

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Jenkins HE, Aylward RB, Gasasira A, et al. Implications of a circulating vaccine-derived poliovirus in Nigeria. *N Engl J Med* 2010;362:2360-9.

Implications of a circulating vaccine-derived poliovirus (cVDPV) in Nigeria for polio eradication – Supplementary Information

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Supplementary Methods

Clinical attack rate for poliomyelitis caused by each poliovirus

To estimate the clinical attack rate, incidence of reported cases of each of the three types of poliomyelitis (associated with serotype 1 wild poliovirus (WPV1), serotype 3 wild poliovirus (WPV3) and serotype 2 vaccine-derived poliovirus (cVDPV2)) were calculated by year and district per 100,000 children aged under 5 years old. Total population numbers were taken from the 2006 census¹, scaled up or down for years after or before 2006 using a population growth rate of 2.38% per annum¹ and multiplied by the proportion of the population aged under 5 years old². Districts were only included that had reported at least one case of each type of paralytic polio during the study period to ensure comparison of areas infected by all three types of poliovirus. The mean clinical attack rate for each poliovirus was estimated for each district across years and then across all included districts, weighted by the populations in the districts¹. The variances in the clinical attack rates for each poliovirus type in each district were estimated across years to allow equal weighting for years 2005 to 2008 and half the weight of one year for 2009 (as we only include cases to the mid-point of 2009). The variance across districts was then based on the Poisson assumption such that the variance is

given by $\sum_{d=1}^D \left(\frac{1}{Z}\right)^2 A_d$ where A_d is the attack rate in district d estimated across years as per the previous

sentence and $1/Z$ is the weighting given to that district depending on its population size. Confidence intervals were based on the Normal approximation to this distribution.

To estimate the clinical attack rate per 100,000 ‘susceptible’ children, the above method was repeated with the under 5 year old population numbers multiplied by the estimated proportion unprotected through direct vaccination in the relevant state. Therefore the attack rate here is equal to (number of cases reported)/(under 5 population * (1-proportion of the population protected through direct vaccination)). Variances in the estimates are complicated by inclusion of the proportion of the population protected through direct vaccination. Bayesian confidence intervals were therefore calculated using the hierarchical model described below (*Estimation of vaccine-induced population immunity and resulting confidence intervals*).

Conditional logistic regression of 1:1 matched cases and controls

The probability that a child who has received m doses of monovalent oral polio vaccine (mOPV) against serotype i and t doses of trivalent oral polio vaccine (tOPV) is protected against paralysis by that serotype is:

$$p_i(m,t) = 1 - (1-v_t)^t (1-v_m)^m \quad (\text{eq. 1})$$

where v_m and v_t give the effectiveness of mOPV and tOPV, respectively, against the serotype under consideration.

The effectiveness of mOPV1, mOPV3 and tOPV was estimated using conditional logistic regression, which estimates the $\ln(\text{odds})$ of paralysis by serotype i as

$$\ln(\text{odds}) = \beta_1 m + \beta_2 t + E$$

where the β 's are the regression coefficients and each matched case-control pair has a particular level of exposure to wild poliovirus, E , which is unknown and is eliminated from the analysis by maximising the conditional likelihood^{3,4}. Vaccine effectiveness is related to the relevant regression coefficient by $1 - e^{-\beta}$.

To assess the validity of reporting a constant effectiveness per dose received of tOPV, the estimated number of tOPV doses received was entered as a continuous and categorical variable in separate models and these models were compared via a likelihood ratio test. The same test was carried out to assess a constant effectiveness per dose of mOPV1 and mOPV3 against serotype 1 and 3 respectively. Because of the method of estimating the number of doses of monovalent and trivalent OPV received by AFP cases, fractional dose numbers were possible. Dose number was therefore rounded to the nearest whole dose in the categorical analysis of mOPV1 and tOPV effectiveness against serotypes 1 and 3, and to the nearest half-dose for tOPV against serotype 2 and mOPV3 against serotype 3 (due to the smaller number of doses of these vaccines distributed).

Comparisons of the fit of the models with variable and constant effectiveness per dose received showed that the constant effectiveness per dose assumption was reasonable for mOPV1, mOPV3 and tOPV (no significant differences in the goodness of fit assessed by the likelihood ratio, $p=0.81$ and $p=0.21$ for mOPV1 and tOPV respectively against wild poliovirus type 1, $p=0.82$ for tOPV against serotype 2 cVDPV and

p=0.61 and p=0.95 for mOPV3 and tOPV respectively against wild poliovirus type 3) (Supplementary Figure 3).

