

Outbreak of Type 2 Vaccine-Derived Poliovirus in Nigeria: Emergence and Widespread Circulation in an Underimmunized Population

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(See the article by Neal et al., on pages 889–90.)

Wild poliovirus has remained endemic in northern Nigeria because of low coverage achieved in the routine immunization program and in supplementary immunization activities (SIAs). An outbreak of infection involving 315 cases of type 2 circulating vaccine-derived poliovirus (cVDPV2; >1% divergent from Sabin 2) occurred during July 2005–June 2010, a period when 23 of 34 SIAs used monovalent or bivalent oral poliovirus vaccine (OPV) lacking Sabin 2. In addition, 21 “pre-VDPV2” (0.5%–1.0% divergent) cases occurred during this period. Both cVDPV and pre-VDPV cases were clinically indistinguishable from cases due to wild poliovirus. The monthly incidence of cases increased sharply in early 2009, as more children aged without trivalent OPV SIAs. Cumulative state incidence of pre-VDPV2/cVDPV2 was correlated with low childhood immunization against poliovirus type 2 assessed by various means. Strengthened routine immunization programs in countries with suboptimal coverage and balanced use of OPV formulations in SIAs are necessary to minimize risks of VDPV emergence and circulation.

The cornerstone of the Global Polio Eradication Initiative is immunization of children with multiple doses of oral poliovirus vaccine (OPV), via both routine immunization (RI) and supplementary immunization activities (SIAs) [1]. The key advantages of OPV are ease of administration and efficient induction of mucosal immunity, thereby limiting poliovirus shedding and person-to-person transmission [2]. Through widespread implementation of this approach and with standardized

virologic surveillance, indigenous wild poliovirus (WPV) transmission has stopped in all but 4 countries (Nigeria, Pakistan, Afghanistan, and India) [1]. WPV type 2 (WPV2) circulation apparently stopped in Africa in the mid-1990s (F. Adu and C. Koffi; unpublished data), and WPV2 was last detected (in India) in 1999 [3].

Despite its advantages, OPV use carries the infrequent risks of vaccine-associated paralytic poliomyelitis among OPV recipients and their direct contacts [2] and the emergence of genetically divergent vaccine-derived polioviruses (VDPVs) [4, 5], both a consequence of selection against the attenuated phenotype during intestinal replication [6]. VDPVs are operationally defined as OPV-related isolates having >1% nucleotide (nt) sequence divergence from the parental OPV strain in the ~900-nt region encoding the major capsid surface protein, VP1 [4, 5]. This arbitrary demarcation represents ~1 year of poliovirus (PV) replication after administration of the initiating OPV dose [7], substantially longer than the normal postvaccination excretion period of 4–6 weeks [2, 8]. VDPVs are further

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categorized as circulating (cVDPVs) when there is clear evidence of transmission beyond close contacts [4, 5]. cVDPV outbreaks have occurred in settings of widening susceptibility to ≥ 1 poliovirus serotype in association with weak RI programs and in locations where the corresponding WPVs of the same serotype have been eliminated [4, 5, 9, 10]. The risk of cVDPV emergence appears to be highest for the Sabin type 2 (Sabin 2) OPV strain [4, 5, 10], particularly in areas with high densities of non-immune persons, poor sanitation, and tropical or subtropical climates [11].

Northern Nigeria had remained a major reservoir for WPV1 and WPV3 [12, 13], leading to extensive international spread of WPV1 in 2003–2006 [14] and 2008–2009 [13, 15] and limited WPV3 international spread in 2008–2009 [13, 15]. Low trivalent OPV (tOPV) coverage in the RI program, suspension of SIAs in some states in 2003–2004, and low coverage in SIAs have contributed to ongoing WPV transmission [14]. To more efficiently stop WPV1 and WPV3 transmission, monovalent OPV type 1 (mOPV1) was regularly used in SIAs starting in March 2006, and mOPV3 was intermittently used starting in July 2007 [12, 13]. During the period July 2005–June 2010, 11 of 34 SIA rounds in northern Nigeria used tOPV, including only 4 rounds during the period March 2006–April 2009.

In 2002, a case involving VDPV type 2 (VDPV2) was detected in Plateau state, but no related cases involving VDPV2 or any other VDPVs were detected over the next 4 years [16]. In August 2006, virologic investigations detected a cluster of acute flaccid

paralysis (AFP) cases associated with Sabin 2-related isolates in northern Nigeria; sequence analysis revealed that the isolates were VDPVs [17]. Retrospective analyses found an early outbreak isolate in 2005, and continued screening through mid-2010 detected a total of 315 VDPV2 case isolates. We found an additional 21 cases with “pre-VDPV2” isolates (0.5%–1% VP1 divergent from Sabin 2), sporadically found in settings of high OPV coverage.

Here, we describe epidemiologic characteristics of the outbreak of cVDPV2 infection in Nigeria during the period from July 2005 through 30 June 2010, constituting the largest and second-longest known cVDPV-associated outbreak [5, 17–21]. Furthermore, in accord with the findings of Jenkins et al [21], we compare clinical features of both VDPV2- and pre-VDPV2-associated cases with WPV and non-polio AFP (NP-AFP) cases. We then assess risks of the emergence and spread of cVDPV2 in northern Nigeria and discuss measures needed to prevent further cVDPV outbreaks.

