Effectiveness of poliovirus vaccines against circulating vaccine-derived type 2 poliomyelitis in Nigeria between 2017 and 2022: a case-control study

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Summary

Background Between 2018 and 2022, Nigeria experienced continuous transmission of circulating vaccine-derived type 2 poliovirus (cVDPV2), with 526 cases of cVDPV2 poliomyelitis detected in total and approximately 180 million doses of monovalent type 2 oral poliovirus vaccine (mOPV2) and 450 million doses of novel type 2 oral poliovirus vaccine (nOPV2) delivered in outbreak response campaigns. Inactivated poliovirus vaccine (IPV) was introduced into routine immunisation in 2015, with a second dose added in 2021. We aimed to estimate the effectiveness of nOPV2 against cVDPV2 paralysis and compare nOPV2 effectiveness with that of mOPV2 and IPV.

Methods In this retrospective case-control study, we used acute flaccid paralysis (AFP) surveillance data in Nigeria from Jan 1, 2017, to Dec 31, 2022, using age-matched, onset-matched, and location-matched cVDPV2-negative AFP cases as test-negative controls. We also did a parallel prospective study from March, 2021, using age-matched community controls from the same settlement as the cases. We included children born after May, 2016, younger than 60 months, for whom polio immunisation history (doses of OPV from campaigns and IPV) was reported. We estimated the per-dose effectiveness of nOPV2 against cVDPV2 paralysis using conditional logistic regression and compared nOPV2 effectiveness with that of mOPV2 and IPV.

Findings In the retrospective case-control study, we identified 509 cVDPV2 poliomyelitis cases in Nigeria with case verification and paralysis onset between Jan 1, 2017, and Dec 31, 2022. Of these, 82 children were excluded for not meeting inclusion criteria, and 363 (85%) of 427 eligible cases were matched to 1303 test-negative controls. Cases reported fewer OPV and IPV doses than test-negative controls (mean number of OPV doses 5·9 [SD 4·2] in cases *vs* 6·7 [4·3] in controls; one or more IPV doses reported in 95 [26%] of 363 cases *vs* 513 [39%] of 1303 controls). We found low per-dose effectiveness of nOPV2 (12%, 95% CI –2 to 25) and mOPV2 (17%, 3 to 29), but no significant difference between the two vaccines (p=0·67). The estimated effectiveness of one IPV dose was 43% (23 to 58). In the prospective study, 181 (46%) of 392 eligible cases were matched to 1557 community controls. Using community controls, we found a high effectiveness of IPV (89%, 95% CI 83 to 93, for one dose), a low per-dose effectiveness of nOPV2 (–23%, –45 to –5) and mOPV2 (1%, –23 to 20), and no significant difference between the per-dose effectiveness of nOPV2 and mOPV2 (p=0·12).

Interpretation We found no significant difference in estimated effectiveness of the two oral vaccines, supporting the recommendation that the more genetically stable nOPV2 should be preferred in cVDPV2 outbreak response. Our findings highlight the role of IPV and the necessity of strengthening routine immunisation, the primary route through which IPV is delivered.

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Introduction

Outbreaks of circulating vaccine-derived type 2 poliovirus (cVDPV2) have caused more poliomyelitis cases than outbreaks of wild poliovirus since 2017.[1] The Global Polio Eradication Initiative (GPEI) has achieved eradication of wild poliovirus types 2 and 3, and only 30 cases of type 1 wild poliovirus were reported in 2022, with endemic circulation restricted to Pakistan and Afghanistan.[1] The success of vastly reducing wild poliovirus transmission globally is due to use of the live-attenuated oral polio vaccine (OPV), which induces a strong mucosal response and is cheap and easy to administer. However, in rare instances in populations with low poliovirus immunity, the Sabin vaccine virus loses its attenuating mutations during replication in the gut, regaining transmissibility and pathogenicity similar to that of wild poliovirus, resulting in outbreaks of circulating vaccine-derived poliovirus (cVDPV).[2] As type 2 poliovirus caused the majority of VDPV cases and wild type 2 poliovirus had been eradicated, type 2 OPV was globally withdrawn and trivalent OPV (tOPV, containing Sabin 1, 2, and 3) was replaced with bivalent OPV (bOPV, containing Sabin 1

Research in context

Evidence before this study

We reviewed published literature and conference proceedings for studies on the immunogenicity and individual-level effectiveness of novel type 2 oral poliovirus vaccine (nOPV2) since the first phase 1 nOPV2 clinical trial in 2017. We searched PubMed in October, 2023, using the following search terms: ("novel type 2 oral poliovirus vaccine") AND ("seroprevalence" OR "serosurvey" OR "serology" OR "immunogenicity" OR "efficacy" OR "effectiveness"). We identified six immunogenicity studies: one in Panama, two in Bangladesh, one in Tajikistan, one in The Gambia, and one in Liberia. Immune response following a single dose varied from 49% in infants in The Gambia to 96% in young children (aged 1–4 years) in Panama. The study in Liberia measured seroprevalence at a single timepoint, finding 42% seropositivity after two nOPV2 campaigns. No studies assessed individual-level effectiveness of nOPV2 against poliomyelitis. Only the Panama study directly compared the immunogenicity of nOPV2 with that of monovalent type 2 oral poliovirus vaccine (mOPV2). This study found that two nOPV2 candidate vaccines were non-inferior to mOPV2 in historical controls from 2 years before, except for the low-dose concentration of candidate 1. Another study, based in Bangladesh (Dhaka city), found significantly lower seroconversion in infants after one or two doses of nOPV2 compared with a study conducted using mOPV2 at the same site and in the same age group 5 years before, but this finding could be explained by unintentional exposure to trivalent oral poliovirus vaccine in the earlier study, or by differences in household exposure to other factors that might affect OPV efficacy (children in the nOPV2 study were required to have a sibling).