Sensitivity of estimated vaccine effectiveness to routine coverage assumptions

Routine immunisation in Nigeria consists of 4 doses of tOPV administered at birth, 6, 10 and 14 weeks. The percentage of children receiving 3 routine doses by 52 weeks of age by state, as reported in the National Immunisation Coverage Survey (NICS)⁵, was used (since coverage with the birth dose is typically low, the NICS reports the percentages of children receiving 3 doses instead of 4). To test the assumption that all vaccine doses in our analysis were received from Supplementary Immunisation Activities (SIA) we examined the sensitivity of the estimate to the assumption that the first three reported doses of vaccine were tOPV received through routine services among a randomly chosen proportion of AFP cases corresponding to reported routine coverage with 3 doses in the corresponding zone (North West : 21.4%, North East : 28.3%, North Central: 36.0%, South West: 53.7%, South South: 41.8%, South East: 47.1%⁵). The remaining doses were assumed to have been received through SIA and the number of monovalent and trivalent vaccine doses calculated as described in the main text. We ignored routine coverage with fewer than 3 doses of tOPV, assuming that children were more likely to receive either all 3 doses or none at all. Vaccine effectiveness was calculated using conditional logistic regression as described above. This analysis was repeated 100 times and the percentiles for the estimated effectiveness were recorded (Supplementary Tables 4a-c).

The analysis was then repeated for the estimates of the effectiveness of tOPV against cVDPV2 assuming only control children received routine tOPV doses, on the basis that cVDPV2 cases may not have received this effective vaccine (instead, they are more likely to have received the monovalent vaccines against serotypes 1 and 3). Similarly, analyses were repeated for WPV1 and WPV3 assuming that only cases had received the routine tOPV doses on the basis that they were less likely to have received the more effective monovalent vaccines against type 1 or 3. These analyses attributing routine doses to either all cases or all controls are extreme assumptions and the reality is likely to be between these and the assumption that routine doses are split equally between cases and controls. These assumptions then assume differing

estimates of effectiveness of tOPV, for example, an increase to 52% (median estimate with range 35-65%) against cVDPV2 (see Supplementary Tables 4a-c).

Estimation of vaccine-induced population immunity and resulting confidence intervals

The fraction of children protected against paralysis by serotype i poliovirus is given by

$$F_i = \frac{\sum_j n_j p_i(m_j, t_j)}{\sum_j n_j} \quad (\text{eq. 2})$$

where j is an index over all unique possible combinations of doses received, n_j is the number of children that have received the j^{th} combination of doses, t_j is the estimated number of tOPV doses in the j^{th} combination, m_i is the estimated number of mOPV doses of the relevant serotype in the j^{th} combination and $p_i(m, t)$ is defined in equation 1.

To estimate the fraction of children protected against paralysis by serotype i poliovirus and attack rates per 100,000 ‘susceptible’ children, we used a hierarchical model implemented with the WinBUGS software⁶. Given that tOPV is the only vaccine currently licensed in Nigeria that protects against cVDPV2 and that National Immunisation Days have focused increasingly on monovalent vaccines to protect against the greater burden of types 1 and 3 poliovirus, the impact of routine immunisation on population immunity to cVDPV2 should be accounted for. For consistency, the same methods have also been applied to estimation of immunity levels against wild poliovirus types 1 and 3. The model is defined as follows. In each state, the number of doses of mOPV1, mOPV3 and tOPV vaccine received by non-polio AFP cases was modeled as a mixture distribution with two components, where the mixture probability r_s equals the fraction of children receiving 3 routine doses of tOPV in state s according to the NICS⁷ (as described above). In the first component, which was associated with the probability $1-r_s$, the number of doses was modeled as a constrained random vector $(m1, m3, t)$ for each control individual k . Let nD be the total number of vaccine doses reported for k . The components of the vector $(m1, m3, t)$ are then defined as follows. Let $(e1, e3, eT)$ be the calculated rounds of exposure for the three vaccine types, respectively. Let $(q1, q3, qT)$ be the vector of corresponding probabilities obtained by dividing the elements of $(e1, e3, eT)$ with their sum. In the rare cases where the sum of $(e1, e3, eT)$ equals zero we set $qT = 1$ to reflect the fact that any reported doses must