METHODS

Background

Nigeria, the most populous country in Africa (population, ~ 140 million) [22], has a population growth rate of 2.4% [23]. Population densities (national mean, 152 persons/km²) vary widely by state and are highest in the states of the tropical south (median, 390 persons/km²; highest, 2162 persons/km² [in Lagos

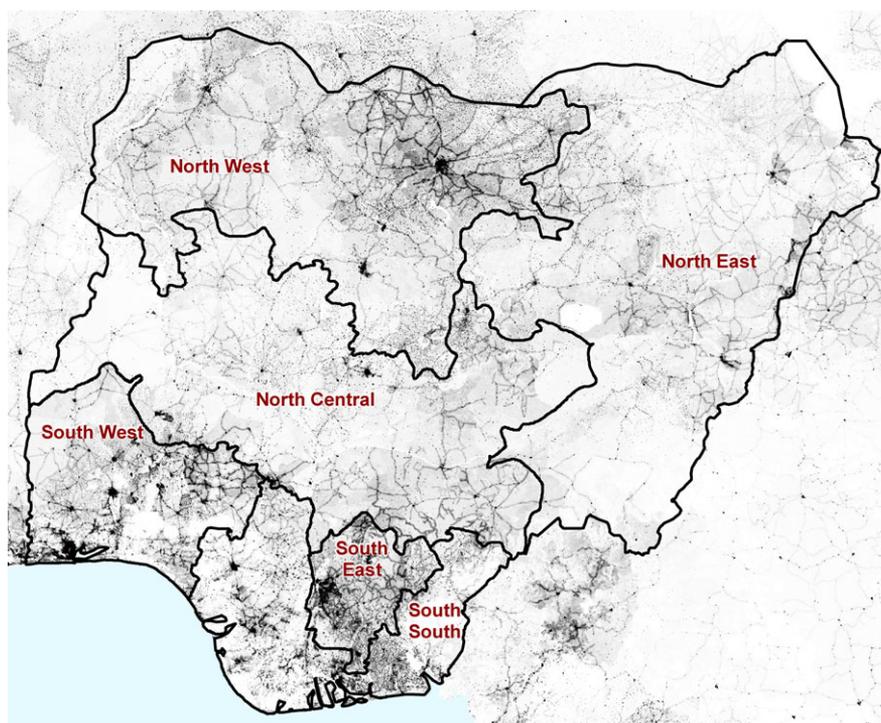


Figure 1. Map of Nigeria showing state geopolitical zones and population density by LandScan [36].

state]) and lower in the semi-arid north (median, 106 persons/km²; highest, 449 persons/km² [in Kano state]) [22–24]. The 36 states (plus the Federal Capital Territory) grouped into 6 zones (Figure 1) are responsible for health policy implementation and secondary health care, and the 774 local government areas (LGAs) are responsible for primary health care. Government health expenditures account for 1.7% of gross domestic product (US\$1089 per capita in 2009) [25, 26].

The RI program, begun in 1979, includes 4 doses of tOPV given at birth and at 6, 10, and 14 weeks of age. National average coverage for ≥ 3 OPV doses (OPV3) rose above 20% in 1986, increased to 55% in 1990, then decreased to $\sim 20\%$ in 1999 [27]. SIAs with OPV began in 1997 [28]; since then, coverage with three doses of diphtheria-tetanus-pertussis vaccine (DTP3) provides a more accurate determination of OPV3 delivery in the RI program. Nationally, estimated DTP3 coverage gradually increased from $\sim 20\%$ in 1997 to $\sim 40\%$ in 2006, remaining at 42% in 2009 [29]. Survey results have been variable. Demographic and Health Surveys in both 2003 and 2008 and a UNICEF survey in 2007 reported $\leq 35\%$ national DTP3 coverage in children aged 12–23 months, whereas large national immunization coverage surveys (NICS) in 2003 and 2006 reported DTP3 coverage in children aged 12–23 months of 40% and 54%, respectively [29–33]. Increases in the estimated national average coverage were observed in serial NICSs and Demographic and Health Surveys since 2003, with wide variation in coverage by state, and increasing coverage along a north-south gradient [30–32]. NICS reported average DTP3 coverage for northern states at 24.4% (range, 4.3%–58.9%) in 2003, and 38.3% (range, 9.2%–83.5%) in 2006; coverage in southern states was 62.1% (range, 33.6%–87.5%) in 2003, and 71.5% (range, 50.6%–93.1%) in 2006 [31, 32].

Case Ascertainment and Classification

During 1996–1998, the Nigerian Ministry of Health and the World Health Organization (WHO) instituted an AFP surveillance system to detect paralytic poliomyelitis. Local government area surveillance officers perform investigations of reported AFP cases, which include a limited clinical history, clinical evaluation, and collection of stool specimens for virologic testing; caretakers of case patients with AFP provide a recall history of the total number of OPV doses received prior to paralysis. Clinical reevaluation for residual paralysis at least 60 days after onset is generally performed when stool specimens are inadequate (ie, because of late collection, insufficient material, or improper transport) [34] and is otherwise performed inconsistently. AFP surveillance quality is monitored by WHO performance standards [35].

In this report, AFP cases are classified as follows: WPV cases, WPV1 or WPV3 isolated from ≥ 1 stool specimen (includes VDPV2 and pre-VDPV2 coinfections) [13]; VDPV2 cases, Sabin 2-related PV with ≥ 10 nt VP1 substitutions

(>1% divergent) [4, 5] isolated from ≥ 1 stool specimen and no WPV isolated; “pre-VDPV2” cases, Sabin 2-related PV with 5–9 nt VP1 substitutions (0.5%–1% divergent) isolated from ≥ 1 stool specimen and no WPV isolated; and NP-AFP cases, no WPV, VDPV, or pre-VDPV isolated. If stool specimens were inadequate and if the case patient had residual paralysis after 60-days, died, or was lost to follow-up, cases were referred to an expert panel for classification as either polio compatible (excluded from our analyses) or NP-AFP cases. All VDPV2s were vaccine/nonvaccine recombinants and were counted as outbreak cVDPV2s. Among 27 pre-VDPV2s, 21 were vaccine/nonvaccine recombinants typical of cVDPVs [2, 4] whose cases clustered temporally and geographically with the cVDPV2s and were included in our analyses. Six pre-VDPV2 isolates (including 2 from the southern states of Lagos and Anambra) that were nonrecombinant or vaccine/vaccine recombinants were excluded from our analyses. Detailed virologic characterization of all cVDPV2/pre-VDPV2 isolates will be described elsewhere (Burns et al; unpublished data). All AFP cases for which vaccine/nonvaccine recombinant cVDPV2/pre-VDPV2 and WPV were isolated were included in the description of the outbreak time course and geographic distribution but were classified as WPV cases. Because all cVDPV2s and the 21 pre-VDPV2s included were isolated from case patients in northern states, we compared clinical features of WPV and NP-AFP cases from those states only.

