

ORIGINAL ARTICLE

Implications of a Circulating Vaccine-Derived Poliovirus in Nigeria

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ABSTRACT

BACKGROUND

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The largest recorded outbreak of a circulating vaccine-derived poliovirus (cVDPV), detected in Nigeria, provides a unique opportunity to analyze the pathogenicity of the virus, the clinical severity of the disease, and the effectiveness of control measures for cVDPVs as compared with wild-type poliovirus (WPV).

METHODS

We identified cases of acute flaccid paralysis associated with fecal excretion of type 2 cVDPV, type 1 WPV, or type 3 WPV reported in Nigeria through routine surveillance from January 1, 2005, through June 30, 2009. The clinical characteristics of these cases, the clinical attack rates for each virus, and the effectiveness of oral polio vaccines in preventing paralysis from each virus were compared.

RESULTS

No significant differences were found in the clinical severity of paralysis among the 278 cases of type 2 cVDPV, the 2323 cases of type 1 WPV, and the 1059 cases of type 3 WPV. The estimated average annual clinical attack rates of type 1 WPV, type 2 cVDPV, and type 3 WPV per 100,000 susceptible children under 5 years of age were 6.8 (95% confidence interval [CI], 5.9 to 7.7), 2.7 (95% CI, 1.9 to 3.6), and 4.0 (95% CI, 3.4 to 4.7), respectively. The estimated effectiveness of trivalent oral polio vaccine against paralysis from type 2 cVDPV was 38% (95% CI, 15 to 54%) per dose, which was substantially higher than that against paralysis from type 1 WPV (13%; 95% CI, 8 to 18%), or type 3 WPV (20%; 95% CI, 12 to 26%). The more frequent use of serotype 1 and serotype 3 monovalent oral polio vaccines has resulted in improvements in vaccine-induced population immunity against these serotypes and in declines in immunity to type 2 cVDPV.

CONCLUSIONS

The attack rate and severity of disease associated with the recent cVDPV identified in Nigeria are similar to those associated with WPV. International planning for the management of the risk of WPV, both before and after eradication, must include scenarios in which equally virulent and pathogenic cVDPVs could emerge.

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SINCE 1988, WHEN THE WORLD HEALTH Assembly resolved to eradicate poliovirus, the annual incidence of paralytic poliomyelitis has fallen by more than 99%. However, the annual number of cases reported for the years 2003 through mid-2009 has remained relatively constant, and continued transmission in endemic countries, especially Nigeria, led to a resurgence of re-infected countries across Africa from 2008 through 2009.^{1,2} The emergence of a serotype 2 circulating vaccine-derived poliovirus (cVDPV) in Nigeria has complicated the epidemiology of polio as well as vaccine selection and scheduling for supplementary immunization activities.³

A cVDPV is defined by the appearance of two or more cases of acute flaccid paralysis with closely related vaccine-derived poliovirus; it occurs when a vaccine poliovirus increases in neurovirulence and transmissibility after mutation.¹ cVDPVs have usually recombined with other enteroviruses, and their spread is associated with inadequate vaccine coverage.⁴ Globally, 12 independent outbreaks of cVDPV have been identified to date.^{1,4,5} However, little is known about their clinical features or the challenges they pose for eradication. Consequently, their significance has been much debated, with some scientists arguing that cVDPVs are the death knell for eradication^{6,7} and others suggesting that these viruses pose a minor risk.⁸

Serotype 2 cVDPVs are of particular concern because serotype 2 wild-type poliovirus (WPV) is considered to have been eradicated.⁹ The ongoing outbreak of paralytic disease associated with this type 2 cVDPV in Nigeria is unique in being the largest recorded to date and in occurring in the presence of extensive transmission of indigenous type 1 and type 3 WPV. Therefore, steps have been taken to intersperse the administration of trivalent oral polio vaccine — the only vaccine currently licensed in Nigeria that provides protection against type 2 WPV — among more aggressive efforts to administer the more effective serotype 1 or 3 monovalent oral polio vaccines in order to limit the national and international spread of WPVs.¹⁰⁻¹³

Despite the fact that both large- and small-scale campaigns using trivalent oral polio vaccine were mounted from 2006 through 2008, the number of cases of acute flaccid paralysis associated with type 2 cVDPV increased in early 2009. To optimize the balance of trivalent, monovalent, and the recently developed bivalent (serotypes

1 and 3) oral polio vaccines¹⁴ in upcoming supplementary immunization activities in Nigeria, and to appropriately plan for risk management after eradication, we need a deeper understanding of the relative pathogenicity of the cVDPV and WPVs, the relative clinical severity of the paralytic polio caused by the viruses, and the relative effectiveness of the control strategies currently being deployed against them.

