenarios, which only differ in the shaded area to the right in Fig. 3(a). For scenario 1, the WPV1 transmission dies out in the first half of 2017, and thus the red solid and dashed lines for scenario 1 go to 0 (i.e., the same as the reported incidence curve) in the shaded area. For scenario 2, the WPV1 transmission and cases continue as shown in the shaded area. The results in Fig. 3a show small but important differences in the behavior of WPV1 transmission after 2016, but the same finding of no transmission after 2019. Because scenario 2 assumes slightly less indirect OPV entering the isolated subpopulations compared to scenario 1 (i.e., just under the threshold), it produces different dynamics of WPV1 transmission after the 2016 detection of cases. For scenario 2, WPV1 transmission continues until late 2019, with 10 and 2 total cases WPV1 in 2018 and 2019, respectively. Of these, the model characterizes 2 and 1 of these cases, respectively, as potentially detectable by the limited surveillance in 2018 and 2019, respectively (i.e., the remaining 8 and 1 cases in 2018 and 2019, respectively, occur in the model in isolated and under-vaccinated populations without any surveillance access and thus characterized by an absence of evidence). The two

scenarios provide different potential transmission dynamics following the latest reported WPV1 cases in 2016 that appear consistent with the available surveillance information, which includes the detection of transmission of cVDPV2s. Accessibility issues and insufficient immunization may allow for prolonged poliovirus transmission and potential undetected paralytic cases, although as of the end of 2019, including responsive program activities as we modeled them in scenarios 1 and 2 suggest die out of WPV1.

Discussion

September 2019 marked the passage of 3 full years since the last reported WPV1 case in Nigeria. However, given the continued inaccessibility of the program to some areas due to insurgency and the experience of unexpected detection in 2016, questions remain about whether transmission of WPV1 still continues in those areas in Borno and Yobe that remain inaccessible for immunization and surveillance (and potentially for WPV3 and cVDPV2 virus transmission as well). As the Nigerian government and the national polio program continue to gain increasing access and to immunize previously inaccessible populations, the probability of sustained transmission without detection in increasingly small population sizes decreases. The relatively good information for surveillance for all of 2019 (including on-going detection of VDPV2s) combined with increased access, the use of special interventions to reach inaccessible populations, and decreasing sizes of the isolated populations, these results suggest that the lack of reported WPV1 cases in 2019 strongly supports qualitative assessments of confidence of the die-off of WPV1 transmission in Borno and Yobe.

This analysis raises some logistical questions. Specifically, if our model assumptions are correct, could the surveillance system still have missed the three detectable cases (i.e., 2 in 2018 and 1 in 2019) in scenario 2? If not, then the lack of reported cases or any evidence of transmission of WPV1 for more than 3 years suggest that scenario 2 does not properly represent the true situation of WPV1 circulation in Borno and Yobe, and therefore points to scenario 1 as a more likely representation. However, some of the special intervention teams provided anecdotal evidence of lame children found during vaccination activities in 2017–2018 among children that they could not evacuate for formal evaluation and investigation. Additionally, some polio-compatible cases reported in 2018 in or on the edge of the inaccessible areas could represent potential WPV1 cases, which would appear more consistent with scenario 2. We emphasize, however, that uncertainty remains about the nature of polio compatible cases due to the lack of information (i.e., insufficient clinical investigation and no laboratory confirmation of any poliovirus), and with known transmission of VDPV2s in the same area. With continued bOPV use, low levels of transmission of OPV-related viruses in isolated areas also contribute to and imply the potential for transmission of cVDPVs serotypes 1 and 3.

Our analysis remains limited by the model structure, assumptions, available information and our reconstruction of the immunization histories. The assumptions we made to characterize the consequences of limited access also drive the model behavior. Notably, if we model the isolated subpopulations as completely isolated, then we would expect the transmission of live polioviruses circulating at the time of isolation could continue for the entire model time