Added value of this study

This study provides the first estimates of individual-level protection of nOPV2 against circulating vaccine-derived type 2 poliovirus (cVDPV2) poliomyelitis in a setting of persistent poliovirus transmission. Our estimate was lower than the immune response measured in all previous nOPV2 clinical trials. We found no significant difference between effectiveness of nOPV2 and mOPV2 against cVDPV2 poliomyelitis in Nigeria, consistent with the study in Panama, but we were also unable to exclude the possibility of certain differences (less than 30% absolute difference).

We also estimated the effectiveness of inactivated poliovirus vaccine (IPV) against cVDPV2 poliomyelitis. In contrast to OPV, we found the magnitude of IPV effectiveness was similar to the magnitude measured in seroconversion studies.

This is also the first study, to our knowledge, to quantify the impact of recall error on poliovirus vaccine effectiveness estimates. We found that recall error tends to result in underestimation of true vaccine effectiveness, but it would need to be substantial to fully explain the lower estimate in this study.

Implications of all the available evidence

The immunogenicity of nOPV2, like that of other OPVs, is highly variable. Most evidence, including our own, suggests that nOPV2 has similar immunogenicity to mOPV2 or that nOPV2 is not substantially worse than mOPV2. This finding supports the global recommendation that nOPV2, which is more genetically stable than mOPV2, should be preferred for cVDPV2 outbreak response to minimise the risk of new emergences. Recall error might partly explain low effectiveness or immunogenicity observed in this study and in the Liberia seroprevalence survey. IPV is as effective in preventing poliomyelitis as immunogenicity studies in other settings suggested, even in settings where OPV performance might be inhibited.

and 3) in routine immunisation in 2016. Unfortunately, since the withdrawal of type 2 OPV, outbreaks of cVDPV2 linked to undetected pre-withdrawal transmission required responses using Sabin monovalent type 2 OPV (mOPV2). The use of this vaccine led to new emergences of cVDPV2 and cycles of outbreak and response.[3] In total, 2960 cVDPV2 cases were reported globally between 2016 and 2022.[1]

Novel type 2 oral polio vaccine (nOPV2) was designed with greater genetic stability to create a vaccine with similar immunogenicity to mOPV2 but with reduced likelihood of creating future VDPV outbreaks.[4] Emergency use listing of nOPV2 was granted in November, 2020, based on well established surrogates and demonstrated safety and genetic stability.[5] Given that previous studies have shown decreased seroconversion and lower effectiveness of Sabin OPV in settings with poor sanitation and a high burden of gastrointestinal infections,[6,7] it is of importance to assess the effectiveness of nOPV2 during its use under emergency use listing in outbreak response.

Between Jan 10, 2018, and Dec 31, 2022, Nigeria experienced continuous cVDPV2 transmission, with 526 cases of cVDPV2 poliomyelitis detected in total and a large outbreak in 2021 (420 cases). Between January, 2017, and February, 2021, Nigeria delivered approximately 180 million doses of mOPV2 in outbreak response campaigns.[1] In March, 2021, Nigeria became the first country to use the more genetically stable nOPV2 in outbreak response, delivering 450 million doses and accounting for 60% of global usage in 2021–22.[1] 12 of 31 states conducted five or more vaccination campaigns over 2021–22 while still detecting breakthrough cVDPV2 transmission.[1]

A single dose of inactivated poliovirus vaccine (IPV) at 14 weeks of age was introduced into routine immunisation

in Nigeria in 2015 in preparation for type 2 OPV withdrawal. In addition, 16 million doses of full-dose IPV and 19 million doses of fractional-dose IPV were delivered in supplementary immunisation activities (SIAs) between May, 2017, and October, 2020, to complement the mOPV2 outbreak response campaigns and boost IPV coverage.[2] National coverage increased from 42% at introduction in 2015 to 62% by 2022.[8] A second dose of IPV was introduced at 6 weeks of age in 2021.

We aimed to estimate the per-dose individual-level effectiveness of nOPV2 in outbreak response against cVDPV2 poliomyelitis in Nigeria during emergency use listing of the vaccine. Our secondary aim was to estimate the relative effectiveness of nOPV2 compared with mOPV2 and IPV.

Methods

Study design

We conducted a retrospective matched case-control study using routinely collected acute flaccid paralysis (AFP) surveillance data from Jan 1, 2017, to Dec 31, 2022, in Nigeria. These data are from the database maintained by the WHO Nigeria Country Office, Abuja, Nigeria. Moreover, we prospectively collected vaccination histories from community controls living in the same settlement as cVDPV2 cases from April 10, 2021 (following the first use of nOPV2 on March 13, 2021) and conducted a parallel case-control study using community controls. Before undertaking the statistical analysis, we developed a written analysis plan including power calculations and methods for conditional logistic regression, estimating doses of nOPV2 and mOPV2, and sensitivity analyses to related assumptions (appendix pp 25–30). Other analyses presented here are post-hoc. We followed STROBE guidelines for reporting observational studies (appendix p 34).