have been obtained through routine immunization activity involving only tOPV vaccine. The number of doses $m1$ is modeled as a truncated binomial $(nD, q1)$ variate by setting $m1$ equal to $e1$ for the binomial events where $m1 > e1$. The number of doses $m3$ is analogously defined by truncating a binomial $(nD, q3)$ variate. Finally, the number of doses t is defined as $nD - m1 - m3$. In the second component, which was associated with probability r_s , the number of doses was modeled as a sum of routinely administered tOPV vaccine rounds and a random vector $(m1, m3, t)$. The number of routinely administered tOPV doses equals 3 in those cases where the number of reported doses is at least 3, and equals the number of reported doses otherwise. The random vector of doses $(m1, m3, t)$ is defined analogously to the above description, except that the sum of its components is set equal to the total number of reported doses nD minus the routinely administered doses.

In addition to the uncertainty related to the dose distribution for each individual, it was necessary to represent the uncertainty about the estimated vaccine effectiveness given the information provided by the conditional logistic regression. Each regression parameter was assigned a normal distribution with mean equal to the maximum likelihood estimate and standard deviation equal to the standard error of the estimate. Thus, this part of our hierarchical model represents the uncertainty remaining about the vaccine effectiveness given the results of the conditional logistic regressions described above.

Throughout, the quantity, F_i , is calculated for each of the five age groups within a state and an average of these five numbers is calculated, weighting each number by the proportion of children in Nigeria under five years old that are in that age group². The fraction protected in a zone further weights the estimates from each state in that zone according to the proportion of the population of the whole zone that is in each state¹.

By fitting the hierarchical model to each annual dataset from each state, it was possible to simulate the marginal posterior distribution of any function of the vaccine effectiveness and the doses administered. The marginal posterior distribution takes efficiently into account the uncertainty related to all nuisance parameters and enables inferences to be made similarly to a profile likelihood method. The two functions of interest here were the proportion of the under-five population protected through direct immunisation (eq. 2)

and the attack rates per 100,000 ‘susceptible’ children. By simulating 10,000 values from the marginal distribution we constructed the estimates using the means and the 95% Bayesian confidence intervals by the 2.5% and 97.5% percentiles of the simulated values. The convergence of the individual simulations was assessed using the standard tools available in WinBUGS and the simulated chains were concluded to have desirable characteristics.

Estimation of hazard of reporting a cVDPV2 case

The hazard of a district reporting its first case of cVDPV2 was estimated using proportional hazards regression as follows

$$\ln[h(t)] = \ln[h_0(t)] + \eta_1 x_1 + \dots + \eta_p x_p$$

which can be written as

$$h(t) = h_0(t) \exp(\eta_1 x_1 + \dots + \eta_p x_p)$$

where $h(t)$ is the overall hazard (or risk) of a district reporting a case at time t , $h_0(t)$ is the baseline hazard, x_1, \dots, x_p are explanatory covariates and η_1, \dots, η_p are their associated coefficients. When maximising the likelihood of this function, $h_0(t)$ integrates out (as it is a constant) and from maximising the remaining partial likelihood we obtain the estimates of the coefficients η_1, \dots, η_p , which are the hazard ratios informing us of the impact of each variable on the overall hazard⁸.

The proportional hazards model allows the baseline hazard to vary but assumes that the coefficients are independent of time⁸. To assess the potential impact of a number of explanatory variables which changed over the course of the outbreak, we used a proportional hazards regression with time-varying covariates. The time period analysed was 26 May 2006 to 30 June 2009 as the second case had date of onset of 26 May 2006 (the first case was in July 2005 and as this was more than six months before the second it was excluded from the analysis). Each district formed a separate observation and time-varying covariates were updated monthly through the time period analysed resulting in 37 observations for each district. A sliding window of 6-months was used such that all covariates were estimated based on data in the six months leading up to the month in question.

Several different variables describing the force of infection in an area at a given time were examined for their explanatory power. Those based on distance assumed that the location of a case was the centroid of the district of residence since more detailed location data are unavailable (the average area of a district is 1,200km²). Variables and their polynomials were entered into univariable proportional hazards models and the model with the maximum likelihood chosen. Variables examined were:

Measure
Distance from the nearest case reported in the previous six months
Median distance from all cases reported in the previous six months
Mean distance from all cases reported in the previous six months
Number of cases reported in the previous six months within x km (where x was increased systematically by 1 until an optimal x was found which maximised the likelihood compared to all other x)
A “gravity” variable ⁹ equal to $N_k \sum_j \frac{I_j}{d_{jk}}$ where k is the district in question, j represents other districts in the country, N is the population in district k , I is the incidence of cVDPV in each of the j districts in the previous six months and d is the distance between j and k .