horizon (Duintjer Tebbens et al., 2019). Similarly, if the model did not allow any secondary spread or OPV entry into the isolated populations following their isolation, then we expect the modeled sizes of the peaks of cases would also become much larger. Although we include heterogeneous mixing between the subpopulations, the assumption of homogeneous mixing within subpopulations can imply rapid transmission across relatively large groups of individuals. Allowing for the continuous, low-level transmission in the populations that become isolated from vaccination and surveillance leads to the accumulation of susceptible individuals and consequently to relatively explosive peaks of transmission due to the homogeneous mixing within those small subpopulations. The use of the differential equation-based transmission and OPV evolution model permits us to reproduce reasonable average behavior of poliovirus transmission, however it misses potentially important population micro dynamics that impact the die-out of transmission. In reality, each of the two isolated subpopulations that we modeled includes significant heterogeneity, which our simplified population structure cannot reproduce. Although it was challenging to reconstruct historical immunization and surveillance information, and to use an aggregate model to capture some of the special interventions, we used all available information. We faced substantial challenges with respect to obtaining and interpreting environmental surveillance information for Borno and Yobe, and consequently we used this information only qualitatively. Finally, this type of modeling inherently misses critical aspects of the stochastic nature of transmission events in real populations. Despite its limitations, deterministic modeling can help to support the development of assumptions for use in stochastic models that explore the confidence of no circulation (Kalkowska et al., 2015; Kalkowska et al., 2019). A separate analysis explores the confidence about no undetected circulation as a function of time since the last detected events using a stochastic model (Kalkowska & Thompson, 2020).

The broader context of challenges experienced with national polio elimination efforts in Nigeria as a whole (i.e., not limited to Borno and Yobe) warrant some discussion with respect to important lessons learned. Limited access, poor quality immunization and surveillance in multiple parts of Nigeria (as in other countries), and the resulting relatively low population immunity to transmission poses risks for other areas (Thompson, Kalkowska, & Duintjer Tebbens, 2015). For example, following the suspension of SIAs in some northwestern Nigerian states (i.e., Kaduna, Kano, Zamfara) in 2003–2004 (Centers for Disease Control and Prevention, 2005), the resulting low population immunity to transmission led to outbreaks and subsequent costly exportations of WPV1 into previously polio-free states and countries that led to additional outbreaks (Centers for Disease Control and Prevention, 2006). These same conditions also made Nigeria one of the most challenging areas for managing cVDPV2s. Continued transmission of cVDPV2s despite outbreak response efforts in Nigeria and other areas pose a significant threat to the polio endgame, and contribute to the global risk of potentially needing to restart production of OPV2-containing vaccines (Duintjer Tebbens & Thompson, 2018; Thompson & Kalkowska, 2019).

The challenging nature of limited immunization and surveillance associated with insurgency in the Borno and Yobe states of Nigeria makes it hard to completely resolve whether the lack of reported WPV1 cases indicates the complete die out of WPV1 transmission or remaining

critical gaps in surveillance, although our modeling suggests die out of transmission occurred by the end of 2019. The deterministic DEB model including small (almost completely) isolated subpopulations comes with some limitations, but modeling the bounds of potential transmission provide some confidence about die out. Estimating the confidence about no undetected circulation requires further stochastic modeling, as discussed in a separate analysis (Kalkowska & Thompson, 2020). Consistent with the available epidemiology and virology evidence, the modeling results strongly suggests die-out of WPV1 transmission in Borno and Yobe.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AFP	acute flaccid paralysis
cVDPV	circulating VDPV
GPEI	Global Polio Eradication Initiative
IPV	inactivated poliovirus vaccine
OPV	oral poliovirus vaccine
VDPV	vaccine-derived poliovirus
WPV	wild poliovirus