Data and definitions

Global surveillance for poliomyelitis is conducted through notification of AFP cases.[9] For each child up to 15 years of age investigated with AFP, information collected from guardians includes the individual's age, sex, and residence (first and second administrative region, hereafter referred to as "state" for first administrative region and "local government area" [LGA] for second administrative region), the date of onset of paralysis, the reported number of doses of OPV received through routine immunisation and through SIAs, the most recent date of OPV received through SIA, and the reported number of doses of IPV received (see sample AFP case investigation form; appendix pp 31–32). In Nigeria, AFP cases are revisited within 2 weeks of initial case investigation, whereby these data are verified by specially trained WHO surveillance officers.

cVDPV2 poliomyelitis cases were confirmed through culture and sequencing of poliovirus in stool. Laboratories in the Global Polio Laboratory Network follow strict procedures to ensure a high quality of results.[10] We defined cVDPV2 poliomyelitis cases as children with AFP and with cVDPV2 in their stool or in the stool of their contacts identified following global surveillance guidelines.[9] Test-negative controls were children with AFP with no wild poliovirus or VDPV in their stool or their contacts' stool.

To provide an alternative data source for controls, we prospectively collected data from community controls under routine surveillance following nOPV2 use, using a different methodology to AFP case investigation.[11] These surveys collected vaccination histories from randomly selected age-matched healthy children residing in the same settlement as each cVDPV2 case. Details on random selection are described in the nOPV2 surveillance guide.[11] To maximise power while allowing the field teams to make best use of their time, data for 12 controls were collected per case. Surveys were conducted for a subset of cVDPV2 cases due to logistical constraints during the COVID-19 pandemic and the large number of cVDPV2 cases in 2021.

We restricted our study to children with AFP (cases and test-negative controls) or community controls with recorded age, LGA of residence, date of onset of paralysis, date of case investigation, and polio vaccination histories (both SIA OPV doses and IPV doses recorded). We excluded children born before May 1, 2016, to avoid those exposed to tOPV, and children aged 60 months or older to minimise recall error.

The GPEI maintains a calendar of SIAs worldwide including LGA-level information on the dates of implementation, age groups targeted, and vaccine formulation. We obtained data for SIAs implemented between January, 2016, and December, 2022, accessed through the Polio Information System.[1]

See Online for appendix

All the data used in this study were collected as part of routine polio surveillance activities.[9,11] Caregivers provided verbal consent to participate in surveillance on behalf of their children with the understanding that data might be used for multiple purposes to assist in polio eradication efforts. Institutional ethics approval for this study was granted by the Imperial College Research Governance and Integrity Team (reference ID 21IC6996).

Statistical analysis

We matched cases to test-negative controls by age (within 12 months), date of onset of paralysis (within 30 days), and location of residence (within 50 km of the case's LGA, but restricting to the same state) and maximised the number of cases matched to one or more controls (appendix p 3).

As information on the total number of OPV doses received by each child is recorded and not the dose number by vaccine type (mOPV2, nOPV2, or bOPV), we estimated the number of doses of each vaccine type using

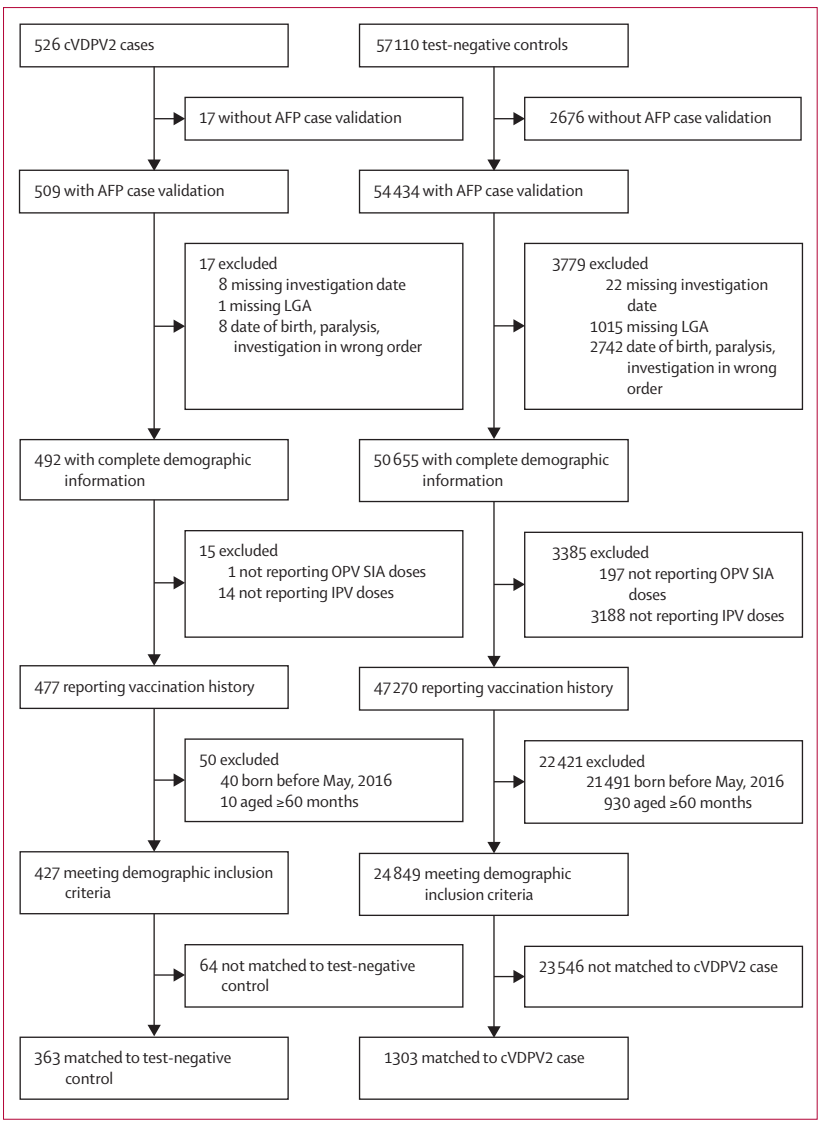

Figure 1: **Study profile**
Summary of inclusion criteria for cVDPV2 cases and test-negative controls to estimate nOPV2 and mOPV2 effectiveness between Jan 1, 2017, and Dec 31, 2022. AFP=acute flaccid paralysis. cVDPV2=type 2 circulating vaccine-derived poliomyelitis. IPV=inactivated poliovirus vaccine. LGA=local government area. mOPV2=monovalent type 2 oral poliovirus vaccine. nOPV2=novel type 2 oral poliovirus vaccine. SIA=supplementary immunisation activity.