Where median and mean distances were used, the first 9 cases and their associated time periods were excluded so that the median and mean distances were based on sufficient numbers. Therefore these analyses were based on data from September 06 instead of May 06.

Vaccine-induced population immunity levels were estimated as described above. After selection of a force of infection variable, immunity levels were entered into the model and this multivariable model compared with one without the immunity levels via a likelihood ratio test.

Similarly, the variables population and population density were assessed via likelihood ratio tests. Any confounding effects were also assessed and considered in selection of the final model.

Supplementary Table 1a Annual incidence of paralysis due to WPV1 in Nigeria by state

Zone	State	Year					
		2005	2006	2007	2008	2008*	2009*
North West	Jigawa	54	102	6	38	35	1
	Kaduna	67	35	5	47	33	0
	Kano	118	304	10	264	189	1
	Katsina	41	157	8	73	42	1
	Kebbi	83	13	17	9	3	1
	Sokoto	37	31	12	28	16	3
	Zamfara	57	29	2	82	60	2
NORTH WEST		457	671	60	541	378	9
North East	Adamawa	2	1	2	1	1	0
	Bauchi	46	82	16	43	29	1
	Borno	11	24	20	24	18	2
	Gombe	8	11	3	13	7	0
	Taraba	3	1	2	2	2	0
	Yobe	15	25	8	20	13	1
NORTH EAST		85	144	51	103	70	4
North Central	Benue	5	0	0	2	2	5
	FCT	2	2	1	8	4	1
	Kogi	2	0	1	7	0	5
	Kwara	1	1	0	8	2	2
	Nasarawa	8	7	0	5	2	4
	Niger	10	17	3	14	10	5
	Plateau	2	4	0	13	11	1
NORTH CENTRAL		30	31	5	57	31	23
South West	Ekiti	0	0	0	0	0	0
	Lagos	1	0	0	3	0	4
	Ogun	0	0	0	1	0	13
	Ondo	0	0	0	1	0	0
	Osun	0	0	0	2	0	0
	Oyo	0	0	0	11	10	2
SOUTH WEST		1	0	0	18	10	19
South South	Akwa Ibom	0	0	0	0	0	0
	Bayelsa	0	0	0	0	0	4
	Cross River	0	0	0	0	0	0
	Delta	0	0	0	0	0	6
	Edo	0	0	0	0	0	1
	Rivers	0	0	0	0	0	0
SOUTH SOUTH		0	0	0	0	0	11
South East	Abia	0	0	0	0	0	0
	Anambra	0	0	0	0	0	0
	Ebonyi	0	0	0	0	0	1
	Enugu	0	0	0	2	1	0
	Imo	0	0	0	0	0	0
SOUTH EAST		0	0	0	2	1	1
Whole country		573	846	116	721	490	67

* Numbers to end of June of that year, hence the column 2008* is a subset of the totals in 2008.

Supplementary Table 1b Annual incidence of paralysis due to cVDPV2 in Nigeria by state

Zone	State	Year					
		2005	2006	2007	2008	2008*	2009*
North West	Jigawa	0	1	5	5	2	10
	Kaduna	0	1	6	0	0	11
	Kano	0	17	27	4	3	32
	Katsina	0	1	12	4	4	20
	Kebbi	0	0	4	3	1	3
	Sokoto	0	0	5	8	7	4
	Zamfara	0	0	3	14	5	15
NORTH WEST		0	20	62	38	22	95
North East	Adamawa	0	0	0	0	0	1
	Bauchi	1	1	3	8	5	1
	Borno	0	0	2	1	1	8
	Gombe	0	0	0	0	0	0
	Taraba	0	0	0	0	0	0
	Yobe	0	0	1	7	3	4
NORTH EAST		1	1	6	16	9	14
North Central	Benue	0	0	0	0	0	1
	FCT	0	0	0	0	0	0
	Kogi	0	0	0	1	0	0
	Kwara	0	0	0	0	0	1
	Nasarawa	0	0	0	1	1	2
	Niger	0	0	0	6	4	10
	Plateau	0	0	0	0	0	1
NORTH CENTRAL		0	0	0	8	5	15
South West	Ekiti	0	0	0	0	0	0
	Lagos	0	0	0	0	0	0
	Ogun	0	0	0	0	0	0
	Ondo	0	0	0	0	0	0
	Osun	0	0	0	0	0	1
	Oyo	0	0	0	0	0	0
SOUTH WEST		0	0	0	0	0	1
South South	Akwa Ibom	0	0	0	0	0	0
	Bayelsa	0	0	0	0	0	0
	Cross River	0	0	0	0	0	0
	Delta	0	0	0	0	0	0
	Edo	0	0	0	0	0	0
	Rivers	0	0	0	0	0	0
SOUTH SOUTH		0	0	0	0	0	0
South East	Abia	0	0	0	0	0	0
	Anambra	0	0	0	0	0	0
	Ebonyi	0	0	0	0	0	0
	Enugu	0	0	0	0	0	1
	Imo	0	0	0	0	0	0
SOUTH EAST		0	0	0	0	0	1
Whole country		1	21	68	62	36	126