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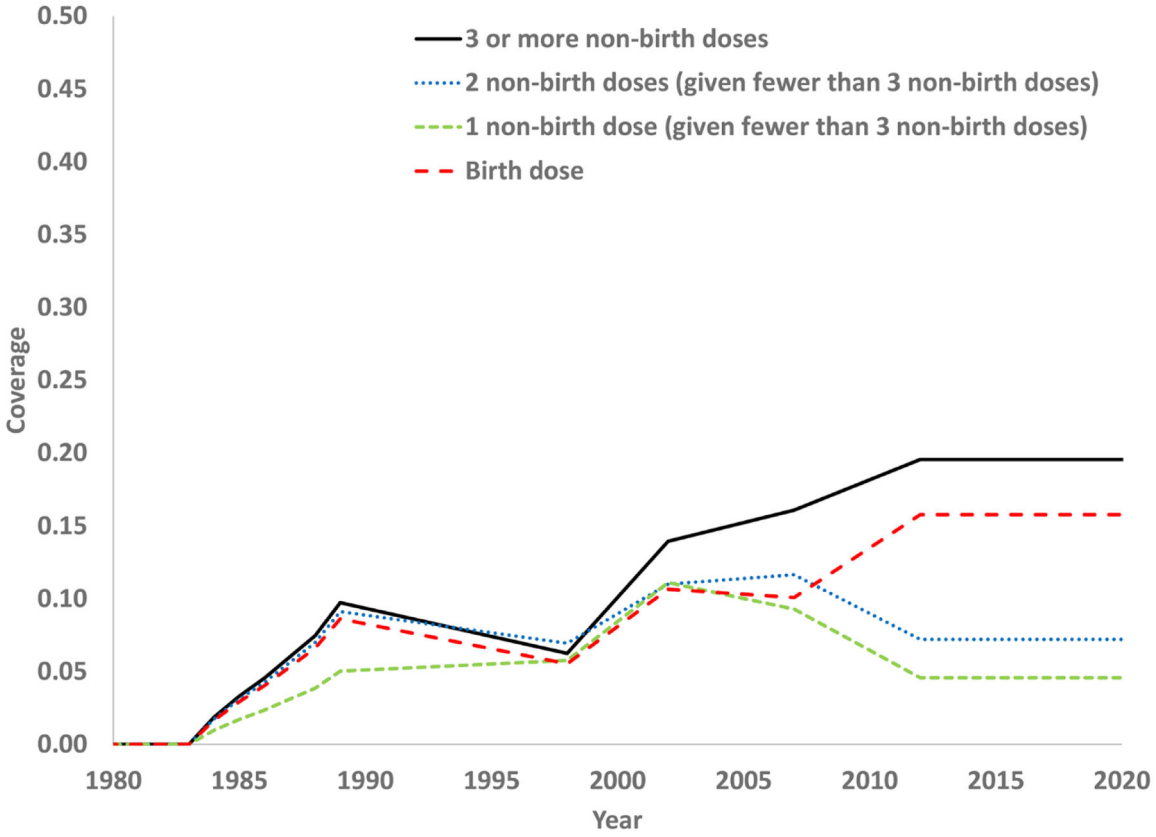


Figure 1.
Assumed routine immunization (RI) coverage with oral poliovirus vaccine (OPV) for birth dose and one nonbirth dose, two nonbirth doses, and three or more nonbirth doses.