information from the SIA calendar and the child's age and residence (LGA), assuming the number of doses received of each vaccine type was proportional to the number of campaigns the child was exposed to, after accounting for date of last OPV dose from SIA, if reported (appendix p 3). We tested the correlation between reported OPV SIA doses and the number of campaigns the child was exposed to using the Pearson correlation coefficient.[12]

The number of IPV doses (either fractional dose or full dose) from routine immunisation and SIAs was reported separately. From Jan 1, 2022, IPV doses received through routine immunisation were recorded separately to those received through SIAs. For reported IPV doses before this date, we estimated the source (routine immunisation *vs* SIA) on the basis of the total doses reported, the date of birth, and IPV SIAs in the child's LGA (appendix p 4).

Because our study is a matched case-control design, we used a conditional logistic regression implemented in the R survival package[13] to estimate the per-dose effectiveness of nOPV2 (v_n) and mOPV2 (v_m), and the effectiveness of one dose (v_{i1}) or two or more doses (v_{i2}) of full or fractional IPV:

$$log(Odds\ cVDPV2\ poliomyelitis) = bn\ xn + bm\ xm + bi1\ xi1 + bi2\ xi2 + E$$

where $v_n = 1 - e^{b_n}$; $v_m = 1 - e^{b_m}$; $v_{i1} = 1 - e^{b_{i1}}$; $v_{i2} = 1 - e^{b_{i2}}$; E was the level of cVDPV2 exposure of each matched case-control set, which was eliminated by maximising the conditional likelihood; x_n was the number of doses of nOPV2; x_m was the number of doses of mOPV2; $x_{i1}=1$ if the number of doses of IPV was one or 0 if otherwise; and $x_{i2}=1$ if the number of doses of IPV was two or more or 0 if otherwise.

We assumed that OPV generates an all-or-nothing protective response to vaccination such that the relationship between vaccine effectiveness and number of doses is log-linear, while the relationship for IPV is non-parametric, allowing for a prime–boost response to be estimated.[14]

We did sensitivity analyses on assumptions relating to matching cases and controls, inferring vaccination history, inclusion criteria, and relaxing the assumption of a log-linear relationship between OPV doses and protection against poliomyelitis. Further methods are given in the appendix (pp 4–6).

To validate our case-control method and inference of OPV dose history, we simulated matched case-control data with known vaccine efficacy and different levels of inaccurate dose reporting, following methods detailed in the appendix (pp 6–8).

We tested for the difference in two odds ratios by taking a p value for the ratio, z, from the standard normal:

$$z = |x_1 - x_2| / {}^2\sqrt{s_1 + s_2}$$

where x was the log-odds and s was the standard error. We used a p value threshold of 0·01 to define significance, using a Bonferroni correction with five tests and a family error rate of 0·05. All analyses were done in R version 4.2.1.

Role of the funding source

Employees of the Bill & Melinda Gates Foundation participated in data interpretation and reviewing of the final manuscript, but not in data collection, data analysis, writing of the manuscript, or decision to submit for

