Key issues in the persistence of poliomyelitis in Nigeria: a case-control study

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Summary

Background The completion of poliomyelitis eradication is a global emergency for public health. In 2012, more than 50% of the world’s cases occurred in Nigeria following an unanticipated surge in incidence. We aimed to quantitatively analyse the key factors sustaining transmission of poliomyelitis in Nigeria and to calculate clinical efficacy estimates for the oral poliovirus vaccines (OPV) currently in use.

Methods We used acute flaccid paralysis (AFP) surveillance data from Nigeria collected between January, 2001, and December, 2012, to estimate the clinical efficacies of all four OPVs in use and combined this with vaccination coverage to estimate the effect of the introduction of monovalent and bivalent OPV on vaccine-induced serotype-specific population immunity. Vaccine efficacy was determined using a case-control study with CIs based on bootstrap resampling. Vaccine efficacy was also estimated separately for north and south Nigeria, by age of the children, and by year. Detailed 60-day follow-up data were collected from children with confirmed poliomyelitis and were used to assess correlates of vaccine status. We also quantitatively assessed the epidemiology of poliomyelitis and programme performance and considered the reasons for the high vaccine refusal rate along with risk factors for a given local government area reporting a case.

Findings Against serotype 1, both monovalent OPV (median 32·1%, 95% CI 26·1–38·1) and bivalent OPV (29·5%, 20·1–38·4) had higher clinical efficacy than trivalent OPV (19·4%, 16·1–22·8). Corresponding data for serotype 3 were 43·2% (23·1–61·1) and 23·8% (5·3–44·9) compared with 18·0% (14·1–22·1). Combined with increases in coverage, this factor has boosted population immunity in children younger than age 36 months to a record high (64–69% against serotypes 1 and 3). Vaccine efficacy in northern states was estimated to be significantly lower than in southern states (p≤0·05). The proportion of cases refusing vaccination decreased from 37–72% in 2008 to 21–51% in 2012 for routine and supplementary immunisation, and most caregivers cited ignorance of either vaccine importance or availability as the main reason for missing routine vaccinations (32·1% and 29·6% of cases, respectively). Multiple regression analyses highlighted associations between the age of the mother, availability of OPV at health facilities, and the primary source of health information and the probability of receiving OPV (all p<0·05).

Interpretation Although high refusal rates, low OPV campaign awareness, and heterogeneous population immunity continued to support poliomyelitis transmission in Nigeria at the end of 2012, overall population immunity had improved due to new OPV formulations and improvements in programme delivery.

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Introduction

In May, 2012, after more than 20 years of mass vaccination campaigns, the 65th World Health Assembly declared that the completion of poliomyelitis eradication was a “programmatic emergency for global public health”. Substantial financial and political pledges to poliomyelitis eradication have recently intensified efforts, and prevalence of poliomyelitis is at a historical low, although transmission in Afghanistan, Pakistan, and Nigeria remains persistent. Globally, case numbers have fallen (1651 cases in 2008 vs 223 in 2012), and India, once one of the most entrenched reservoirs, is now free of indigenous poliovirus transmission. However, in Nigeria, poliomyelitis cases doubled between 2011 and 2012, with sustained transmission of all three serotypes in 2012 (103 and 19 cases due to serotypes 1 and 3 wild poliovirus and eight due to circulating vaccine-derived poliovirus type 2 [cVDPV2]). In 2012, Nigeria was the global epicentre of poliovirus outbreaks, astonishing those who commended its success during 2010 when case numbers fell by 95%.

The 2011 Nigeria Emergency Action Plan has been refined to further involve key political and traditional leaders, and hundreds of volunteer community mobilisers have been charged with reaching every child in Nigeria to administer the vaccines to combat the recent setbacks. The 2012 plan built on lessons learnt in previous years, aiming to integrate almost real-time feedback from teams on the ground with the highest level of governance to ensure chronically missed children are protected and supplies reach the most vulnerable children. Additionally, in November, 2009, the Advisory Committee on Poliomyelitis Eradication recommended the introduction of bivalent oral poliovirus vaccine (bOPV) to supplementary immunisation activities in areas with sustained transmission of wild-type poliovirus.
serotypes 1 and 3, but the efficacy of bOPV in Nigeria has not yet been assessed. Such an assessment is especially important during this period of rapid increase in demand and manufacture of the vaccine and when discussions are underway regarding its potential use during routine immunisation in place of trivalent vaccine (tOPV).3

In this Article we explain why Nigeria has been experiencing continued high caseloads despite achieving record successes in vaccine coverage and political and community engagement by identifying the key factors driving poliovirus transmission.