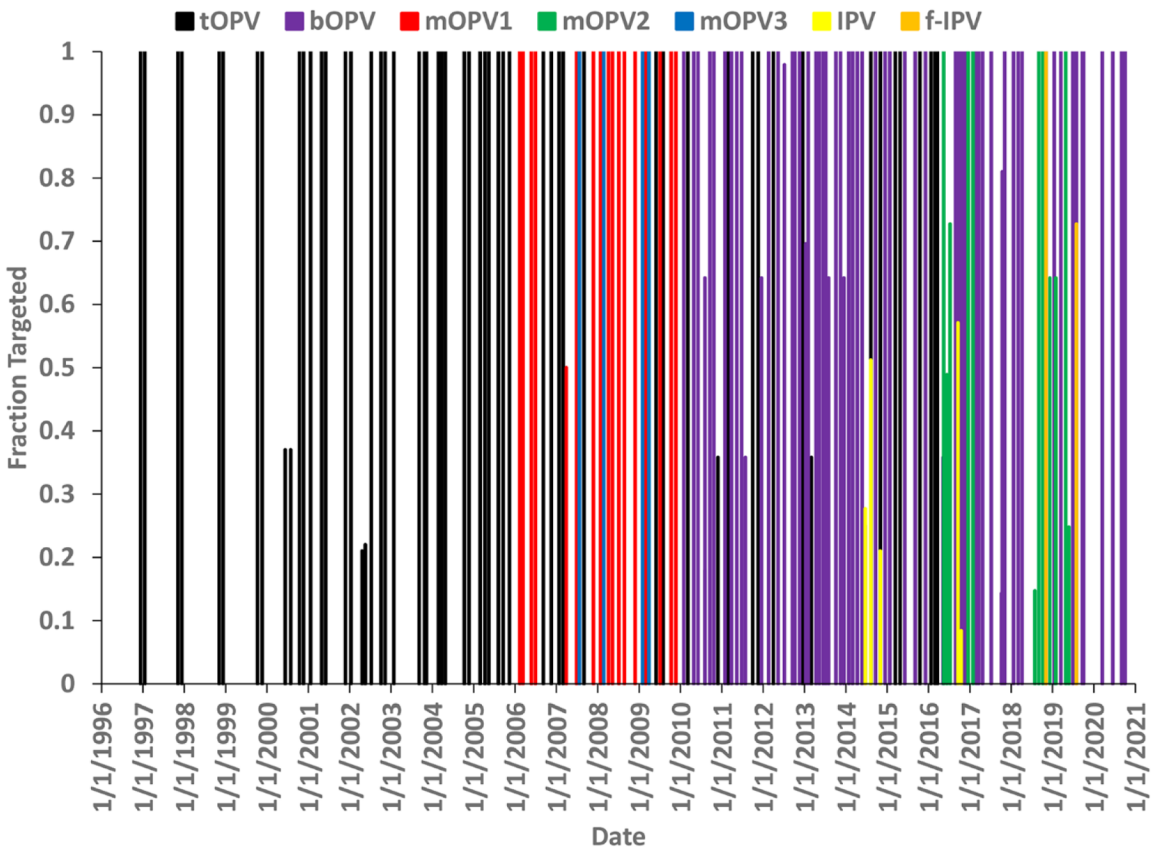
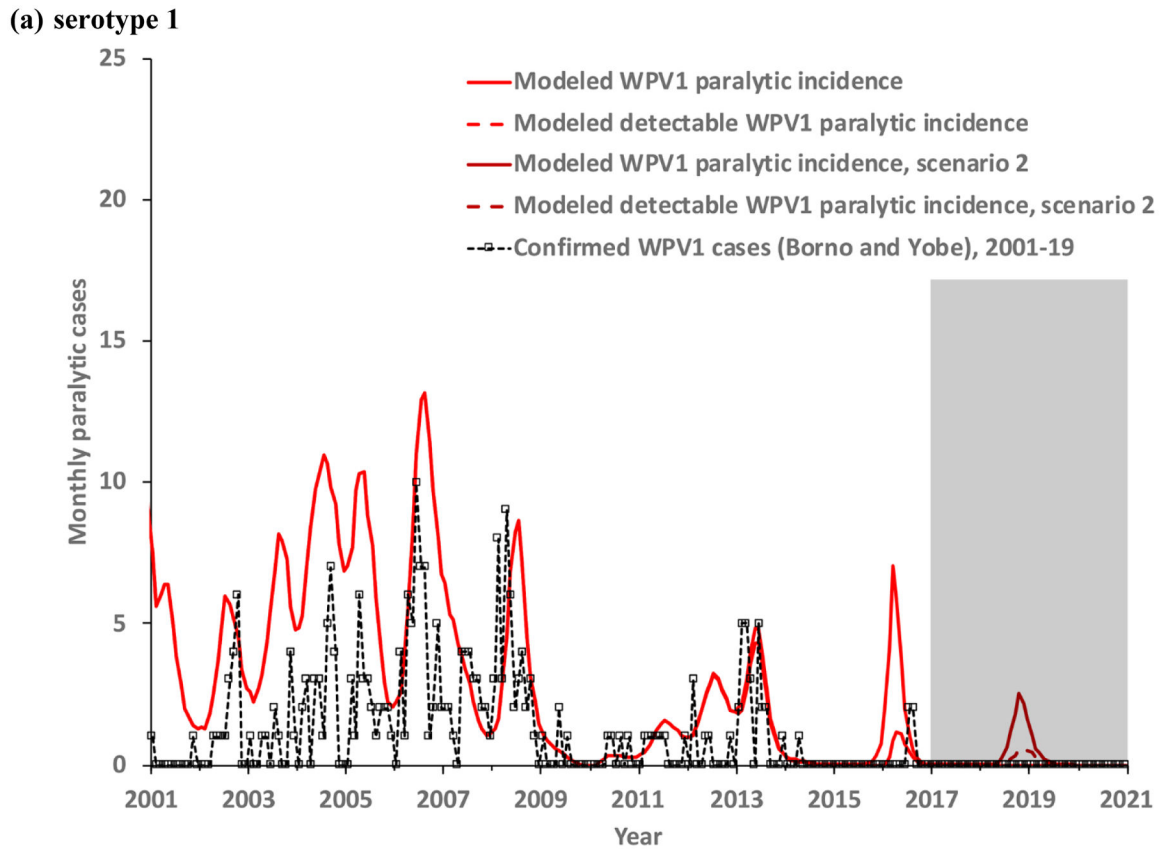