* Numbers to end of June of that year, hence the column 2008* is a subset of the totals in 2008.

Supplementary Table 1c Annual incidence of paralysis due to WPV3 in Nigeria by state

Zone	State	Year					
		2005	2006	2007	2008	2008*	2009*
North West	Jigawa	29	30	27	2	1	14
	Kaduna	16	18	2	2	2	16
	Kano	109	51	49	7	4	95
	Katsina	38	22	16	9	9	32
	Kebbi	9	59	10	0	0	13
	Sokoto	16	11	12	0	0	12
	Zamfara	8	20	4	3	3	9
NORTH WEST		225	211	120	23	19	191
North East	Adamawa	1	0	0	0	0	1
	Bauchi	12	18	12	12	3	40
	Borno	1	20	5	7	0	16
	Gombe	1	4	0	0	0	9
	Taraba	0	1	1	2	2	0
	Yobe	5	16	10	9	4	14
NORTH EAST		20	59	29	30	9	80
North Central	Benue	0	0	1	0	0	1
	FCT	3	0	0	1	1	0
	Kogi	1	0	0	1	0	0
	Kwara	0	0	1	1	1	0
	Nasarawa	2	0	3	1	1	5
	Niger	2	5	2	1	1	5
	Plateau	0	1	2	8	3	3
NORTH CENTRAL		8	6	9	13	7	14
South West	Ekiti	0	0	0	0	0	0
	Lagos	0	0	4	0	0	0
	Ogun	0	0	0	3	3	0
	Ondo	0	0	0	0	0	0
	Osun	0	0	0	0	0	0
	Oyo	0	0	6	7	6	0
SOUTH WEST		0	0	10	10	9	0
South South	Akwa Ibom	0	0	0	0	0	0
	Bayelsa	0	0	0	0	0	0
	Cross River	0	0	0	0	0	0
	Delta	0	0	0	0	0	0
	Edo	0	0	0	0	0	0
	Rivers	0	0	1	0	0	0
SOUTH SOUTH		0	0	1	0	0	0
South East	Abia	0	0	0	0	0	0
	Anambra	0	0	0	0	0	0
	Ebonyi	0	0	0	0	0	0
	Enugu	0	0	0	0	0	0
	Imo	0	0	0	0	0	0
SOUTH EAST		0	0	0	0	0	0
Whole country		253	276	169	76	44	285

* Numbers to end of June of that year, hence the column 2008* is a subset of the totals in 2008.

Supplementary Table 2 Site of paralysis of paralytic polio cases by poliovirus type

Left Arm	Right Arm	Left Leg	Right Leg	cVDPV2, n (%)	WPV1, n (%)	WPV3, n (%)
No	No	No	No	0 (0)	11 (<1)	5 (1)
			Yes	81 (29)	626 (27)	126 (12)
		Yes	No	27 (10)	389 (17)	83 (8)
			Yes	39 (14)	604 (26)	127 (12)
	Yes	No	No	3 (1)	26 (1)	4 (<1)
			Yes	9 (3)	92 (4)	21 (2)
			Yes	0 (0)	9 (<1)	3 (<1)
		Yes	No	2 (1)	17 (<1)	4 (<1)
			Yes	31 (11)	156 (7)	24 (2)
			Yes	38 (14)	201 (9)	18 (2)
Yes	No	No	No	18 (6)	81 (3)	23 (2)
			Yes	5 (2)	34 (1)	6 (1)
		Yes	No	0 (0)	9 (<1)	0 (0)
			Yes	3 (1)	13 (1)	2 (<1)
	Yes	No	No	0 (0)	4 (<1)	5 (<1)
			Yes	12 (4)	44 (2)	17 (2)
		Yes	No	10 (4)	7 (<1)	2 (<1)
			Yes	278	2323	1059
Missing data						
Total						