Methods

Study design and procedures

We used acute flaccid paralysis (AFP) surveillance data from Nigeria collected between January, 2001, and December, 2012, to estimate the clinical efficacies of all four oral poliovirus vaccines (OPVs) using a case-control study. This was combined with vaccination coverage to estimate the effect of the introduction of monovalent OPV (mOPV) and bOPV on vaccine-induced serotype-specific population immunity.

To assess efficacy, children aged under 15 years with confirmed poliomyelitis (due to wild-type 1 or 3 poliovirus or cVDPV2) were matched with up to five randomly selected control children with non-polio AFP chosen from the AFP surveillance database produced by the government of Nigeria (appendix). Cases were matched to controls by state and by date (within 1 month) and age at onset of paralysis (within 6 months). These criteria were chosen to maximise the number of matches while controlling for differential exposure to poliovirus. Vaccine efficacy was also estimated separately for north and south Nigeria, by age of the children, and by year.

To investigate vaccine-induced population immunity, we estimated the proportion of children younger than 36 months who were protected against each poliovirus serotype, on the basis of the reported vaccination history of children with non-polio AFP and our estimates of vaccine efficacy. These children were assumed to be representative of the underlying population. Detailed 60-day follow-up data were collected from children with confirmed poliomyelitis and were used to assess correlates of vaccine status.

Finally, we quantitatively assessed the epidemiology of poliomyelitis and programme performance and considered the reasons for the high vaccine refusal rate along with risk factors for a given local government area (LGA) reporting a case. Institutional ethics approval was not sought because this is a retrospective study using anonymised national surveillance data detailing the use of standard vaccines licensed by the National Regulatory Authority of the Government of Nigeria.

Statistical analysis

We assumed that all vaccines were received through supplementary immunisation activities, because the database does not distinguish between routine vaccinations or supplementary immunisation activities. We used bootstrap resampling methods to minimise the effect of outliers and bias introduced by the matching process. Vaccine efficacy was estimated by conditional logistic regression for 1000 randomly matched sets, producing a distribution of estimates for each vaccine type. 95% CIs (2·5th and 97·5th percentiles of bootstrapped estimates) around the median estimate represent the uncertainty introduced by the matching criteria. Sensitivity of the vaccine efficacy estimates to the matching criteria was examined and the analysis was repeated under the assumption that the first three doses received were through routine immunisation (ie, tOPV) and the remainder via supplementary immunisation activities. The prevalence of non-polio AFP enteroviruses by region was examined and compared by the Fisher’s exact test.

The probability of vaccine-induced immunity in each child was estimated on the basis of the number of doses of each OPV type received and a randomly sampled value for the efficacy of each OPV using the range of estimates from the case-control study and accounting for covariance of the estimates. The mean of this quantity for children with non-polio AFP was calculated and weighted by age to match the age distribution of the population.

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Data are median values from the distribution of vaccine efficacy estimates with 95% CIs (2·5th and 97·5th percentile intervals) derived from conditional logistic regression on 1000 matched sets. Controls were matched to cases by date of onset (within 1 month), age at onset (within 6 months), and state. Estimates for vaccine efficacy in north and south Nigeria use the assumption of no routine coverage. mOPV=monovalent oral poliovirus vaccine. bOPV=brivalent oral poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine. NA=not applicable. *p<0·05 compared with tOPV estimate. †p≤0·05 compared with matched to cases by date of onset (within 1 month), age at onset (within 6 months), and state. Estimates for vaccine efficacy in north and south Nigeria use the assumption of no routine coverage. mOPV=monovalent oral poliovirus vaccine. bOPV=brivalent oral poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine. NA=not applicable. *p<0·05 compared with tOPV estimate. †p≤0·05 compared with

Table 1: Estimated efficacy of one dose of trivalent oral poliovirus vaccine, serotype 1 or 3 monovalent oral poliovirus vaccine, and bivalent oral poliovirus vaccine
We present median estimates and intervals on the basis of the 2.5th and 97.5th percentiles of the distribution from 1000 bootstrap replicates (95% CIs).