Comparisons between case types for categorical variables were made using χ^2 tests for homogeneity or exact tests as necessary or using Cochran-Mantel-Haenszel test to control for age. Kruskal-Wallis tests were used for continuous variables. Population density mapping used LandScan (Oak Ridge National Laboratory) estimates for 2007 compiled on a 30" \times 30" latitude/longitude grid [36].

Virus Isolation and Characterization

Viruses in stool specimens were isolated in RD and L20B cells in accordance with standard protocols [37] and were characterized by reverse-transcriptase polymerase chain reaction (RT-PCR) assays using enterovirus-specific and poliovirus group-, serotype-, and Sabin strain-specific primer sets [38, 39] and enzyme-linked immunosorbent assays using cross-absorbed hyperimmune sera [37, 40]. Since August 2006, vaccine-related poliovirus isolates were screened for VDPVs using a real-time RT-PCR assay [20]. VDPVs were identified by VP1 sequencing [41].

Outbreak Trends

Changes in annualized incidence of cVDPV2 and pre-VDPV2 cases for birth cohorts (2000 to mid-2010) were assessed for the period January 2005–June 2010. The denominator for incidence calculations was the sum of annual state-level population estimates based on the 2006 national census adjusted for infant and child survival and population growth [22, 23, 30].

OPV Population Coverage Estimates

OPV coverage data are available from administrative reporting of routine immunization, coverage surveys [29-33], and immunization histories collected during investigation of AFP cases. Because national administrative coverage estimates have been consistently higher than survey estimates [29], we used data from surveys and AFP surveillance.

Many immunization coverage surveys of children aged 12–23 months were conducted during 2003–2008 [30-33]. Vaccination recall histories (total doses, not distinguishing between RI or SIAs) collected during investigation of case patients with NP-AFP aged 6–35 months in 2005 were used as a coverage proxy for the SIA target population. Vaccination history was an exclusive indicator of PV2-specific immunization prior to the introduction of mOPV SIAs in March 2006, because SIAs after that date included different vaccine formulations. Demographic and Health Survey coverage history of ≥ 3 DTP doses (a proxy for ≥ 3 RI OPV doses) for children aged 12–23 months in 2008 (2007 birth cohort) [30] was mapped by state to reflect the immunity status against PV2 for the population at risk for WPV, cVDPV2, and pre-VDPV2 early in the outbreak.

Risk Assessment

State-level cumulative incidence rates of cVDPV2/pre-VDPV2 cases were compared with coverage levels and estimates of the proportion of children without polio immunization (OPV0). Correlations of incidence with coverage were assessed using 3 proxies for state-level routine OPV3 coverage: OPV3 history among case patients with NP-AFP aged 6–35 months from 2005, DTP3 coverage from the 2006 NICS (2005 birth cohort), and DTP3 coverage from the 2008 Demographic and Health Survey (2007 birth cohort). The proportion of OPV0 children was also taken from each coverage data source; for surveys, this was estimated as $100\% - \%DTP1$. LOESS, a method using local polynomial regression fitting [42], was used to describe the correlation between estimated OPV3 coverage (or OPV0) and incidence of cVDPV2/pre-VDPV2 cases. Spearman rank correlation coefficients were used to quantify the strength of correlation.

RESULTS

Descriptive Epidemiology

From July 2005 through June 2010, 315 cVDPV2 cases, 21 pre-VDPV2 cases, and 10 cVDPV2/pre-VDPV2 coinfections detected in WPV cases were identified in Nigeria (Figure 2). One cVDPV2 case was detected in July 2005, 21 cases were detected in 2006 (after March 2006), 68 cases were detected in 2007, 63 cases were detected in 2008, 153 cases were detected in 2009, and 9 cases were detected through June 2010. Sixteen pre-VDPV2 cases were detected in 2006, 4 were detected in 2007, and 1 was detected in 2009.

Median ages for case patients with cVDPV2, pre-VDPV2, and WPV (including co-infections) were similar (24 months), and case patients were predominantly male (57%–64%) (Table 1). The clinical presentations (ie, fever at onset, asymmetric paralysis, rapid progression of paralysis, and number of affected limbs) were also similar for these 3 categories of cases. Among children with 60-day evaluation reported, the proportion with residual paralysis was not significantly different for those with cVDPV2 cases (77%), compared with those who had WPV (85%) or pre-VDPV2 cases (100%) (Table 1).

Most case patients with cVDPV2, pre-VDPV2, and WPV were undervaccinated children (Tables 1 and 2). Only 43% of patients with cVDPV2, 15% of those with pre-VDPV2, and 28% of those with WPV received ≥ 3 doses of OPV; 20% of patients with cVDPV2, 50% of those with pre-VDPV2, and 36% of those with WPV received no OPV dose. By contrast, OPV3 coverage was significantly higher (64%; $P < .001$) for patients with NP-AFP than all other case types, and the proportion OPV0 was significantly lower (13%; $P < .001$) when controlled for age.

During the 5 years of emergence and spread, cases were reported from all 7 northwest (NW) zone states, 4 of 6 northeast (NE) zone states, and 5 of 7 north central (NC) zone states (Figures 1 and 3). The NW zone accounted for 249 cVDPV2 cases (79%) and 17 pre-VDPV2 cases (81%), and 7 of 10 WPV-mixed infections; the NE zone accounted for 42 cVDPV2 cases (13%) and 3 pre-VDPV2 cases (14%), and 3 of 10 WPV-mixed infections; and the NC zone accounted for 24 cVDPV2 cases (8%) and 1 pre-VDPV2 case (5%). A major focus of the outbreak was Kano State, which has high population density (Figure 1) and accounted for 95 (36%) of 266 NW zone cVDPV2/pre-VDPV2 cases during the entire outbreak period and 23 (62%) of 37 cVDPV2/pre-VDPV2 cases in 2006 (Figure 3). The geographic distribution of WPV for the period July 2005–June 2010 showed a similar pattern, with 3312 (98%) of 3390 cases in the northern states, including 2508 (74%) in the NW zone, 604 (18%) in the NE zone, and 200 (6%) in the NC zone.