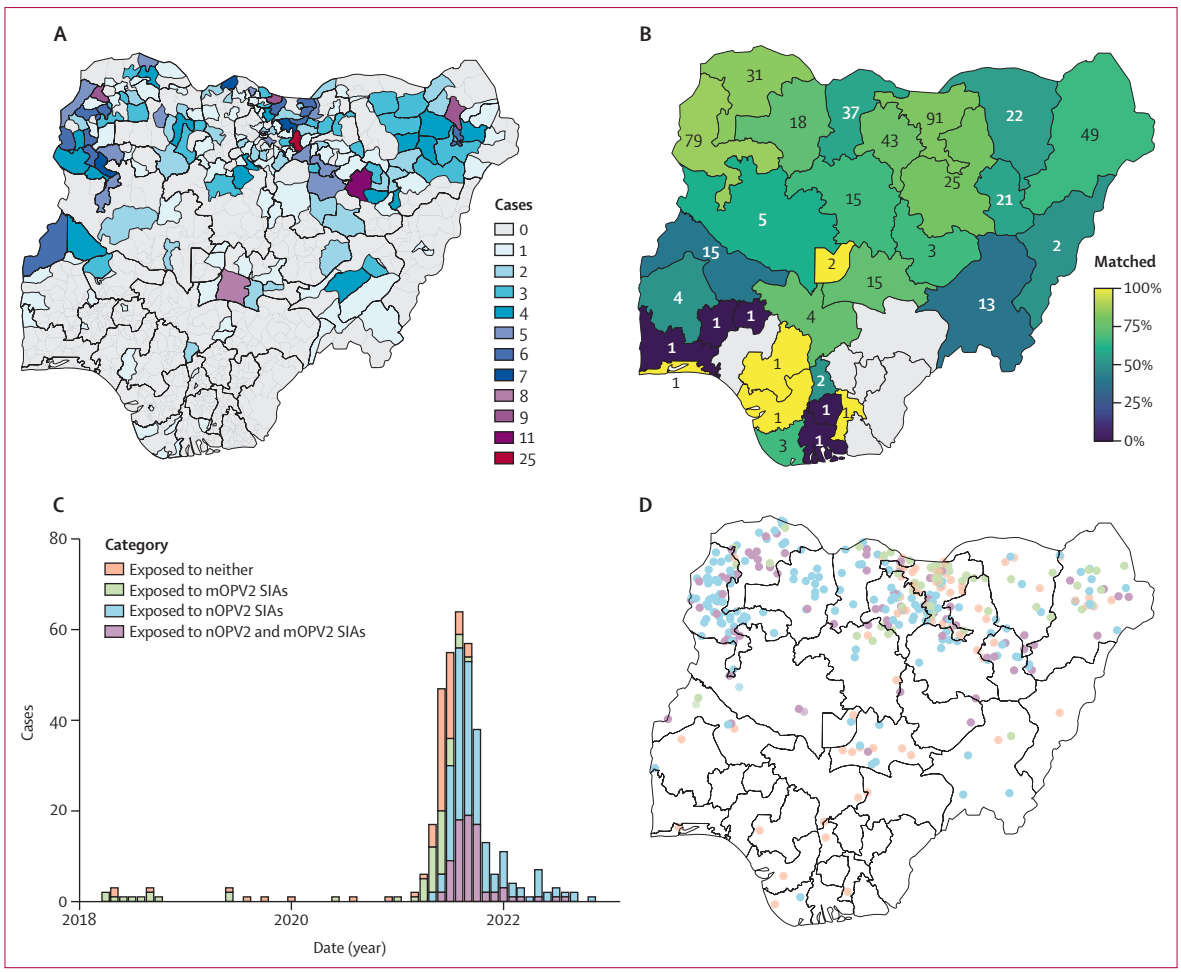

Figure 2: **Spatial and temporal distribution of cVDPV2 poliomyelitis cases in Nigeria**
(A) All validated cVDPV2 cases with onset between Jan 1, 2017, and Dec 31, 2022, mapped per LGA. (B) Proportion of validated cases by state matched to controls using the following criteria: within 50 km of case LGA, control age within 12 months of case age, and control paralysis onset within 30 days of case onset. Numbers show total validated cases per state. (C) Matched cases by month of onset, coloured by exposure to type-specific OPV2 SIAs. (D) Location of matched cases, coloured by exposure to type-specific OPV2 SIAs. cVDPV2=type 2 circulating vaccine-derived poliovirus. LGA= local government area. mOPV2=monovalent type 2 oral poliovirus vaccine. nOPV2=novel type 2 oral poliovirus vaccine. OPV2=type 2 oral poliovirus vaccine. SIA=supplementary immunisation activity.

publication. The UK Medical Research Council had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 509 cVDPV2 poliomyelitis cases in Nigeria with case verification and paralysis onset between Jan 1, 2017, and Dec 31, 2022 (figure 1). 408 (80%) of 509 cases occurred in 2021, with 293 (58%) occurring between June 1 and Sept 30, 2021. Cases were concentrated in the northwestern (n=314) and northeastern states (n=132), with most cases reported in Jigawa (n=91), Kebbi (n=79), and Borno (n=49) states (figure 2A).

We excluded 82 children with AFP who did not meet our inclusion criteria, mostly those born before May 1, 2016 (n=40). 363 (85%) of 427 eligible cases were matched to 1303 test-negative controls (figure 1). The median number of controls per case was 4 (IQR 3–6). Slightly more cases were excluded for not meeting inclusion criteria (82 [16%] of 509) than for absence of suitable matched test-negative controls (64 [13%] of 509). Matching did not substantially differ by geographical region (figure 2B), and cases and controls had similar demographic characteristics (table 1).

77 (21%) of 363 matched cases were exposed to both mOPV2 and nOPV2 SIAs, 53 (15%) of 363 matched cases were exposed to only mOPV2 SIAs, 163 (45%) were exposed to only nOPV2 SIAs, and 70 (19%) were exposed to no type 2 OPV SIAs (figure 2C). 345 (98%) of 363 matched cases were in the northern states. There was no clear geographical difference in the exposure of cases to SIAs (figure 2D). Cases reported receiving fewer OPV doses through SIAs than controls (mean number of doses was 5·9 [SD 4·2] in cases *vs* 6·7 [SD 4·3] in controls) and were exposed to similar numbers of mOPV2 and nOPV2 SIA doses (figure 3). There was a positive correlation between the number of doses of OPV reported to have

	Cases (n=363)	Test-negative controls (n=1303)
Sex		
Female	170 (47%)	565 (43%)
Male	193 (53%)	738 (57%)
Age		
0–11 months	15 (4%)	61 (5%)
12–23 months	132 (36%)	407 (31%)
24–35 months	127 (35%)	520 (40%)
36–60 months	89 (25%)	315 (24%)
OPV routine immunisation doses		
0	223 (61%)	635 (49%)
1	20 (6%)	29 (2%)
2	15 (4%)	53 (4%)
3 or more	100 (28%)	568 (44%)
Unknown	5 (1%)	18 (1%)
IPV doses		
0	268 (74%)	790 (61%)
1	84 (23%)	477 (37%)
2 or more	11 (3%)	36 (3%)

Data are n (%). OPV=oral poliovirus vaccine. IPV=inactivated poliovirus vaccine.

Table 1: **Categorical demographic and immunisation history data from poliomyelitis cases due to type 2 circulating vaccine-derived poliovirus and matched test-negative controls in Nigeria with onset of paralysis between Jan 1, 2017, and Dec 31, 2022**

been received through SIAs and the number of OPV SIAs to which test-negative controls were exposed based on the SIA calendar (n=24849 controls, Pearson's rho 0·68, appendix p 9). This correlation was weakest in Borno state (0·09) and strongest in Ekiti state (0·88).