We used logistic regression to estimate the association between OPV vaccination status and the socioeconomic background of cases, the primary source of health information, and provision of local health facilities. We also examined the reported individual reasons for children with poliomyelitis to miss OPV doses during routine or supplementary immunisation.

To assess the risk of a LGA reporting a poliomyelitis case, we used an over-dispersed Poisson mixed-effects model that incorporated the spatial and temporal pseudoreplication of our data (ie, data are nested within LGAs and LGAs are repeatedly measured over time). The minimum model was calculated using a backwards stepwise deletion process with Akaike’s information criterion, and explanatory variables were retained in the model if they were significant (p<0.05) or reduced the Akaike’s information criterion value. Variables examined in the model include poliomyelitis incidence within 50 km of the centrepoint of the LGA, population immunity, and population density (calculated using the area and population size). Spatial resolution was fixed at the LGA level and variables were calculated over 12-month intervals.

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Bootstrapped bOPV efficacy estimates were higher than the corresponding tOPV estimates in 97.9% of models (p=0.04) assuming no routine coverage and 66.7% of models (p=0.7) assuming 100% coverage (table 1). There were no significant differences between bOPV and mOPV1 or mOPV3 under either assumption (all p>0.1). The lower tOPV efficacy against serotype 2 assuming 100% routine coverage compared with no routine coverage is a result of the higher number of doses received by children with poliomyelitis under this assumption compared with no routine coverage, which drives down the per-dose efficacy estimate. Adjustment of the matching criteria did not alter the general finding of lower tOPV efficacy compared with mOPV (appendix).

There was no improvement in model fit when vaccine efficacy was assessed by age (likelihood ratio test for each matched set for serotype 1 median p=0.04, 95% CI 0.01–0.88; serotype 3 p=0.21, 0.01–0.81; and cVDPV2 p=0.07, 0.01–0.29) or year of onset (serotype 1 p=0.07, 0.01–0.29; year of onset). When efficacy was assessed by region, the model fit for serotype 1 improved (median p=0.03, 95% CI 0.01–0.88).

![Figure 1: Effects of oral poliovirus vaccine use on poliomyelitis during 2001–12](image-url)

(A) Monthly incidence of poliomyelitis associated with serotypes 1 and 3 wild poliovirus and cVDPV2. (B) Median estimated age-standardised vaccine-induced population immunity against poliomyelitis due to serotype 1, serotype 3, and cVDPV2 poliovirus on the basis of vaccination histories of children younger than 36 months with non-poliomyelitis AFP by year of onset of paralysis. Estimates not standardised to show geographic population distribution and therefore biased towards areas with a high incidence of non-poliomyelitis AFP. Bars=2.5th and 97.5th percentile intervals (95% CIs) based on bootstrap resampling. (C) Mean numbers of doses of OPV received by children younger than 36 months with non-poliomyelitis AFP under the assumption that all OPV doses were received via SIAs. Arrows depict timings of SIAs, with length of arrows proportional to number of local government areas that participated. AFP=acute flaccid paralysis. bOPV=bivalent oral poliovirus vaccine. cVDPV2=circulating vaccine-derived poliovirus type 2. mOPV=monovalent oral poliovirus vaccine. OPV=oral poliovirus vaccine. SIA=supplementary immunisation activity. tOPV=trivalent oral poliovirus vaccine.
0·0003–0·40), with a higher estimated efficacy in the south than the north for tOPV and mOPV1 in 97·5–100% of matched sets (both ps<0·05). A higher prevalence of enteroviruses was found in north than in south Nigeria (odds ratio 0·60, 95% CI 0·57–0·64 p<0·0001, Fisher’s exact test).