Supplementary Table 3a Estimated per dose effectiveness of mOPV1 against paralysis by wild poliovirus type 1 when cases were matched to controls on age at onset of paralysis (within 6 months), date of onset of paralysis (within 6 months), sex and location of residence (district or state, see table)

	Cases matched to controls by district	Cases matched to controls by state
Year†	mOPV1 effectiveness (%) (95% CI)	mOPV1 effectiveness (%) (95% CI)
2005	N/A*	N/A*
2006	74 (38, 91)	69 (43, 83)
2007	30 (0, 84)	0 (0, 39)
2008	45 (24, 60)	42 (28, 54)
2009	52 (0, 81)	37 (3, 59)
Overall	45 (30, 57)	43 (33, 51)
P-value for interaction	0.39	0.03

†mid-point between date of onset of paralysis for case and control;

*mOPV1 was only introduced in Nigeria in 2006

Supplementary Table 3b Estimated per dose effectiveness of tOPV and mOPV1 against paralysis by wild poliovirus type 1 when cases are matched to controls on age at onset of paralysis (within 6 months), date of onset of paralysis (within 6 months), sex and location of residence (district or state, see table)

Zone	Cases matched to controls by district		Cases matched to controls by state	
	mOPV1 effectiveness (%) (95% CI)	tOPV effectiveness (%) (95% CI)	mOPV1 effectiveness (%) (95% CI)	tOPV effectiveness (%) (95% CI)
	North West	42 (22, 56)	11 (1, 20)	46 (35, 55)
North East	44 (0, 83)	35 (0, 58)	38 (0,62)	29 (15, 40)
North Central	27 (0, 60)	3 (0, 29)	12 (0, 37)	17 (3, 29)
South	89 (5, 99)	81 (0, 100)	75 (37, 90)	88 (0, 99)
Overall	45 (30, 57)	13 (4, 21)	43 (33, 51)	13 (8, 18)
P-value for interaction	0.14	0.31	0.03	0.002

Supplementary Table 4a Estimated per dose effectiveness of mOPV1 and tOPV against paralysis from wild poliovirus type 1 assuming randomly selected cases and controls, or cases only, received 3 doses of tOPV through routine services. The estimated fraction of children receiving 3 doses through routine services was based on the National Immunisation Coverage Survey⁵ (see Supplementary Methods).

Randomly chosen recipients of routine tOPV	Percentile*	mOPV1 effectiveness (%) (95% CI)	tOPV effectiveness (%) (95% CI)
Cases and controls	5 th	40 (30, 48)	18 (13, 22)
	50 th	35 (25, 43)	16 (12, 20)
	95 th	30 (20, 39)	15 (10, 19)
Cases only	5 th	61 (54, 67)	8 (3, 13)
	50 th	59 (51, 65)	7 (2, 11)
	95 th	56 (48, 62)	6 (1, 11)

*based on rank after the analysis was repeated 100 times

Supplementary Table 4b Estimated per dose effectiveness of tOPV against paralysis from cVDPV

assuming randomly selected cases and controls, or controls only, received 3 doses of tOPV through routine services. The estimated fraction of children receiving 3 doses through routine services was based on the National Immunisation Coverage Survey⁵ (see Supplementary Methods).

Randomly chosen recipients of routine tOPV	Percentile*	tOPV effectiveness (%) (95% CI)
Cases and controls	5 th	33 (15, 47)
	50 th	23 (6, 37)
	95 th	14 (0, 29)
Controls only	5 th	55 (37, 68)
	50 th	52 (35, 65)
	95 th	49 (31, 62)

*based on rank after the analysis was repeated 100 times

Supplementary Table 4c Estimated per dose effectiveness of mOPV3 and tOPV against paralysis from wild poliovirus type 3 assuming randomly selected cases and controls, or cases only, received 3 doses of tOPV through routine services. The estimated fraction of children receiving 3 doses through routine services was based on the National Immunisation Coverage Survey⁵ (see Supplementary Methods).