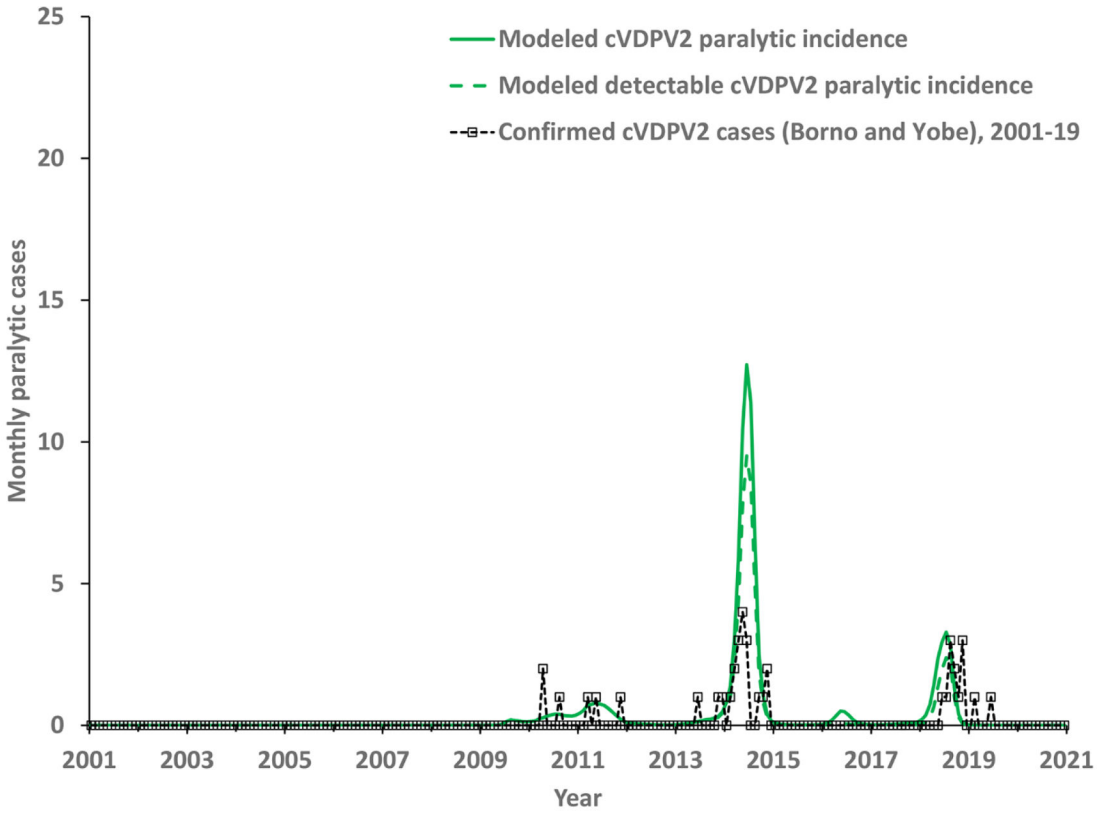