The first cVDPV2 outbreak case occurred in Bauchi state in the NE zone in July 2005. On basis of the 1.1% VP1 nt divergence of the isolate, we estimate that the initiating OPV dose was administered in mid-2004. At least 7 independent cVDPV2 lineages, identified by VP1 sequence relationships, emerged during the period 2005–2009 (Figures 2 and 3). cVDPV2 lineages 1, 3, 4, and 7 were limited to 2–3 cases primarily localized within a single state, but lineages 5 and 6 were associated with 6–7 cases and spread to multiple states (Figure 3). Lineage 2, associated with 291 cVDPV2 cases, predominated in the NW zone by late 2006 and spread widely across the northern states into mid-2010. Of 21 pre-VDPV2 isolates, 16 (76%) were ancestral to subsequent cVDPV2 isolates (Figure 3); the remaining 5, including the pre-VDPV2 from mid-2009, were unrelated to each other or to the cVDPV2 isolates and signaled additional independent emergences.

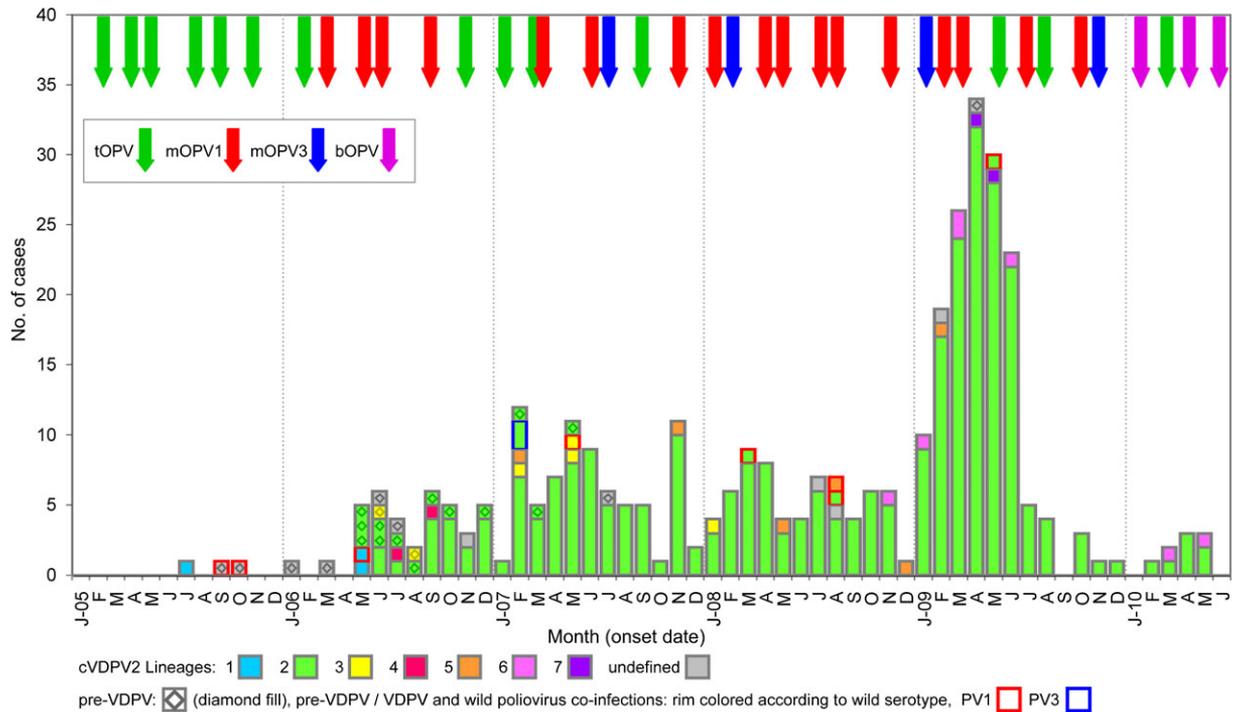


Figure 2. Acute flaccid paralysis (AFP) cases associated with circulating vaccine-derived poliovirus type 2 (cVDPV2), pre-VDPV2, and co-infections with wild poliovirus type 1 (WPV1) or type 3 (WPV3), by month of onset and timing of supplementary immunization activities (SIAs) for northern states by oral poliovirus vaccine (OPV) formulation, Nigeria, 1 January 2005 through 30 June 2010. bOPV, bivalent oral poliovirus vaccine types 1 and 3; mOPV1, monovalent oral poliovirus vaccine type 1; mOPV3, monovalent oral poliovirus vaccine type 3; tOPV, trivalent oral poliovirus vaccine.

Outbreak Trends

tOPV SIAs were implemented in the affected states 6 times annually during 2004–2005 and in February 2006. Of 30 SIAs conducted in the northern states during March 2006–June 2010, 16 used mOPV1 only, 4 used mOPV3 only, and 3 used bivalent OPV types 1 and 3 (bOPV) [1, 13, 43] (Figure 2). Four tOPV SIAs were conducted during March 2006–September 2007; no further tOPV SIAs were conducted until May 2009 [13]. The monthly incidence of cVDPV2/pre-VDPV2 cases, which averaged 5–6 per month in 2007–2008, increased substantially during January–June 2009, peaking at >30 cases per month during the period April–May. Of 154 cases occurring in 2009, 71 (46%) were in children born during 2007, who had the highest annualized incidence of all birth cohorts, followed by children born in 2006 and 2008 (Figure 4). After 2 tOPV SIAs conducted in May and August 2009, the monthly incidence decreased sharply to 0–3 cases during September 2009–June 2010 (total of 14) (Figure 2).