METHODS

DATA COLLECTION

Intensified surveillance for poliomyelitis involving the detection and reporting of cases of acute flaccid paralysis¹⁵ among all children in Nigeria younger than 15 years of age began in December 1996.¹⁶ Case investigation involves conducting detailed clinical and epidemiologic investigations, including the collection of two stool samples for laboratory testing for poliovirus. Samples with positive results are investigated with the use of intratypic differentiation tests and genetic sequencing (carried out by the U.S. Centers for Disease Control and Prevention) to determine whether the virus is vaccine-related or wild-type.¹⁷ The number of doses of oral polio vaccine received before the development of acute flaccid paralysis is recorded during initial interviews with a senior medical officer. A follow-up visit at 60 days includes testing for residual paralysis. Clinical data collected during the initial interview include age, sex, presence or absence of asymmetrical paralysis, progression to paralysis within 3 days or over a longer period, presence of fever at onset or absence of paralysis, and number of limbs paralyzed.

We defined a case of cVDPV paralysis as any case of acute flaccid paralysis in which vaccine-related poliovirus isolated from at least one stool sample differed from the original Sabin vaccine strain by 1 to 15% of nucleotides in the region encoding the viral capsid protein VP1.¹⁸ Cases of wild-type poliomyelitis virus were defined as cases of acute flaccid paralysis in which the wild-type virus was detected in at least one stool sample. Cases of nonpolio acute flaccid paralysis were defined as those in which neither wild-type nor vaccine-related poliovirus was isolated in two adequate stool samples collected within 2 weeks after the onset of paralysis, at least 24 hours apart. All cases of acute flaccid paralysis with a reported date of onset between January 1, 2005, and June 30, 2009, were included in this analy-

sis. Cases without two adequate stool samples and with residual paralysis (assessed at least 60 days after the onset of paralysis) that were compatible with poliomyelitis were excluded, as were cases in which more than one serotype of WPV was isolated. Estimates of vaccine effectiveness and population immunity also excluded cases of acute flaccid paralysis in which the number of oral polio vaccine doses received or the age at onset of paralysis were not reported.

Most doses of oral polio vaccine received by children in Nigeria are delivered through supplementary immunization activities rather than routine services. The number of doses of each type of oral polio vaccine received by children with acute flaccid paralysis was therefore estimated on the basis of the reported total number of oral polio vaccine doses they received and the type of vaccine they were exposed to through supplementary immunization activities, calculated on the basis of their age and district of residence (for details, see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org).

STATISTICAL ANALYSIS

The clinical characteristics of acute flaccid paralysis associated with isolation of type 1 WPV, type 3 WPV, and type 2 cVDPV were compared with the use of Fisher's exact test (for categorical variables) or Student's *t*-test (for age, allowing for unequal variances).

Clinical attack rates among districts reporting all three types of poliovirus during the study period were estimated on the basis of the annual incidence of acute flaccid paralysis associated with each poliovirus per 100,000 children younger than 5 years of age and per 100,000 children younger than 5 years of age who were estimated to be unprotected by vaccination against the relevant serotype (for details, see the Methods section in the Supplementary Appendix). For example, 10 cases of type 1 WPV poliomyelitis isolated from a population of 100,000 children with 80% vaccine-induced immunity against serotype 1 would represent a clinical attack rate of 10 cases per 100,000 children and 50 per 100,000 susceptible children. Bayesian confidence intervals for the clinical attack rate per 100,000 susceptible children were calculated with the use of a hierarchical model (for details, see the Methods section in the Supplementary Appendix).