Figure 2. Historical supplementary immunization activities (SIAs) for Borno and Yobe by type of vaccine used and fraction of the population targeted

Abbreviations: f-PV, fractional IPV; IPV, inactivated poliovirus vaccine; bOPV, bivalent OPV; mOPV(1,2,3), monovalent OPV (serotype 1, 2, 3 containing); OPV, oral poliovirus vaccine; tOPV, trivalent OPV.



(b) serotype 2



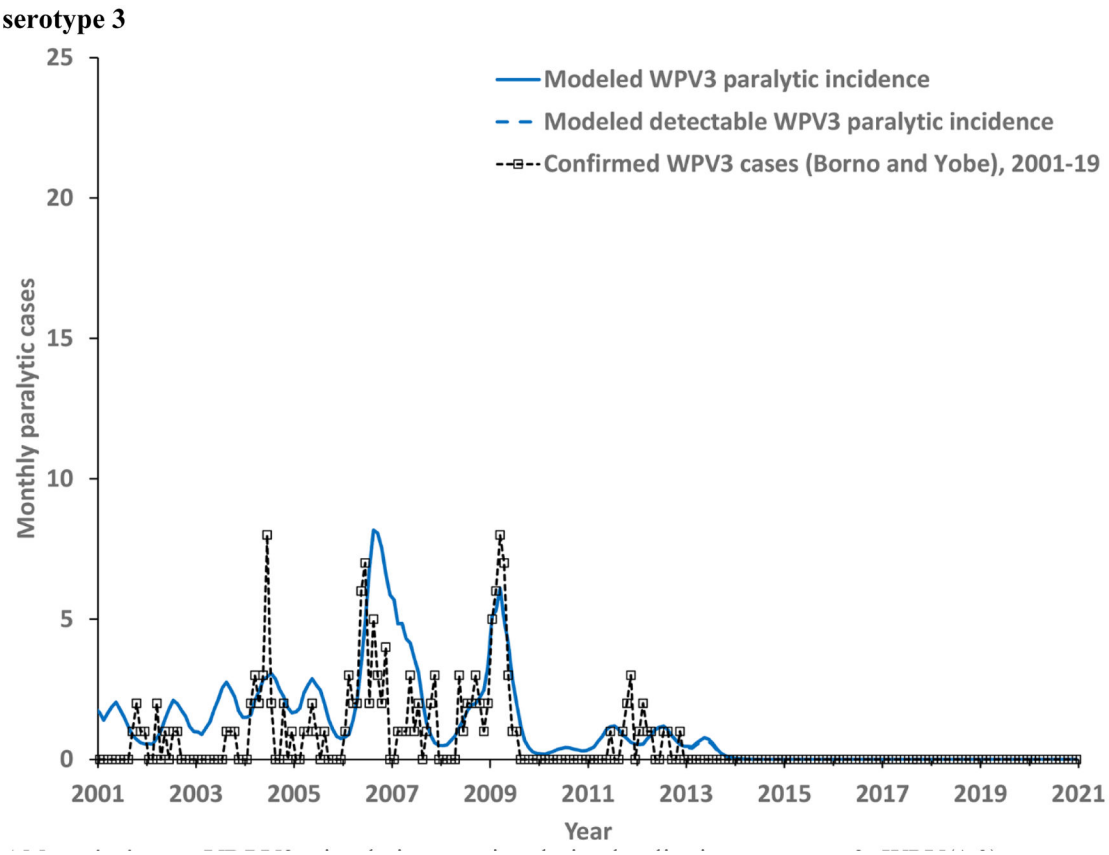


Figure 3. Reported poliovirus cases for 2001–2019, modeled paralytic incidence, and modeled detectable paralytic incidence for Borno and Yobe

Abbreviations: cVDPV2, circulating vaccine derived poliovirus serotype 2; WPV(1,3), wild poliovirus serotype 1, 3

Table 1.

Constant inputs specific for the northeast Nigeria model

Model input	Best estimate	Notes and sources
Relative population size compared to all of Nigeria	0.045	
Number of subpopulations	4	
Size of subpopulations relative to total population:		
- general	0.4	
- isolated	0.022	
- North (N)	0.0097	
- Central (C)	0.0123	
- under-vaccinated	0.578	
Number of age groups	11	0–2, 3–11 months; 1; 2; 3; 4; 5–9; 10–14; 15–24; 25–39 *; ≥ 40 years *
Number of mixing age groups	3	0–4; 5–14; ≥ 15 years *
Proportion of contacts reserved for individuals within the same mixing age group (κ)	0.4	Measure of strength of preferential mixing between age groups; value similar to other high-risk settings *
Average basic reproductive number (R_0)		Seasonal variation occurs around the average, ratios by serotype based on generic model inputs, values previously assumed for northwest Nigeria *
- serotype 1	8.0	
- serotype 2	7.2	
- serotype 3	6.0	
Proportional change in R_0 due to seasonality (α)	0.05	Based on judgment and calibration within ranges used for other populations to match incidence pattern, values previously assumed for northwest Nigeria *
Day of seasonal peak in $R_{0(pd)}$	100 (April 30)	Broadly consistent with typical precipitation patterns and nonpolio enterovirus isolation rates, calibrated to match incidence patterns, values previously assumed for northwest Nigeria *
Proportion of transmissions via oropharyngeal route (p^{oro})	0.3	Value used for high R_0 developing country settings *
Per-dose take rate (tr) (serotype 1, 2, 3)		Values based on review of seroconversion studies and previously used to model northwest Nigeria *
- tOPV	0.45, 0.70, 0.35	
- mOPV	0.60, 0.70, 0.60	
- bOPV	0.54, NA, 0.54	
- IPV	0.63, 0.63, 0.63	
Time of IPV introduction in RI	March 16, 2015	
Time of switch from tOPV to bOPV	April 30, 2016	
Time of isolation	January 1, 2015	
Demographics	Time series	Surviving birth rates and age-specific mortality rates over time computed from U.N.-estimated medium variant annual number of surviving infants and population in each age group and country *
Transmission threshold	5/1,000,000	Effective infectious proportion below which we assume 0 force-of-infection *

* (Kalkowska et al., 2014)

Abbreviations: bOPV, bivalent oral poliovirus vaccine; IPV, inactivated poliovirus vaccine; mOPV, monovalent oral poliovirus vaccine; NA, not applicable; RI, routine immunization; tOPV, trivalent oral poliovirus vaccine; U.N., United Nations.