Risk Assessment

An inverse relationship was found between disease incidence and type 2-containing OPV3 coverage (or DTP3 coverage proxies) by state using coverage data from 2005 NP-AFP cases (Figure 5A), NICS 2006 (Figure 5C), and Demographic and Health Survey 2008 (Figure 5E). The risk of pre-VDPV2/cVDPV2 emergence and spread nears 0 when OPV3 coverage

(or DTP3 coverage proxies) exceeded 90% (2005 NP-AFP), 60% (NICS 2006), or 55% (Demographic and Health Survey 2008). Similarly, a positive relationship was found between pre-VDPV2/cVDPV2 incidence and OPV0 coverage (Figure 5B, 5D, and 5F). The LOESS curves indicate that the risks of pre-VDPV2/cVDPV2 emergence and spread increases above 0 when the proportion of OPV0 children exceeded 10% (2005 NP-AFP), 25% (NICS 2006), or 20% (Demographic and Health Survey 2008). Some states with particularly high incidence and low coverage clearly stand out; the northern-state annualized incidence of cVDPV2/pre-VDPV2 cases was 0.09 cases per 100,000 persons ($n = 336$), yet state-level incidence was as high as 0.23 cases per 100,000 persons in Zamfara ($n = 39$) and 0.19 cases per 100,000 persons in Kano ($n = 95$).

DISCUSSION

The 336 pre-VDPV2/cVDPV2 cases and the 10 pre-VDPV2/cVDPV2-WPV coinfections found in northern Nigeria during the period July 2005–June 2010 constitute the largest reported outbreak of cVDPV infection in terms of the number of cases and in geographic extent [5, 17, 20, 21]. Phylogenetic analyses identified ≥ 7 independent cVDPV outbreak lineages with a combined 5 years of transmission despite intermittent tOPV SIAs [5, 13].

Table 1. Comparison of Select Variables for Patients With Cases of Circulating Vaccine-derived Poliovirus Type 2 (cVDPV2), Pre-VDPV2, Wild Poliovirus (WPV), and Nonpolio Acute Flaccid Paralysis (NP-AFP), Northern Nigeria, January 2005–June 2010

Variable ^a	cVDPV2	pre-VDPV2	WPV ^b	NP-AFP	P ^c
No. of cases by year of onset					
2005	1	0	804	2532	
2006	21	16	1108	2546	
2007	68	4	273	2320	
2008	63	0	771	2878	
2009	153	1	351	3041	
2010 ^d	9	0	5	1683	
Total	315	21	3312	15,000	
Demographic characteristics					
Male sex	64	62	57	57	.09
Age, months					
Mean	27	24	26	36	
Median (range)	24 (0–270)	24 (5–60)	24 (0–172)	26 (0–784)	<.001 ^{e,f}
Interquartile range	18–36	12–30	17–34	18–45	
Region^f and population, per 2006 census					
North West (n = 35,786,944)	79	81	76	48	<.001
North Central (n = 20,266,257)	8	5	6	29	
North East (n = 18,971,965)	13	14	18	23	
OPV coverage, doses^{g,h}					
0	20	50	36	13	<.001
1–2 d	37	35	36	23	
> 3	43	15	28	64	
Clinical features					
Fever at onset ⁱ	99	100	99	98	<.001
Asymmetric paralysis ^j	77	76	75	77	.07
Rapid progression of paralysis (≤ 3 days) ⁱ	99	100	99	98	.03 ^k
No. of affected limbs^l					
0	0	0	1	0	.006
1	56	62	52	54	
2	40	33	42	42	
3	4	0	3	2	
4	0	5	2	2	
60-day follow-up status					
Percentage of subjects with follow-up data ^m	49	29	21	10	
Statusⁿ					
Residual paralysis	77	100	85	56	<.001 ^k
No residual paralysis	20	0	13	41	
Lost to follow-up	2	0	1	1	
Died before follow-up	1	0	1	2	

NOTE. Data are percentage of subjects, unless otherwise indicated. OPV, oral poliovirus vaccine.

^a Data on variables analyzed are missing for some cases; <2% of data are missing for any one variable, except that OPV data are missing for 3% of cVDPV2 cases, 4% of pre-VDPV2 cases, 3% of WPV and WPV/cVDPV2 coinfection cases, and 3% of NP-AFP cases.

^b WPV cases include 8 cases with WPV and cVDPV2 coinfection and 2 cases with WPV and pre-VDPV2 coinfection.

^c Determined using the χ^2 test, unless otherwise indicated.

^d Data available from 1 January through 31 July 2010.

^e The Kruskal-Wallis test for comparison of medians was used.

^f Although the overall comparison is statistically significant, the only significant pairwise comparisons are between cVDPV2, pre-VDPV2, and WPV with NP-AFP cases.

^g Reflects total OPV doses, including tOPV, mOPV1, mOPV3, and bOPV (in 2010).

^h Overall comparison is statistically significant. All pairwise comparisons between case types are significant, with the exception of the comparison between WPV and pre-VDPV2 cases.

ⁱ Overall comparison is statistically significant. Pairwise comparisons between case types are not significant, with the exception of the comparison between WPV and NP-AFP cases.

^j Overall comparison is not statistically significant. The only significant pairwise comparison is between WPV and NP-AFP cases.

^k Determined using the Monte Carlo estimate of exact χ^2 test, with 10,000 samples.

^l Overall comparison is statistically significant. Pairwise comparisons between case types are not significant, with the exception of the comparison between cVDPV2 and WPV to NP-AFP cases.

^m Follow-up data were not available for 2010 cases.

ⁿ The overall comparison is statistically significant. Significant pairwise comparisons are seen between cVDPV2 to WPV and, cVDPV2 and WPV to NP-AFP cases.