The effectiveness per dose of the different oral

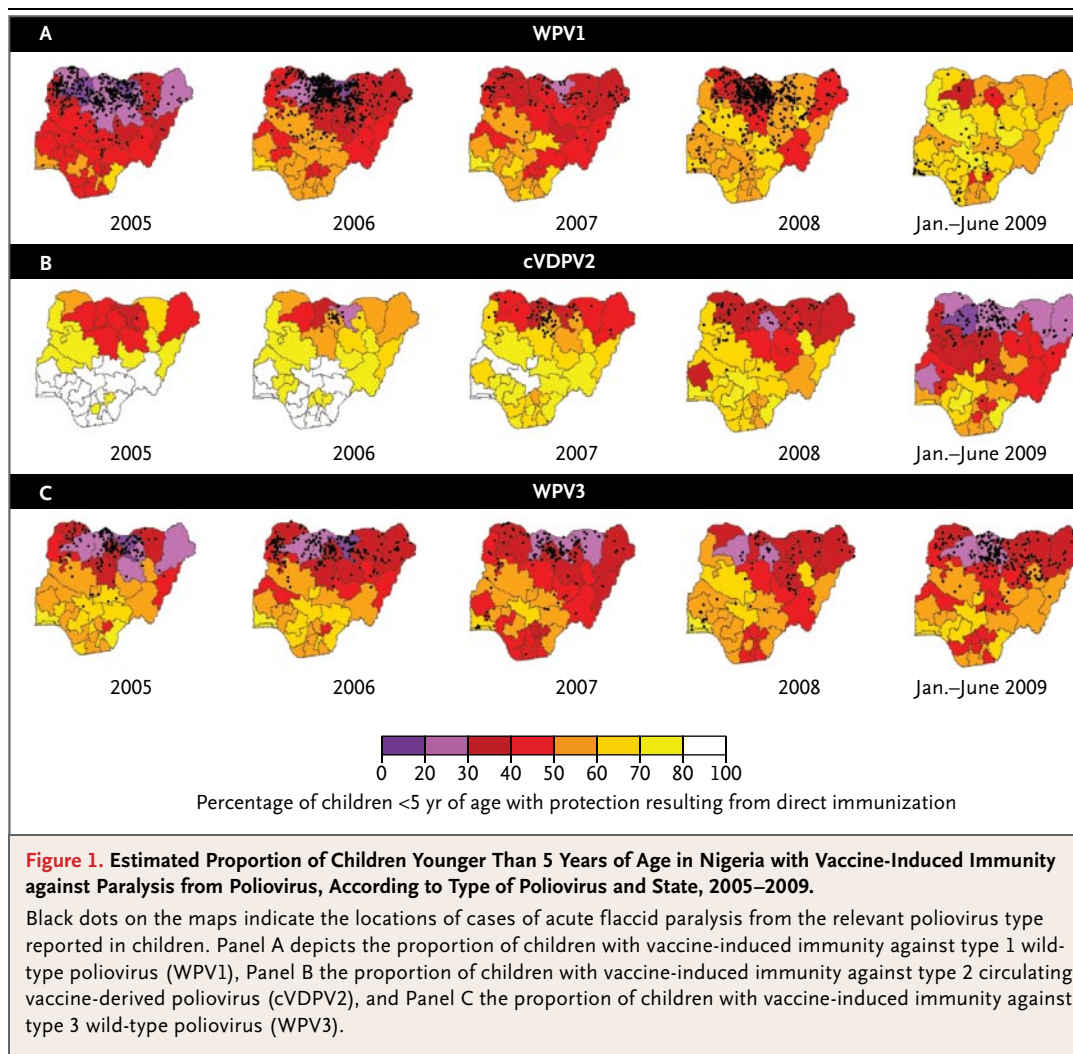
polio vaccines in providing protection against paralysis from each poliovirus was estimated with the use of a matched (1:1) case-control approach as described previously^{11,12,19} (for details, see the Methods section in the Supplementary Appendix). Population immunity from paralysis induced by means of direct immunization with oral polio vaccine among children under 5 years of age was estimated according to state and year on the basis of reports of the number of oral polio vaccine doses received by children with nonpolio acute flaccid paralysis and the estimated effectiveness of the vaccines.^{11,12} Estimates were weighted by single years of age to reflect the underlying age distribution of the population,²⁰ and estimates by zone were weighted to reflect the underlying population distribution by state.²¹ The effect of routine immunization coverage with trivalent oral polio vaccine on population immunity was assessed on the basis of coverage reported by the National Immunization Coverage Survey, with a hierarchical model used to assign trivalent oral polio vaccine doses to cases of nonpolio acute flaccid paralysis (see the Methods section in the Supplementary Appendix). Changes in population immunity were assessed by fitting a linear trend to the yearly estimates, with each year weighted by the sample size.

Monthly estimates of the hazard of a district reporting its first case of acute flaccid paralysis caused by type 2 cVDPV were examined as a function of variables representing the force of infection from cases reported in the previous 6 months, vaccine-induced population immunity, population size, and population density. These values were entered as time-varying covariates with the use of proportional-hazards regression, and the final model was chosen on the basis of maximum likelihood (see the Methods section in the Supplementary Appendix). The proportional-hazards assumption was assessed with the use of Schoenfeld's global test.