Fewer children had received IPV among cases (95 [26%] of 363) than among controls (513 [39%] of 1303; table 1). Controls also reported higher coverage of routine immunisation OPV, with 568 (44%) of 1303 controls and 100 (28%) of 363 cases reporting three or more doses. Few cases or controls reported two or more IPV doses (11 [3%] of 363 cases, 36 [3%] of 1303 controls). OPV and IPV dose reporting changed gradually over time, with caregivers reporting more doses of IPV and OPV from routine immunisation and fewer doses of OPV from SIAs (appendix p 9).

We found low per-dose effectiveness of nOPV2 (12%, 95% CI –2 to 25) and mOPV2 (17%, 3 to 29; table 2). We observed no significant difference between the per-dose effectiveness of nOPV2 and mOPV2 (p=0·67). If we relaxed the assumption of a log-linear relationship between additional OPV doses and protection, we found a consistently increasing trend of protection from one to three doses, with lower protection from five and six or more doses for mOPV2 and from four, five, and six or more doses for nOPV2 (appendix p 10). 77 (46%) of 168 cases and controls from Sokoto and Zamfara were assigned four or more doses of mOPV2 or nOPV2, compared with 85 (6%) of 1498 children from other states. In a post-hoc analysis, we found a higher per-dose effectiveness of nOPV2 (26%, 95% CI 7 to 40) and mOPV2 (22%, 6 to 35) when we excluded cases and controls from Sokoto and Zamfara, where coverage of recent nOPV2 SIAs was likely to be poor relative to the coverage of mOPV2 SIAs (appendix p 11), but this difference in Sokoto and Zamfara versus other states was not significant (p value for difference in nOPV2=0·049, p value for difference in mOPV2=0·10). All other sensitivity analyses to inclusion and matching criteria and dose modelling assumptions had negligible effects on estimates of vaccine effectiveness (appendix pp 20–24).

The estimated effectiveness of one dose of IPV was 43% (95% CI 23–58). This result was robust to all sensitivity analyses (appendix pp 20–24). There were too few individuals reporting two or more IPV doses to accurately estimate the effectiveness of a second dose (table 1). For both cases and controls, we found that IPV was delivered predominantly through routine immunisation (appendix p 11). 68 (72%) of 95 cases and 394 (77%) of 513 test-negative controls reporting one or more IPV doses presented a routine immunisation card for verification (appendix p 12).

In our prospective study using community controls, 181 (46%) of 392 eligible cases with paralysis onset since the introduction of nOPV2 could be matched to 1557 community controls within 12 months of age (appendix p 12). Because of the low matching rate, this analysis was underpowered according to our statistical analysis plan (appendix pp 25–30). Using community controls, we found a high effectiveness of IPV (89% [95% CI 83 to 93] for one dose, 97% [90 to 99] for two or more doses), a low per-dose effectiveness of nOPV2 (–23% [–45 to –5]) and mOPV2 (1% [–23 to 20]), and no significant difference between the per-dose effectiveness of nOPV2 and that of mOPV2 (p=0·12; appendix p 12).

The proportion of cases who were matched to community controls was not random in space and time, with the lowest proportion matched in Nasarawa and Kaduna states, and the highest proportion matched in Sokoto and Zamfara states. Fewer cases were matched at the beginning of implementation of community control surveys (appendix p 12).

162 cases were matched to both community controls (n=1388) and test-negative controls (n=609). Community controls were less well matched to cases than test-negative controls in terms of age (median age difference 7 months [IQR 3–10] *vs* 4 months [1–8], respectively), timing of survey (median 59 days [IQR 50–88] between case paralysis onset and community survey *vs* 12 days [5–21] between case paralysis onset and test-negative control paralysis onset), and routine immunisation coverage (appendix p 13). We found no significant difference in effectiveness of nOPV2 or mOPV2 when comparing test-negative and community controls (p=0·046, p=0·44, respectively), but we did estimate