Our findings are in accord with previous studies suggesting that the key risk factor for cVDPV emergence and spread is low population immunity [4, 10, 44]. Jenkins et al [21] reached similar conclusions using NP-AFP and NICS 2006 data to estimate coverage with type 2-containing OPV. When we attempted to estimate the tOPV coverage threshold necessary to prevent cVDPV2 emergence and spread in northern Nigeria, there were broad inconsistencies in coverage estimates for states by source. The OPV history of persons with NP-AFP by caregiver recall, expected to be higher than DTP3 estimates due to SIA doses, is of uncertain accuracy and representativeness. Although the LOESS curve shapes differed, NICS 2006 and Demographic and Health Survey 2008 data described similar thresholds of tOPV coverage (60% vs 55%, respectively) and of zero-dose (25% vs 20%, respectively). All available data suggest that the tOPV SIAs, despite substantial coverage gaps, were the primary sources of PV2 immunity for the at-risk population in the northern states. Because the only other source of vaccine-induced PV2 immunity was from low-coverage RI with tOPV, PV2 immunity gaps widened with the emphasis on the use of mOPV1 and mOPV3 in SIAs. The independent emergence of ≥ 7 cVDPV2 lineages during 2005–2009 suggests that population immunity to PV2 fell further below a critical threshold in many areas across the northern states. The burst of cases in January–June 2009 signaled the widening PV2 immunity gap 4 years into the outbreak,

particularly among children reaching 2 years of age who had not received tOPV in SIAs during the period October 2007–April 2009. Because of the high immunogenicity of the Sabin 2 vaccine strain [2, 45, 46], 1 or 2 tOPV SIAs reaching most unvaccinated children should quickly close immunity gaps to PV2 [5, 10]. The sharp decrease in monthly incidence after June 2009 suggests coverage was higher during the tOPV SIAs in May and August 2009 than in previous tOPV SIAs, consistent with trends in WPV incidence, but not yet sufficient to interrupt cVDPV transmission to date [13].

Most previous cVDPV outbreaks were recognized at least 1 year after initial emergence [9, 18, 44, 47], because low OPV coverage is usually accompanied by suboptimal AFP surveillance performance. By contrast, AFP surveillance in Nigeria was generally good despite weaknesses in OPV coverage, allowing investigation of early outbreak events, especially the role of pre-VDPVs. Available clinical follow-up data from this report showed that $>75\%$ of case patients with cVDPV2 and with WPV AFP had residual paralysis after 60 days, similar to the report of Jenkins et al [21]. This finding is consistent with previous reports of outbreaks of cVDPV1 infection, for which a cumulative 74% of cVDPV-associated AFP cases involved residual paralysis typical of poliomyelitis [9, 18, 44, 47]; outcome data were not reported from previous outbreaks of cVDPV2 infection [5, 10]. We also found that all case patients with pre-VDPV2 with follow-up data had residual paralysis after 60 days. Thus, both pre-VDPV2s and

Table 2. Distribution of Caretaker Recall History of Oral Poliovirus Vaccine (OPV) Vaccination Status for Children with Acute Flaccid Paralysis (AFP), by Case Classification, Northern Nigeria, January 2005–June 2010

Year of onset	No. of OPV doses	No. (%) of subjects		
		cVDPV2/pre-VDPV2	WPV	NP-AFP
2005	0	1 (100)	378 (48)	606 (25)
	1-2	0	244 (31)	631 (26)
	≥ 3	0	167 (21)	1221 (50)
2006	0	15 (45)	408 (38)	442 (18)
	1-2	11 (33)	417 (39)	684 (28)
	≥ 3	7 (21)	236 (22)	1302 (54)
2007	0	28 (39)	72 (27)	260 (11)
	1-2	28 (39)	101 (38)	644 (28)
	≥ 3	15 (21)	96 (36)	1383 (60)
2008	0	10 (16)	231 (31)	302 (11)
	1-2	26 (42)	293 (39)	674 (24)
	≥ 3	26 (42)	231 (31)	1850 (65)
2009	0	16 (11)	56 (16)	177 (6)
	1-2	53 (35)	112 (32)	554 (18)
	≥ 3	82 (54)	180 (52)	2280 (76)
2010	0	1 (11)	1 (20)	72 (4)
	1-2	4 (44)	4 (80)	206 (12)
	≥ 3	4 (44)	0	1385 (83)

NOTE. Percentages may not sum to 100 due to rounding. OPV doses can include trivalent, monovalent type 1, monovalent type 3, and bivalent types 1 and 3 formulations. cVDPV2, circulating vaccine-derived poliovirus type 2; NP-AFP, nonpolio AFP; WPV, wild poliovirus.