RESULTS

SEVERITY OF DISEASE AND CLINICAL ATTACK RATES

A total of 23,004 children were reported to have acute flaccid paralysis over the course of the study period. Among these children, 278 had type 2 cVDPV in their stool, 2323 had type 1 WPV, 1059 had type 3 WPV, and 2 had both type 1 and type 3 WPV (Fig. 1, and Fig. 1 and 2 and Table 1, Sections A through C, in the Supplementary Appen-



dix). The cases of acute flaccid paralysis with type 2 cVDPV were broadly similar to those with type 1 WPV or type 3 WPV in terms of the distribution of age and sex. There were no significant differences in the severity of clinical disease (Table 1).

In districts reporting all three types of poliovirus, the estimated clinical attack rates (measured according to annual incidence) of paralytic polio per 100,000 susceptible children under 5 years of age were 6.8 for type 1 WPV, 2.7 for type 2 cVDPV, and 4.0 for type 3 WPV (Table 2).

VACCINE EFFECTIVENESS

The estimated effectiveness of a dose of trivalent oral polio vaccine was greater against paralysis resulting from infection with type 2 cVDPV than against paralysis from type 1 WPV ($P=0.04$) and type 3 WPV ($P=0.12$) (Table 2 and Fig. 2). Sero-

type 1 monovalent oral polio vaccine was significantly more protective than trivalent oral polio vaccine against paralysis from type 1 WPV ($P<0.001$), and serotype 3 monovalent oral polio vaccine was nonsignificantly more protective than trivalent oral polio vaccine against paralysis from type 3 WPV ($P=0.08$). A regression model with a variable effectiveness per dose of oral polio vaccine did not provide a significantly better fit than a model with constant effectiveness per dose (P values for all vaccine and poliovirus types are available in Fig. 3 in the Supplementary Appendix).

The majority of cases of poliomyelitis were matched to a suitable control. There were no substantial differences in vaccine effectiveness across the country or when effectiveness was estimated separately according to year or age. For instances in which some significant interactions were noted

Table 1. Characteristics of Children with Acute Flaccid Paralysis and Type 1 Wild-Type Poliovirus, Type 2 Circulating Vaccine-Derived Poliovirus, or Type 3 Wild-Type Poliovirus, Isolated from Stool.*

Variable	Type 1 WPV (N=2323)	Type 2 cVDPV (N=278)	Type 3 WPV (N=1059)	P Value†	
				Type 2 cVDPV vs. Type 1 WPV	Type 2 cVDPV vs. Type 3 WPV
Sex — no. (%)					
Male	1312 (56)	172 (62)	609 (58)	0.04	0.11
Female	1010 (43)	101 (36)	449 (42)		
Missing data	1 (<1)	5 (2)	1 (<1)		
Mean age — yr	2.36±0.03	2.57±0.10	2.44±0.05	0.04	0.74
Missing data — no. (%)	255 (11)	35 (13)	87 (8)		
Asymmetric paralysis — no. (%)					
Yes	1719 (74)	209 (75)	779 (74)	0.37	0.34
No	570 (25)	60 (22)	265 (25)		
Missing data	34 (1)	9 (3)	15 (1)		
Progression to paralysis within 3 days — no. (%)					
Yes	2278 (98)	269 (97)	1038 (98)	>0.99	>0.99
No	25 (1)	3 (1)	13 (1)		
Missing data	20 (1)	6 (2)	8 (1)		
Fever at onset — no. (%)					
Yes	2286 (98)	269 (97)	1039 (98)	>0.99	0.75
No	18 (1)	2 (1)	13 (1)		
Missing data	19 (1)	7 (3)	7 (1)		
No. of limbs affected — no. (%)					
0	11 (<1)	0 (0)	9 (1)	0.06	0.17
1	1197 (52)	142 (51)	567 (54)		
2	996 (43)	104 (37)	423 (40)		
3	68 (3)	10 (4)	35 (3)		
4	44 (2)	12 (4)	23 (2)		
Missing data	7 (<1)	10 (4)	2 (<1)		
Residual paralysis at 60-day follow-up — no. (%)					
Yes	541 (23)	129 (46)	370 (35)	0.12	0.06
No	98 (4)	33 (12)	60 (6)		
Lost to follow-up	2 (<1)	1 (<1)	3 (<1)		
Dead at follow-up	4 (<1)	1 (<1)	6 (1)		
Missing data	1678 (72)	114 (41)	620 (59)		

* Plus-minus values are means ±SE. Percentages may not total 100 because of rounding. cVDPV denotes circulating vaccine-derived poliovirus, and WPV wild-type poliovirus.