After the introduction of bOPV in 2009, the incidence of poliomyelitis fell substantially (figure 1A), and the proportion of children in Nigeria with vaccine-induced immunity against poliovirus was at its highest in 2012, reaching 64–69% against serotypes 1 and 3 (figure 1B). The advances in immunity were driven by the more effective mOPV and bOPV formulations introduced in 2005 and 2009, respectively, along with an increase in the overall number of doses reported (mean 5·6 doses [SD 3·5] in 2012 vs 3·9 [2·2] in 2009; figure 1C). AFP surveillance sensitivity consistently exceeded the recommended minimum of one reported case annually per 100 000 children and has progressively improved (data not shown). Immunity in children younger than 36 months within the high-risk states (defined by the 2012 Nigeria Polio Eradication Emergency Plan) was heterogeneous in 2012 and 60 (20%) of 297 LGAs still had fewer than 50% of children protected against poliomyelitis (figure 2).

Caregiver refusal of vaccination became less common as a reason for children with poliomyelitis to miss OPV doses, although rates remained high (21·0% for routine and 50·9% for supplementary immunisation activities in 2012; figure 3). The main reported reasons for missing routine OPV doses in 2012 were an ignorance of vaccine importance or vaccine availability (32·1% and 29·6% of cases, respectively). In 2012, 21 (24·1%) of the 87 confirmed cases with a known vaccination history listed in the follow-up database had received no OPV. Multiple logistic regression revealed significant associations between the mother’s age, OPV availability at the nearest health facility, primary source of health information, and year of onset of paralysis with the probability of a case receiving OPV (all p<0·05; table 2). A nomadic lifestyle was not significantly associated with a failure to vaccinate (p=0·88; appendix). To further explore
this factor, we examined variables concerning the presence of a nomadic camp within 5 km of the household, whether the family live in a permanent structure, and in how many different locations the child had lived during the past 12 months as proxy measures of a nomadic or semi-nomadic lifestyle. None of these variables was significantly associated with children with poliomyelitis receiving OPV (appendix).

We found associations between poliomyelitis incidence and estimated population immunity along with the presence of a case within 50 km (appendix). Present immunity within each LGA had the strongest protective effect against incidence (rate ratio 0.49, 95% CI 0.37–0.64), and the presence of cases within the past 12 months marginally decreased risk (0.93, 0.91–0.96; appendix).

Discussion

In this study, we show that the persistence of poliovirus in northern Nigeria is driven by three fundamental issues: first, vaccine efficacy seems to be lower in northern states compared with southern states; second, coverage and population immunity remain too low to interrupt wild poliovirus transmission; and third, despite huge investments in communication, refusals and unawareness of vaccine availability or importance still dominate as reasons for failing to immunise children who develop poliomyelitis (panel).

The higher efficacy of bOPV compared with tOPV against poliomyelitis due to serotype 1, with the assumption of no routine coverage, suggests that a pre-eradication switch from tOPV to bOPV for routine immunisation, as part of the broader poliomyelitis endgame strategy, could also facilitate faster eradication of serotype 1 wild-type polioviruses.15 The recommendation by the Global Polio Eradication Initiative15 for bOPV introduction in supplementary immunisation activities was made on the basis of a study in India,11 which showed non-inferior immunogenicity of bOPV compared with monovalent vaccines, and our data support this finding. Our tOPV efficacy estimates are consistent with those from previous studies in Nigeria, although we found a lower mOPV efficacy against poliomyelitis due to serotype 1.31-33. This finding might be a result of errors in inferring a child’s vaccination history, particularly after a vaccine has been used in a large number of campaigns over a substantial period, as is the case for mOPV. Nonetheless, the monovalent vaccines showed a consistently higher efficacy than tOPV for each serotype, in agreement with findings from earlier studies.34,35 Our countrywide estimates of tOPV efficacy are comparable with those found in Bihar, India, where poliomyelitis has been successfully eliminated despite high population density and poor sanitation.36

Our finding of poor vaccine efficacy in the north of Nigeria might be a result of a higher incidence of enteric infections, including other enteroviruses, which might interfere with the response to the vaccine.37,38 Vaccine efficacy estimates could also be more substantially affected in the north by inaccurate vaccination histories, in view of the frequent rounds of supplementary immunisation activities with differing vaccine types. However, OPV efficacy (regardless of type) was significantly lower in the north (appendix), and weak evidence of lower tOPV efficacy against serotype 1 poliomyelitis in north Nigeria has been reported previously (northern region 13–23%, 95% CI 1–40; southern region 54%, 4–78%).39 Low OPV efficacy would necessitate a higher number of doses to achieve eradication and would support the accelerated
visits have been collated for high-risk states by PolioInfo.\textsuperscript{14} AFP surveillance data and estimates of vaccine coverage and social mobilisation data collected by house to house and 3. No studies so far have estimated bOPV clinical efficacy in Nigeria. Quarterly occurrence of cases.