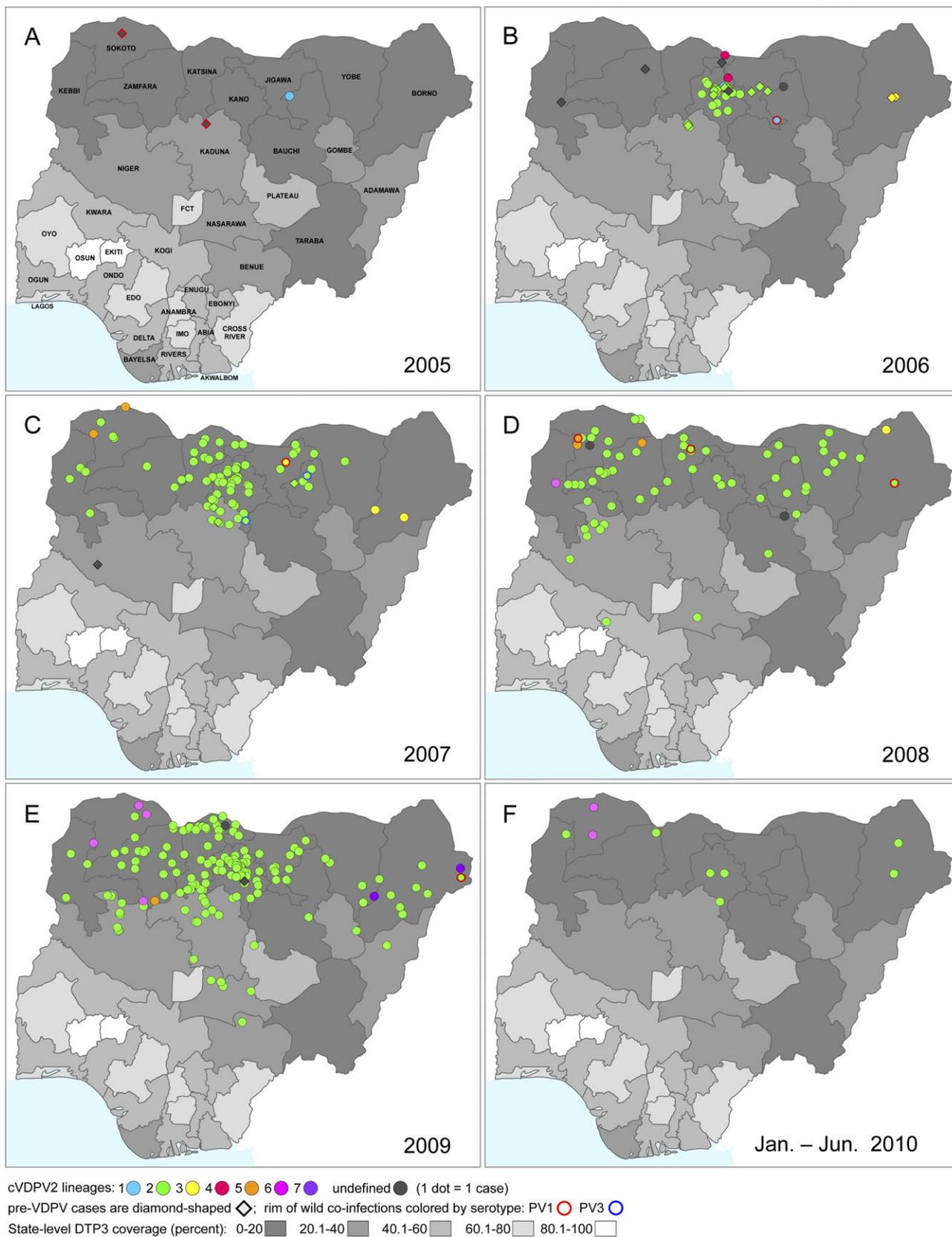


Figure 3. Map of Nigeria showing state by proportion of children with diphtheria-tetanus-pertussis dose 3 (DTP3) coverage at 12–23 months of age (a proxy for oral poliovirus vaccine dose 3 or more [OPV3+] coverage) estimated from the 2008 Demographic Health Survey (2007 birth cohort) overlaid with cases of circulating vaccine-derived poliovirus type 2 (cVDPV2), pre-VDPV2, or coinfections with wild poliovirus type 1 (WPV1) or type 3 (WPV3), 2005–2010 (A–F). 1 dot equals 1 case. Cases were mapped randomly within local government area borders. FCT, Federal Capital Territory.

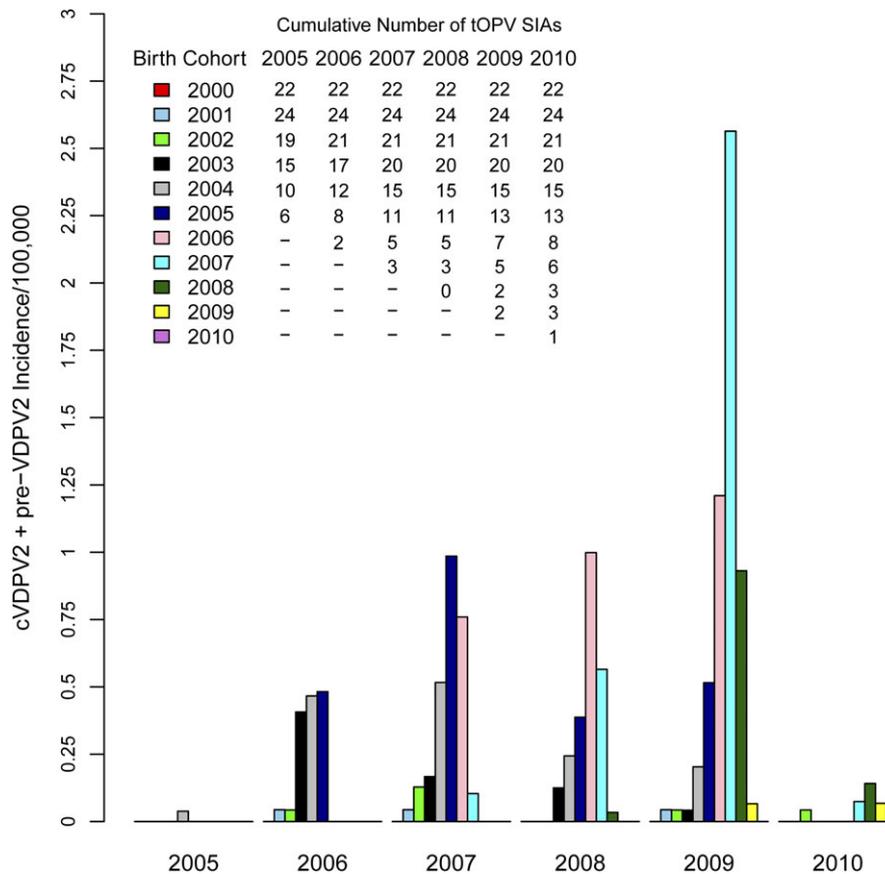


Figure 4. Annual combined circulating vaccine-derived poliovirus type 2 (cVDPV2) and pre-VDPV2 case incidence rates, by year of birth and year of onset, Nigeria, 1 July 2005 through 30 June 2010. *Table insert*, Cumulative number of supplementary immunization activities (SIAs) with trivalent oral poliovirus vaccine (tOPV) in the affected states with cVDPV2 and pre-VDPV2 cases by year of birth since 2000 and year of onset, Nigeria, 2005–2010.

cVDPV2s were indistinguishable from WPVs in their capacities to cause paralytic poliomyelitis. These data have some limitations in that <50% of persons with poliovirus-associated cases underwent follow-up examination, and residual paralysis also was reported in a high proportion of the 10% of persons with NP-AFP who had follow-up data.