† Analyses excluded children with missing data and those lost to follow-up or dead at follow-up.

between vaccine effectiveness and location or year (for serotype 1 only), matching on the basis of district rather than state resolved this bias (which was the result of supplementary immunization activities at the district level rather than the state level), and overall estimates of vaccine effective-
ness were unchanged (see Table 3, Sections A and B, in the Supplementary Appendix). Tighter matching of cases and controls (on the basis of age, date, and residence) did not substantially alter the estimates of vaccine effectiveness. Although matching on the basis of district rather than state

Table 2. Estimated Effectiveness against Paralysis per Dose of Oral Polio Vaccine, According to the Types of Polioviruses Circulating in Nigeria and the Estimated Annual Rates of Clinical Attack.*

Variable	WPV1 (N=2323)	cVDPV2 (N=278)	WPV3 (N=1059)
Per-dose vaccine effectiveness			
Cases matched to controls — no. (%)	1739 (75)	184 (66)	812 (77)
Monovalent oral polio vaccine 1 — % (95% CI)	43 (33–51)	NA†	NA†
Trivalent oral polio vaccine — % (95% CI)	13 (8–18)	38 (15–54)	20 (12–26)
Monovalent oral polio vaccine 3 — % (95% CI)	NA†	NA†	53 (16–74)
Annual clinical attack rate			
No. of cases among children <5 yr old‡	1075	211	508
No./100,000 susceptible children <5 yr old — (95% CI)	6.8 (5.9–7.7)	2.7 (1.9–3.6)	4.0 (3.4–4.7)
No./100,000 children <5 yr old, susceptible and vaccinated combined — (95% CI)	5.3 (4.9–5.6)	1.5 (1.3–1.6)	3.2 (2.8–3.5)

* CI denotes confidence interval, cVDPV circulating vaccine-derived poliovirus, NA not applicable, and WPV wild-type poliovirus.

† The vaccine does not provide protection against this type of polio.

‡ This category represents districts that reported cases of acute flaccid paralysis resulting from each of three poliovirus types during the study period.

increased the estimate of vaccine effectiveness against type 2 cVDPV to 54% per dose, only 21% of cases were matched, which led to wide confidence intervals. Consequently, matching by state was preferable, although it may have slightly underestimated overall vaccine effectiveness.

Sensitivity analyses showed that our results were reasonably robust to varying assumptions regarding the number of doses received through routine immunization and that trivalent oral polio vaccine was consistently more effective against paralysis from type 2 cVDPV than against paralysis from type 1 or type 3 WPV (see Table 4, Sections A through C, in the Supplementary Appendix).

VACCINE-INDUCED POPULATION IMMUNITY

Estimated vaccine-induced population immunity to type 1 WPV poliomyelitis increased significantly in all zones from 2005 to 2009, particularly in the North West and North East zones (by 7.4% and 8.1%, respectively, annually) (Fig. 1). However, estimated vaccine-induced population immunity to type 2 cVDPV poliomyelitis declined significantly during the study period in all zones (range, –4.7% to –8.8% annually). Estimated vaccine-induced population immunity to type 3 WPV poliomyelitis increased significantly (by approximately 1% annually) in the North West and North East zones and declined significantly in two of the other four zones. Annual estimates for each serotype

and results of the tests for trends over time in each zone are given in Table 5 in the Supplementary Appendix.

INCIDENCE OF cVDPV

The final proportional-hazards model for a district reporting its first case of paralysis associated with type 2 cVDPV included a function accounting for the distance from other reported cases of type 2 cVDPV paralysis, vaccine-induced population immunity (according to state) in the previous 6 months, and an interaction term between these two variables (Fig. 3, and Fig. 4 and Table 6 in the Supplementary Appendix). This model suggests a strongly localized risk associated with the well-defined geographic spread of this virus. The interaction term indicates that increases in immunity levels were associated with a greater proportional reduction in the hazard when fewer cases had been reported nearby. Variables based on population numbers or density were excluded from the final model, since they were not significant and did not confound any other variables in the model substantially. The final model satisfied the assumption of proportional hazards ($P=0.25$).