of children under 3 years of age were protected, which explains the continued heterogeneities in vaccine coverage. In 20% of LGAs in high-risk areas fewer than half highest population immunity ever recorded in Nigeria, there are still substantial community engagement if poliomyelitis is to be eradicated. Despite achieving the unacceptably high, and we have provided strong evidence for the importance of areas. We also noted a recent drop in the rate of refusals, although this remains non-significant.\textsuperscript{10} Serological responses to poliovirus vaccine (tOPV), and tOPV efficacy was higher in the south of Nigeria than the oral poliovirus vaccine 1 (mOPV1) in 2008 in Nigeria was higher than trivalent oral poliovirus vaccine (bOPV) have been documented in India and Nigeria (appendix). The routine coverage assumptions we used agreed well with initial reports, with no suggestion of introduction of inactivated poliovirus vaccine in high-risk areas to boost immunity to all three serotypes (as outlined in the endgame strategy).\textsuperscript{15} The principal reason for children with poliomyelitis to miss routine immunisations was an ignorance of its importance, reaffirming the recommendations made by the Independent Monitoring Board of the Global Polio Eradication Initiative that promotion of demand generation is vital to eradication.\textsuperscript{22} The primary source of information on health issues strongly affected an individual’s probability of receiving OPV and so should be a priority for eradication programmes. The strong link between receiving OPV and obtaining health education via town announcers has been previously recognised and used as a way of promoting a positive message about vaccination.\textsuperscript{14,23} In Pakistan and Afghanistan, where vaccine efficacy estimates are comparable with Nigeria, targeted social mobilisation activities aimed at improving community perceptions have seen great success in reducing cases by 66% between 2011 and 2012.\textsuperscript{2,3,24} The availability of immunisation via the routine Expanded Programme on Immunization also affected the likelihood of receiving OPV, although distance to the nearest health facility was non-significant (p=0.40), probably because the supplementary immunisation activity teams undertook house-to-house visits. Our analysis included only those with confirmed poliomyelitis, and factors driving vaccine acceptance in cases might differ from those affecting the wider population. However understanding vaccine perceptions in these high-risk groups is clearly important for the eradication programme. Additionally, we expect that outreach programmes promoting routine immunisation (requiring caregivers to actively attend health facilities) might differ from those promoting supplementary immunisation activities (in which teams of health workers visit any dwellings with children), and this important topic needs further study. Although a commonly cited reason for missing children is the nomadic lifestyle of their families,\textsuperscript{25} our findings suggest that this factor might not be as important as first thought; few cases reported here claim to be nomadic and a nomadic lifestyle was not associated with a failure to vaccinate. Children of nomadic families might be less likely to visit a health facility and therefore be included in the database, but the clinical symptoms of poliomyelitis are sufficiently severe that we would expect most families to seek help.

Our results are reliant on accurate reporting of dose numbers. A more detailed vaccination history obtained at the 60-day follow-up for a subset of poliomyelitis cases agreed well with initial reports, with no suggestion of over-reporting or under-reporting of total dose numbers (appendix). The routine coverage assumptions we used represent two extreme scenarios; the true coverage level is heterogeneous across the population. However, the findings are robust to these assumptions—ie, mOPV

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Table 2: Multiple logistic regression analysis of factors associated with children younger than 15 years with poliomyelitis who received at least one dose of oral poliovirus vaccine from routine immunisation or supplementary immunisation programmes.