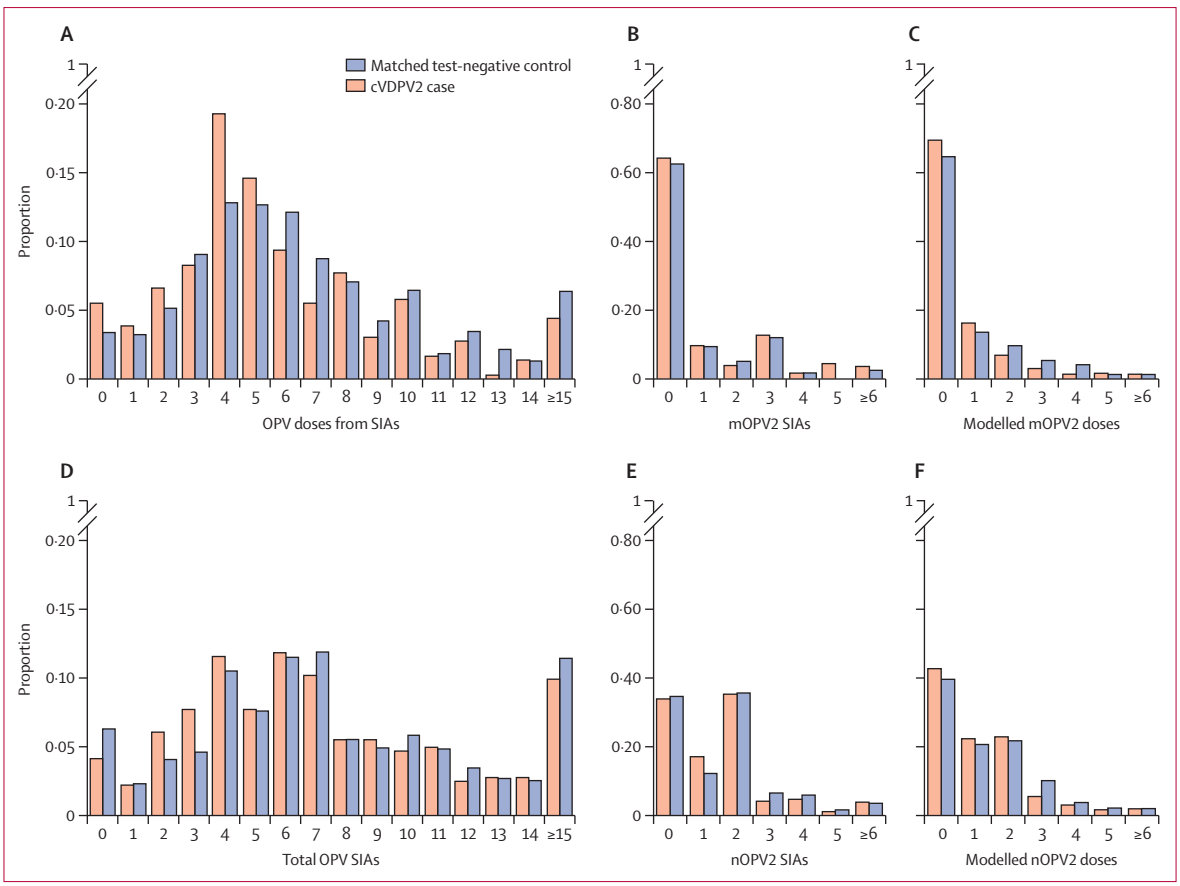

Figure 3: **OPV history of cVDPV2 poliomyelitis cases and test-negative controls in Nigeria between Jan 1, 2017, and Dec 31, 2022**
Distributions of the proportions of reported OPV doses from SIAs (A), mOPV2 SIAs that cases or controls were exposed to (B), modelled number of mOPV2 doses (C), total OPV SIAs that cases or controls were exposed to (nOPV2, mOPV2, or bivalent OPV; D), nOPV2 SIAs that cases or controls were exposed to (E), and modelled number of nOPV2 doses (F). cVDPV2=type 2 circulating vaccine-derived poliovirus. mOPV2=monovalent type 2 oral poliovirus vaccine. nOPV2=novel type 2 oral poliovirus vaccine. OPV=oral poliovirus vaccine. SIA=supplementary immunisation activity.

significantly higher effectiveness of one dose of IPV when using community controls than when using test-negative controls (appendix p 13, p<0·0001).

Our simulations showed that our method for inferring OPV history produced accurate estimates of mOPV2 and nOPV2 effectiveness (appendix p 14), but the method tended to underestimate the true effectiveness as dose recall became more inaccurate (appendix p 15). If true effectiveness were similar to seroconversion observed in phase 3 trials in The Gambia (49%),[15] 90% of dose reports would need to be inaccurate to result in an estimated effectiveness as low as 15%, as observed in our study (appendix p 16). We also found there was only sufficient power to exclude absolute differences in effectiveness between the two vaccines of larger than 20–30% (appendix p 17).

	Odds ratio (95% CI)	p value	Effectiveness (95% CI)
mOPV2 (per dose)	0·83 (0·71–0·97)	0·023	17% (3 to 29)
nOPV2 (per dose)	0·87 (0·75–1·02)	0·084	12% (–2 to 25)
IPV			
0	1·00 (ref)	..	..
1	0·57 (0·42–0·77)	0·00020	43% (23 to 58)
2 or more	1·15 (0·53–2·50)	0·73	–15% (–150 to 47)

Test-negative controls (n=1303) were matched to cVDPV2 cases (n=363) by date of onset (within 30 days), age at onset (within 12 months), state, and local government area (within 50 km distance by centroid). cVDPV2=type 2 circulating vaccine-derived poliovirus. mOPV2=monovalent type 2 oral poliovirus vaccine. nOPV2=novel type 2 oral poliovirus vaccine. IPV=inactivated poliovirus vaccine.

Table 2: **Estimated effectiveness of one dose of mOPV2, nOPV2, and IPV, and one dose or two or more doses of IPV against poliomyelitis due to cVDPV2 in Nigeria, derived from conditional logistic regression**

Discussion

We provide the first individual-level estimates of nOPV2 effectiveness against type 2 poliomyelitis during outbreak response under emergency use listing of the vaccine. Although we found no significant difference in effectiveness of nOPV2 relative to mOPV2, we cannot exclude the possibility of some absolute differences (30% or smaller). This finding of no difference in effectiveness is consistent with a clinical trial

demonstrating non-inferior immunogenicity of nOPV2 relative to historical mOPV2 controls in Panama[5] and a modelling study that found no significant difference between the population impact of nOPV2 and mOPV2 SIAs on cVDPV2 incidence in Nigeria.[16] Two studies conducted 6 years apart in the same age group and at the same study site in Bangladesh found significantly lower seroconversion after one or two doses of nOPV2 compared with mOPV2, but this finding could be explained by unintentional tOPV vaccine exposure in the earlier study, or by differences in household exposure to other factors that might affect OPV efficacy (children in the nOPV2 study were required to have a sibling).[17,18] Overall, these data support the global recommendation that nOPV2, which is more genetically stable than mOPV2, should be preferred for cVDPV2 outbreak response to minimise the risk of new cVDPV2 emergences.[19]

Our findings indicate that nOPV2 and mOPV2 might be less effective against cVDPV2 poliomyelitis in some field settings, such as parts of Nigeria, than in populations where seroprevalence studies were conducted, including Bangladesh,[17,18] Panama,[5] Tajikistan,[20] and The Gambia.[15] Inaccurate recall can partly explain the difference between the estimated effectiveness in Nigeria and seropositivity—a well accepted correlate of protection against poliomyelitis[14]—measured in earlier trials, but recall would need to be extremely unreliable to fully account for this magnitude of difference. Unfortunately, the data required to estimate recall error in this population are currently lacking.