DISCUSSION

This study shows that in Nigeria the pathogenicity of type 2 cVDPV and the severity of paralytic disease resulting from infection are similar to that

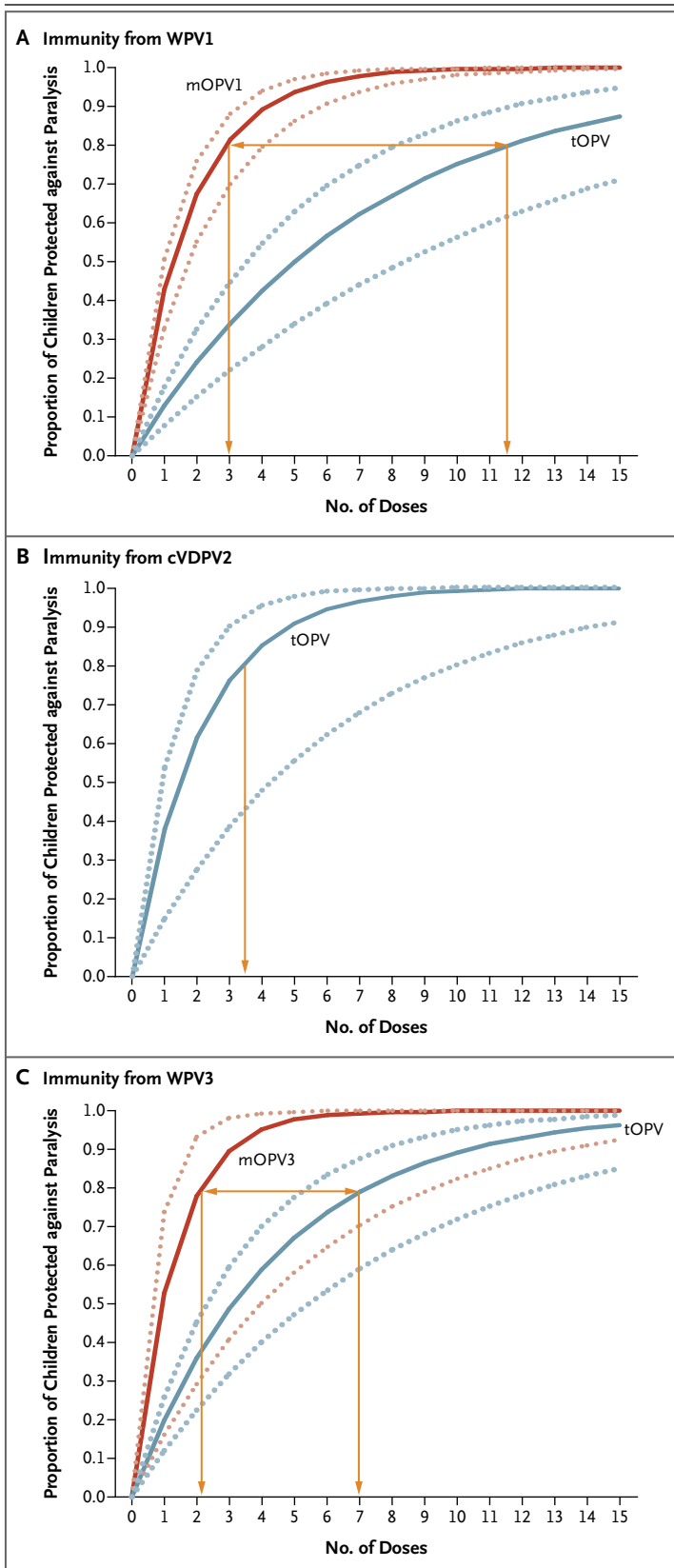


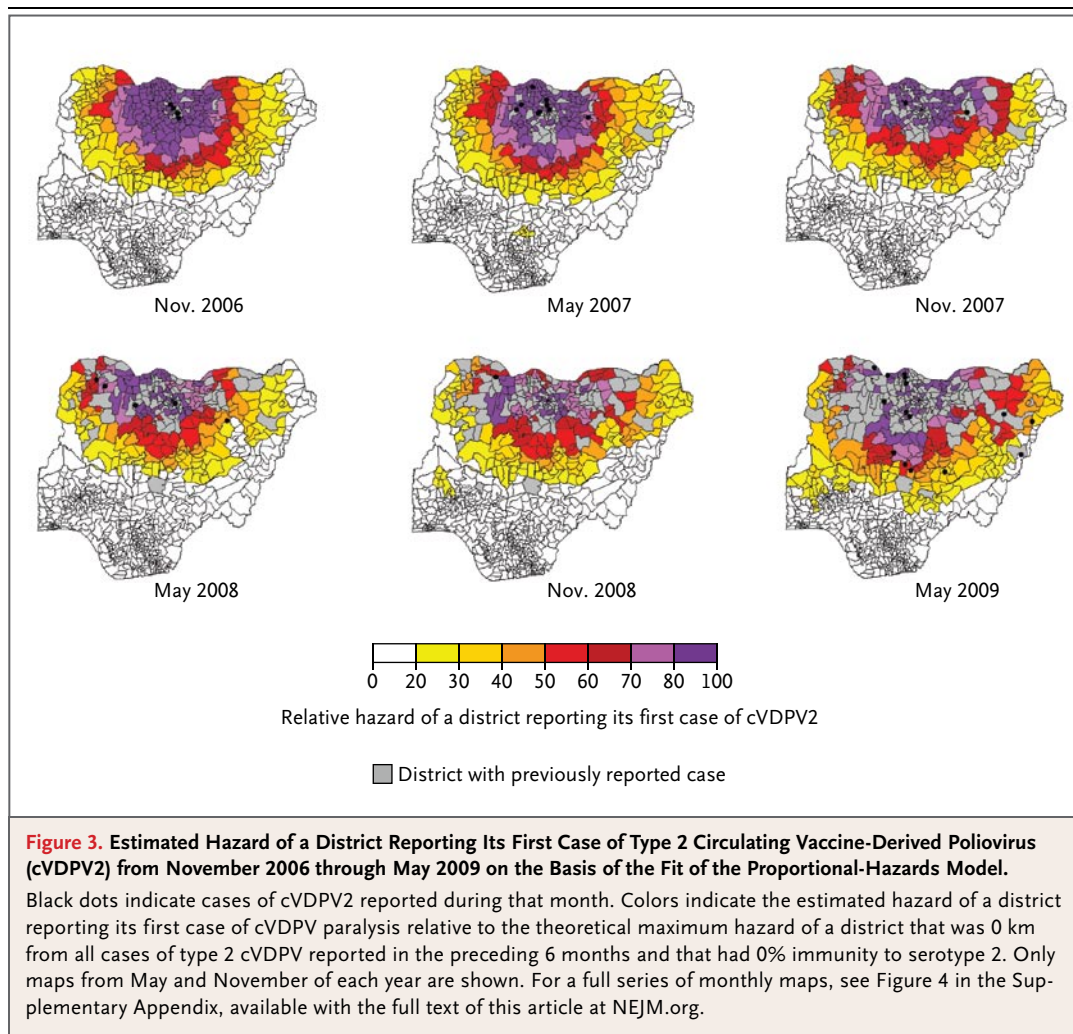
Figure 2. Predicted Proportion of Children Protected against Paralysis, According to Oral Poliovirus Vaccine Type and Number of Doses.

Data are based on the estimated effectiveness per dose. Solid red lines indicate monovalent oral vaccines against type 1 and type 3 polioviruses (mOPV1 and mOPV3, respectively) and solid blue lines the trivalent vaccine (tOPV). Dotted lines indicate 95% confidence intervals. The number of doses required for 80% protection are shown with arrows for purposes of illustration and of comparing the effectiveness of the monovalent vaccine with that of the trivalent vaccine. Panel A depicts the proportion of children with protection against type 1 wild-type poliovirus (WPV1), Panel B the proportion with protection against type 2 circulating vaccine-derived poliovirus (cVDPV2), and Panel C the proportion of children with protection against type 3 wild-type poliovirus (WPV3).

of WPVs. This study also provides an estimate of the effectiveness of an oral polio vaccine against paralysis from infection with a cVDPV and indicates that trivalent oral polio vaccine provides greater protection against infection with type 2 cVDPV than against infection with type 1 WPV or type 3 WPV. This finding is consistent with the higher rates of seroconversion to this serotype observed after administration of trivalent oral polio vaccine in developing countries.²² Our results indicate that interrupting the transmission of a cVDPV can require control measures and levels of population immunity similar to those needed to interrupt an outbreak caused by WPV.