Panel: Research in context

Systematic review

We searched PubMed, with no date limits set, for articles published in English with the search terms “poliomyelitis AND Nigeria”, “bivalent oral poliovirus vaccine”, and “population immunity”. We used the reference lists of related articles to identify other important studies. The last search was done in June, 2013. Clinical efficacy of monovalent oral poliovirus vaccine 1 (mOPV1) in 2008 in Nigeria was higher than trivalent oral poliovirus vaccine (tOPV), and tOPV efficacy was higher in the south of Nigeria than the north, although the latter findings were non-significant.\textsuperscript{10} Serological responses to bivalent oral poliovirus vaccine (bOPV) have been documented in India and Nigeria (combined with tOPV) and clinical efficacy recorded in Pakistan and Afghanistan.\textsuperscript{14,15} Findings from these studies showed bOPV was non-inferior to mOPV against serotypes 1 and 3. No studies so far have estimated bOPV clinical efficacy in Nigeria. Quarterly estimates of vaccine coverage and social mobilisation data collected by house to house visits have been collated for high-risk states by PolioInfo.\textsuperscript{14} AFP surveillance data and poliomyelitis incidence have been recorded by WHO and published in the Weekly Epidemiological Record.\textsuperscript{8}

Interpretation

In our study, we found greater efficacy of mOPV and bOPV compared with tOPV in Nigeria, along with differences in vaccine efficacy between northern and southern regions, potentially resulting in the need for more doses to protect children in high-risk areas. We also noted a recent drop in the rate of refusals, although this remains unacceptably high, and we have provided strong evidence for the importance of community engagement if poliomyelitis is to be eradicated. Despite achieving the highest population immunity ever recorded in Nigeria, there are still substantial heterogeneities in vaccine coverage. In 20% of LGAs in high-risk areas fewer than half of children under 3 years of age were protected, which explains the continued occurrence of cases.
and bOPV are more effective than tOPV. We compared a subset of our population immunity results with those derived from a seroprevalence survey in Kano metropolitan area during 2011 (appendix). Estimated vaccine-induced immunity against serotypes 1 and 3 in selected LGAs in Kano was markedly lower than seroprevalence among children from these same LGAs attending outpatient clinics at Murtala Mohammed Specialist Hospital (p<0.0001). This finding is probably a result of exposure to wild-type virus or secondary exposure to vaccine viruses, differences in the study populations, and, potentially, the tendency for case-control studies to underestimate efficacy when cases and controls differ in their exposure to poliovirus. Despite these differences, the immunity estimates showed good correlation (Spearman’s rank test, p=0.61 and 0.53 for serotypes 1 and 3).

There are probably gaps in immunity not captured by this study (i.e., areas that do not report AFP cases) and this is likely to be an issue in politically unstable regions or hard-to-reach communities. However, population immunity estimated using dose reporting during AFP surveillance was a good predictor of incidence, validating the use of these data in deriving these values. The risk of a case occurring in a given LGA was lower if that area had recorded a case in the previous 12 months, perhaps as a result of natural immunity following local circulation of poliovirus.

Nigeria holds the key to poliomyelitis eradication in Africa and possibly the world. There were substantial improvements in campaign coverage during 2012, as shown by the increasing number of LGAs accepted at a target of 80% coverage according to lot quality assurance sampling, and as shown in the lower case burden during 2013 (49 cases between Jan 1 and Oct 15, 2013). However, continued campaign management problems and security challenges threaten to stall eradication attempts. The factors driving the sustained transmission of poliovirus in Nigeria—for example, continued refusals, lower vaccine efficacy, and instability in worst-affected areas—can be overcome through sustained commitment from the highest level of government right through to the vaccinator on the streets. Children in northern Nigeria need additional OPV doses as an urgent priority, and improvement of vaccine acceptance will be the key to the programme’s success. The introduction of inactivated poliovirus vaccine might help to sustain immunity against serotype 2, while accelerating the eradication of the remaining type 1 and 3 wild polioviruses. Our results highlight the fundamental need for community engagement and education and the substantial benefits in utilising the media and local leaders to positively promote poliomyelitis vaccination and educate mothers. The prospects for global eradication are positive as Nigeria moves towards eliminating poliomyelitis in the last remaining reservoir of infection in Africa.

Contributors
TDM and NCG conceived the study, did the literature search, and analysed data. TDM, NCG, and RBA designed the study, created the figures, and interpreted the data. TDM, NCG, MM, AG, MAP, RBA, and EA collected data. TDM, NCG, RBA, MAP, and EA wrote the manuscript. TDM, NCG, MM, AG, MAP, RBA, and EA approved the final manuscript.

Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgements
We are grateful to all those involved in undertaking AFP surveillance and laboratory confirmation of polioviruses in Nigeria. We thank Christl Donnelly for statistical advice.

References