Reviews of seroprevalence studies have documented substantial variation in OPV immunogenicity, with lower immune responses observed in low-income settings with poor sanitation and high prevalence of malnutrition, enteric infections, and diarrhoeal disease.[7,21] Previous case-control studies have also demonstrated lower effectiveness in poliovirus-endemic areas.[22,23] A case-control study in Nigeria between 2002 and 2012 demonstrated significantly lower effectiveness of OPV against wild poliovirus type 1 in northern states than in southern states but could not estimate spatial differences for effectiveness against cVDPV2 because few cases were reported in the south.[6] The magnitude of effectiveness estimated in this study is more consistent with findings from a cross-sectional seroprevalence study in Liberia, which found 42% seropositivity in children reporting 38% coverage of two-dose nOPV2, 7% coverage of one-dose nOPV2, and 96% coverage of IPV. The study in Liberia also relied on caregiver recall to ascertain nOPV2 history, and it was carried out in a population with a similar income level to the population in this study.[24]

Low effectiveness might partly explain why some regions of Nigeria required as many as nine nOPV2 campaigns to stop cVDPV2 transmission.[16] Standard outbreak response protocols call for two campaigns with high coverage, with additional responses to breakthrough transmission as required.[25] It might be necessary to anticipate additional campaigns in settings where OPV immunogenicity is suspected to be poor.

In a post-hoc analysis, we found lower per-dose effectiveness of nOPV2 and mOPV2 in Sokoto and Zamfara relative to other states. Although these differences were not significant, lower effectiveness in Sokoto and Zamfara than in other states might be due to the campaign coverage in Sokoto and Zamfara being lower than in other regions of Nigeria due to recent insecurity,[26] due to recall being less accurate because of the high number of SIAs that took place, or simply due to chance.

The effectiveness of one dose of IPV estimated in this study is consistent with previous seroconversion studies,[27] perhaps because IPV immunogenicity is less variable than OPV immunogenicity globally.[7] IPV recall might also be more accurate: most were confirmed by routine immunisation card and IPV is administered in lower numbers than OPV. A small fraction of children for whom IPV doses were reported might have received fractional IPV from SIAs, but most IPV was from routine immunisation, in which the full dose is used. We adjusted for all IPV doses, including IPV received from SIAs and either fractional or full dose, but there was insufficient power to estimate effectiveness of fractional IPV separately from full-dose IPV. Our findings demonstrate the role of IPV in providing individual protection against poliomyelitis and the importance of both strengthening routine immunisation and introducing the second IPV dose to increase protection. However, our findings do not indicate whether IPV has any impact on cVDPV2 shedding and thus transmission.

Community control surveys were planned to provide suitable controls in populations with weaker AFP surveillance or if cases accumulated at a low rate.[11] Surveys were only conducted for a subset of cVDPV2 cases due to logistical constraints. Because of its small sample size, difference in survey methodology, and poor matching between cases and community controls, we found that the results of the case-control analysis using community controls were likely to be less reliable than the results using test-negative controls.

Our analysis depends on accurate reporting of OPV doses received through SIAs and accurate curation of data on the dates and locations of SIAs. A systematic review of agreement between different methods for ascertaining routine immunisation status found good agreement between caregiver recall and immunisation cards across 22 low-income and middle-income countries but poor agreement between status based on recall or immunisation cards and facility-based records or serology.[28] Few studies have assessed the validity of recall for vaccinations delivered in SIAs, for which the delivery setting and frequency differ from routine immunisation. We found good correlation between the

number of OPV SIA doses reported by caregivers and the number expected on the basis of the SIA calendar, especially in the states where most cases were located. It is difficult, however, to disentangle when the number of reported doses departs from the number of SIAs in the calendar due to low SIA coverage or recall error.[29]

All cVDPV2 transmission must be stopped to achieve polio eradication. Outbreaks are ongoing across multiple countries. The improved genetic stability of nOPV2 compared with Sabin mOPV2, coupled with the indication of similar effectiveness, promises to stop transmission with fewer subsequent outbreaks. High-quality, timely campaigns must be conducted following detections of new or breakthrough infections to be able to succeed in eradicating poliovirus, but additional strategies might be required in settings where OPV immunogenicity is low.

Contributors

LVC, IMB, and NCG contributed to study concept and design. LVC, IMB, EJG, and NCG developed the statistical methods. TBE, AAD, HWA, KB, USA, FS, NM, SZ, and ASB oversaw polio surveillance data collection and curation. LVC, TBE, and IMB accessed and verified all the data. LVC performed the statistical analysis. LVC, IMB, NCG, SOO, ASB, and TBE interpreted the findings of the statistical analysis. LVC and IMB drafted the original report and were responsible for the decision to submit the manuscript. All authors contributed to critical revision of the manuscript for intellectual content.

Declaration of interests

We declare no competing interests.

Data sharing

Detailed disease surveillance data on which this research is based are available from the WHO Institutional Data Access/Ethics Committee for Global Polio Eradication Initiative research partners who meet the criteria for access to confidential data.

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