Table 2.

Assumed mixing matrices among the three subpopulations in the northeast Nigeria model:

(a) Before isolation (until and including 2012)				
To\From	**Isolated (C)**	**Isolated (N)**	**Under-vaccinated**	**General**
Isolated (C)	0.0181	0.0142	0.8477	0.1200
Isolated (N)	0.0181	0.0142	0. 8477	0.1200
Under-vaccinated	0.0181	0.0142	0. 8477	0.1200
General	0.0025	0.0019	0.1156	0.8800
(b) 2013				
To\From	**Isolated (C)**	**Isolated (N)**	**Under-vaccinated**	**General**
Isolated (C)	0.270	0.270	0.400	0.060
Isolated (N)	0.270	0.270	0.400	0.060
Under-vaccinated	0.010	0.010	0.860	0.120
General	0.005	0.005	0.110	0.880
(c) 2014				
To\From	**Isolated (C)**	**Isolated (N)**	**Under-vaccinated**	**General**
Isolated (C)	0.500	0.270	0.200	0.030
Isolated (N)	0.270	0.500	0.200	0.030
Under-vaccinated	0.010	0.010	0.860	0.120
General	0.005	0.005	0.110	0.880
(d) 2015–2016.1				
To\From	**Isolated (C)**	**Isolated (N)**	**Under-vaccinated**	**General**
Isolated (C)	1.000	0.000	0.000	0.000
Isolated (N)	0.000	1.000	0.000	0.000
Under-vaccinated	0.000	0.000	0.880	0.120
General	0.000	0.000	0.120	0.880
(e) >2016.1–2018.25				
To\From	**Isolated (C)**	**Isolated (N)**	**Under-vaccinated**	**General**
Isolated (C)	0.995	0.000	0.005	0.000
Isolated (N)	0.000	0.995	0.005	0.000
Under-vaccinated	0.005	0.005	0.870	0.120
General	0.000	0.000	0.120	0.880
(f) >2018.25 on				
To\From	**Isolated (C)**	**Isolated (N)**	**Under-vaccinated**	**General**
Isolated (C)	0.990	0.000	0.010	0.000
Isolated (N)	0.000	0.990	0.010	0.000
Under-vaccinated	0.010	0.010	0.860	0.120
General	0.000	0.000	0.120	0.880

Abbreviations: N, north; C, central

Table 3.

Level of indirect vaccination introductions into children in isolated subpopulations as a function of time.

Time period	Target age groups	Duration of OPV introduction	Number vaccinated per age group	Delay (relative to SIA start date)
1/2015 – 7/2016	3–11 mo, 1; 2; 3; and 4 yr	4 days	2/day	1 day
8/2016 on				
Scenario 1	3–11 mo, 1; 2; 3; and 4 yr	7 days	2/day	1 day
Scenario 2	3–11 mo, 1; 2; 3; and 4 yr	6 days	2/day	1 day
10/2018 – 3/2019	3–11 mo, 1; 2; 3; 4; and 5–9 yr	each day	2/day	NA
4/2019 on	3–11 mo, 1; 2; 3; 4; and 5–9 yr	each day	1/day	NA

Abbreviations: NA, not applicable; OPV, oral poliovirus vaccine; SIA, supplementary immunization activity

Table 4.

Assumed accessibility factor for AFP surveillance by subpopulation, as a function of time

Year	Isolated (N & C)	Under-vaccinated	General
2011 (and before)	1.00	1.00	1.00
2012	0.98	0.98	1.00
2013	0.89	0.89	1.00
2014	0.73	0.73	1.00
2015	0.00	0.44	1.00
2016	0.00	0.60	1.00
2017	0.00	0.69	1.00
2018	0.00	0.73	1.00
2019 (and after)	0.00	0.77	1.00

Abbreviations: AFP, acute flaccid paralysis; N, north; C, central