The finding that 16 of 21 pre-VDPV2s were ancestral to subsequently observed cVDPV2 lineages strongly implicates pre-VDPV2s as outbreak intermediates. Recognition of the critical early role of pre-VDPVs in the outbreak has important implications for global VDPV surveillance. The 1% demarcation in VP1 nt divergence defining VDPVs was established to balance specificity with sensitivity in routine global VDPV surveillance, while accommodating variations in rates and sites of initial nt substitution into the 3 Sabin strain genomes [4, 7, 48]. However, this outbreak demonstrates that the detection of vaccine-related isolates with <1% VP1 divergence may have epidemiologic importance, especially in areas with known population immunity gaps, particularly for PV2. Routine screening for VDPVs in AFP surveillance by a combination of molecular and antigenic analyses [5, 20, 37] may be

suitable for detecting early cVDPV1 and cVDPV3 outbreak isolates, but it may lack sensitivity for detecting cVDPV2s early in outbreaks. New real-time RT-PCR screening procedures consistently flag the Nigerian cVDPV2 and pre-VDPV2 isolates for further analysis [20] (D. Kilpatrick; personal communication). Timely detection of cVDPV emergence will require ongoing, sensitive AFP surveillance combined with epidemiologic and virologic screening and analyses.

The cVDPV outbreak in Nigeria exemplifies the risks accompanying low RI OPV coverage and underscores the need to balance poliovirus immunity to all serotypes in all populations. In countries and areas where tOPV3 coverage in RI programs remains low, achieving high coverage in SIAs using an appropriate mix of mOPVs, bOPV, and tOPV is essential to limit and ultimately stop all poliovirus circulation.

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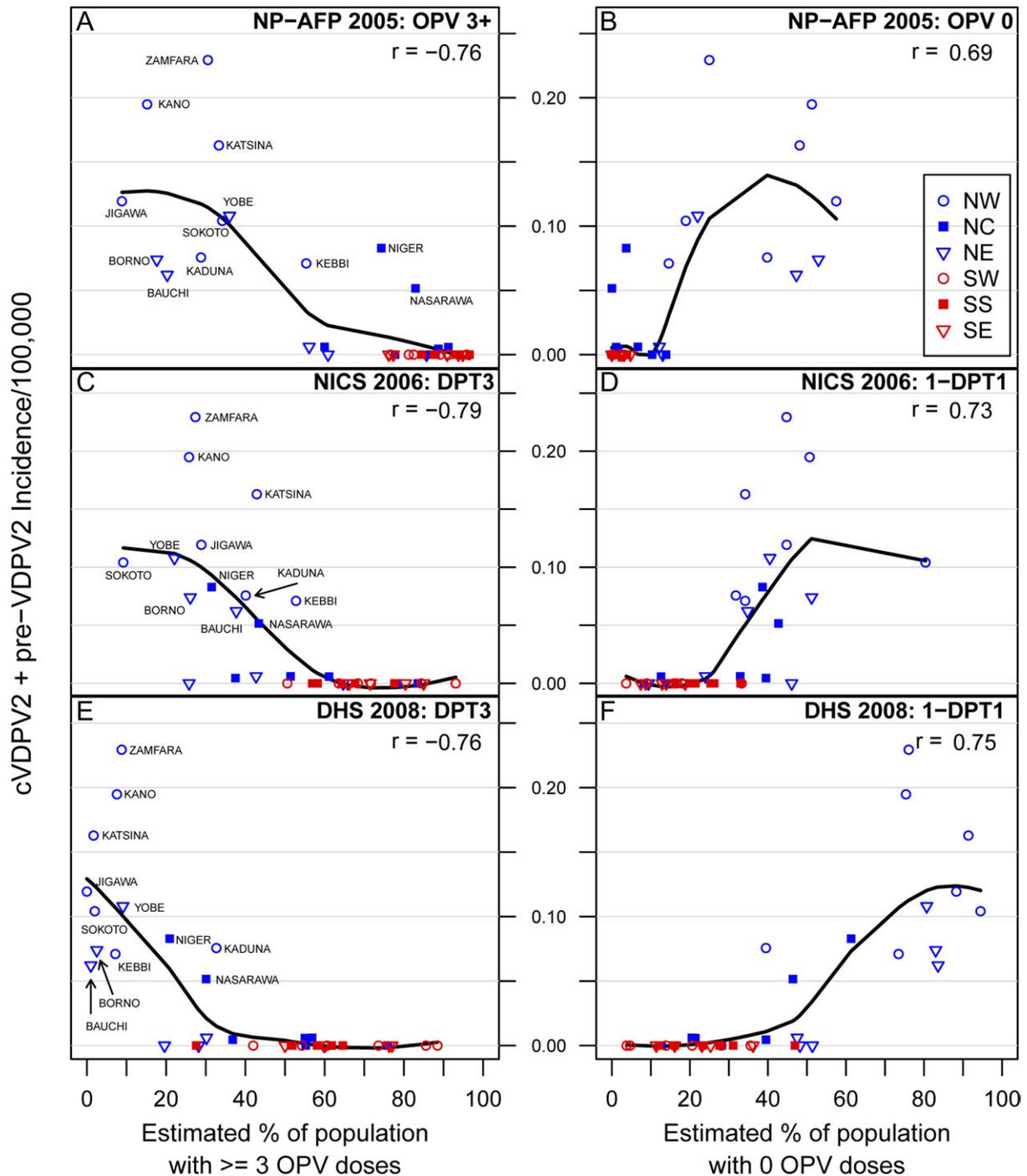


Figure 5. Cumulative incidence of combined circulating vaccine-derived poliovirus type 2 (cVDPV2) and pre-VDPV2, by state, compared with state oral poliovirus vaccine (OPV) immunization coverage using LOESS polynomial regression line (r , Spearman rank correlation coefficients), Nigeria, 1 July 2005 through 30 June 2010. Estimated OPV3+ (≥ 3 doses of OPV) coverage (A) or absence of OPV vaccination (OPV0) (B) from caregiver recall histories for children aged 6–59 months with nonpolio acute flaccid paralysis (NP-AFP) in 2005. Also shown are the estimated diphtheria-tetanus-pertussis dose 3 (DTP3) coverage at 12–23 months of age (C) or absence of vaccination (ie, 100% – %DTP dose 1 [DTP1], [1–DTP1]) (D) from the 2006 national immunization coverage survey (NICS, 2005 birth cohort), as well as the estimated DTP3 coverage (E) or absence of vaccination (1–DTP1) (F) from the 2008 Demographic and Health survey (DHS, 2007 birth cohort). All correlations differed significantly from 0 ($P < .001$).

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