The equivalent severity of disease caused by cVDPVs and WPVs is consistent with the common mechanism of disease responsible for poliovirus-associated paralysis.²³ In districts where type 2 cVDPV and WPV cocirculated, the clinical attack rate for type 2 cVDPV was only slightly lower than that for type 1 and type 3 WPV, which is consistent with the lower rate of clinical attack for type 2 WPV than for type 1 WPV.²⁴ This observation was made despite the recent introduction and spread of type 2 cVDPV, suggesting that both the pathogenicity and transmissibility of type 2 cVDPV are similar to those of type 2 WPV. A study of serotype 1 cVDPV in Indonesia (45 cases), where there was limited cocirculation of type 1 WPV (8 cases), also suggested similar attack rates for these WPVs and cVDPVs.²⁵

Although the 11 previously recognized outbreaks of cVDPV were terminated after one to four immunization campaigns had been conducted with either trivalent oral polio vaccine or sero-



type-specific monovalent oral polio vaccine,⁴ the outbreak in Nigeria persisted in spite of six large-scale and several smaller-scale campaigns carried out with the use of trivalent oral polio vaccine. Given the relatively high estimated effectiveness of trivalent oral polio vaccine against type 2 cVDPV, its persistence can be attributed to inadequate coverage with this vaccine during supplementary immunization activities. Furthermore, the six large campaigns were conducted over the course of 4 years and were interspersed with several rounds of immunization with monovalent oral polio vaccine to control infection with WPVs. By 2009, persistent coverage gaps during supplementary immunization activities, combined with low levels of routine immunization, resulted in a further widening of the immunity gap and the upsurge in the cases of type 2 cVDPV observed

in the first half of 2009. The marked drop in cases of poliomyelitis associated with type 2 cVDPV in the second half of 2009 (10 cases from July through December vs. 138 cases from January through June) after the implementation of just two large-scale campaigns with trivalent oral polio vaccine of moderate quality in May and August is consistent with this vaccine's high level of effectiveness against paralysis from type 2 cVDPV. This finding bodes well for our ability to interrupt transmission of this virus.

We have previously discussed the limitations of estimating vaccine effectiveness and population immunity from reported doses of oral polio vaccine received by children with acute flaccid paralysis.^{11,12,19} Although these limitations may affect the accuracy of our estimates, the finding of a greater protective effect of trivalent oral polio

vaccine against type 2 cVDPV than against type 1 or type 3 WPV and the better performance of the monovalent oral polio vaccines are robust to these limitations. Furthermore, our estimates of population immunity are predictive of the epidemiology of type 2 cVDPV. Since children with polio are less likely than control children to have received the more effective vaccine against the polio serotype with which they were infected, a case-control approach based on the inferred type of vaccine received can underestimate the effectiveness of monovalent oral polio vaccines. Despite this potential bias, the estimated effectiveness of monovalent oral polio vaccines was high as compared with that of the trivalent oral polio vaccine and provides a conservative estimate of the effectiveness of these vaccines as compared with trivalent oral polio vaccine.

Although we did not account for the number of asymptomatic infections associated with polioviruses in our hazard analysis, we made the reasonable assumption that the number of children with acute flaccid paralysis who had poliovirus in their stool was proportional to the number of infections with this virus. In addition, although four lineages of circulating serotype 2 VDPV emerged during the study period, the current outbreak is largely the result of a single lineage (more than 90% of cases).³ Our estimates of vaccine-induced immunity do not account for exposure to oral polio vaccine excreted by vaccinees, the presence of maternal antibodies early in life, or asymptomatic infection with circulating polioviruses. These factors may affect estimates of the attack rates among susceptible children. However, estimates of the attack rates among all children are consistent with our finding of only slightly lower rates for type 2 cVDPV (Table 2).

These findings have important short-term and long-term implications for the Global Polio Eradication Initiative. First, this analysis supports the

strengthening of current recommendations that responses to outbreaks of cVDPVs should be aligned with responses to outbreaks of WPVs. Second, although state-level supplementary immunization activities have been sufficient to interrupt the spread of cVDPVs in most settings, the model shown in Figure 3 indicates that additional, large-scale rounds of immunization with trivalent oral polio vaccine, such as those conducted in May and August 2009, are required across northern Nigeria. Finally, the Global Polio Eradication Initiative's plans for managing risks after the eradication of WPV must include scenarios in which transmissible and pathogenic cVDPVs could emerge, particularly immediately after the worldwide cessation of the use of oral polio vaccine.²⁶

The eradication of type 2 WPV globally in 1999 was a remarkable achievement. However, this study points out the fragility of that achievement, given the pathogenicity and severity of disease that can be associated with type 2 cVDPV. Fortunately, trivalent oral polio vaccine is highly protective against this cVDPV, and modest gains in coverage now appear to be facilitating its rapid interruption. The steep decline in WPV cases in northern Nigeria during the second half of 2009 and the concomitant declines in cases of infection with type 2 cVDPV that followed improvements in coverage through supplementary immunization activities,²⁷ together with the potential role of recently licensed bivalent oral polio vaccine,²⁸ improve the prospects for the eradication of these polioviruses in Nigeria.

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