Randomly chosen recipients of routine tOPV	Percentile*	mOPV3 effectiveness (%) (95% CI)	tOPV effectiveness (%) (95% CI)
Cases and controls	5 th	64 (35, 80)	20 (14, 26)
	50 th	50 (16, 70)	18 (12, 24)
	95 th	40 (1, 64)	16 (10, 22)
Cases only	5 th	84 (67, 92)	12 (5, 18)
	50 th	78 (57, 89)	11 (4, 17)
	95 th	72 (47, 85)	9 (2, 16)

*based on rank after the analysis was repeated 100 times

Supplementary Table 5a The estimated proportions of the population (aged under 5 years old) that are protected against paralysis by wild poliovirus type 1 (WPV1) through direct immunisation by year and zone. Average change per year and statistical significance of this trend also shown.

Zone	Year					Linear trend (average change per year)	P-value for linear trend
	2005	2006	2007	2008	2009*		
North West	0.24	0.32	0.39	0.45	0.55	0.074	<0.001
<i>Sample size</i>	<i>912</i>	<i>858</i>	<i>730</i>	<i>932</i>	<i>548</i>		
North East	0.30	0.40	0.42	0.55	0.62	0.081	<0.001
<i>Sample size</i>	<i>358</i>	<i>334</i>	<i>336</i>	<i>383</i>	<i>340</i>		
North Central	0.45	0.50	0.50	0.61	0.66	0.053	<0.001
<i>Sample size</i>	<i>531</i>	<i>575</i>	<i>525</i>	<i>666</i>	<i>289</i>		
South West	0.52	0.57	0.65	0.58	0.67	0.029	0.01
<i>Sample size</i>	<i>484</i>	<i>438</i>	<i>453</i>	<i>523</i>	<i>269</i>		
South South	0.49	0.55	0.60	0.59	0.61	0.027	<0.001
<i>Sample size</i>	<i>230</i>	<i>279</i>	<i>429</i>	<i>479</i>	<i>237</i>		
South East	0.46	0.49	0.50	0.53	0.54	0.022	<0.001
<i>Sample size</i>	<i>219</i>	<i>228</i>	<i>274</i>	<i>310</i>	<i>154</i>		
All	0.39	0.46	0.51	0.54	0.61	0.050	<0.001
<i>Sample size</i>	<i>2734</i>	<i>2712</i>	<i>2746</i>	<i>3290</i>	<i>1837</i>		

*January – June

Supplementary Table 5b The estimated proportions of the population (aged under 5 years old) that are protected against paralysis by serotype 2 cVDPV through direct immunisation by year and zone). Average change per year and statistical significance of this trend also shown.

Zone	Year					Linear trend (average change per year)	P-value for linear trend
	2005	2006	2007	2008	2009*		
North West	0.47	0.48	0.48	0.38	0.26	-0.047	<0.001
<i>Sample size</i>	<i>912</i>	<i>858</i>	<i>730</i>	<i>932</i>	<i>548</i>		
North East	0.58	0.63	0.56	0.48	0.38	-0.055	<0.001
<i>Sample size</i>	<i>358</i>	<i>334</i>	<i>336</i>	<i>383</i>	<i>340</i>		
North Central	0.81	0.80	0.77	0.64	0.50	-0.072	<0.001
<i>Sample size</i>	<i>531</i>	<i>575</i>	<i>525</i>	<i>666</i>	<i>289</i>		
South West	0.86	0.84	0.78	0.62	0.51	-0.088	<0.001
<i>Sample size</i>	<i>484</i>	<i>438</i>	<i>453</i>	<i>523</i>	<i>269</i>		
South South	0.85	0.83	0.70	0.65	0.62	-0.067	<0.001
<i>Sample size</i>	<i>230</i>	<i>279</i>	<i>429</i>	<i>479</i>	<i>237</i>		
South East	0.83	0.78	0.65	0.60	0.50	-0.083	<0.001
<i>Sample size</i>	<i>219</i>	<i>228</i>	<i>274</i>	<i>310</i>	<i>154</i>		
All	0.71	0.71	0.65	0.54	0.44	-0.068	<0.001
<i>Sample size</i>	<i>2734</i>	<i>2712</i>	<i>2746</i>	<i>3290</i>	<i>1837</i>		

*January – June

Supplementary Table 5c The estimated proportions of the population (aged under 5 years old) that are protected against paralysis by wild poliovirus type 3 (WPV3) through direct immunisation by year and zone. Average change per year and statistical significance of this trend also shown.

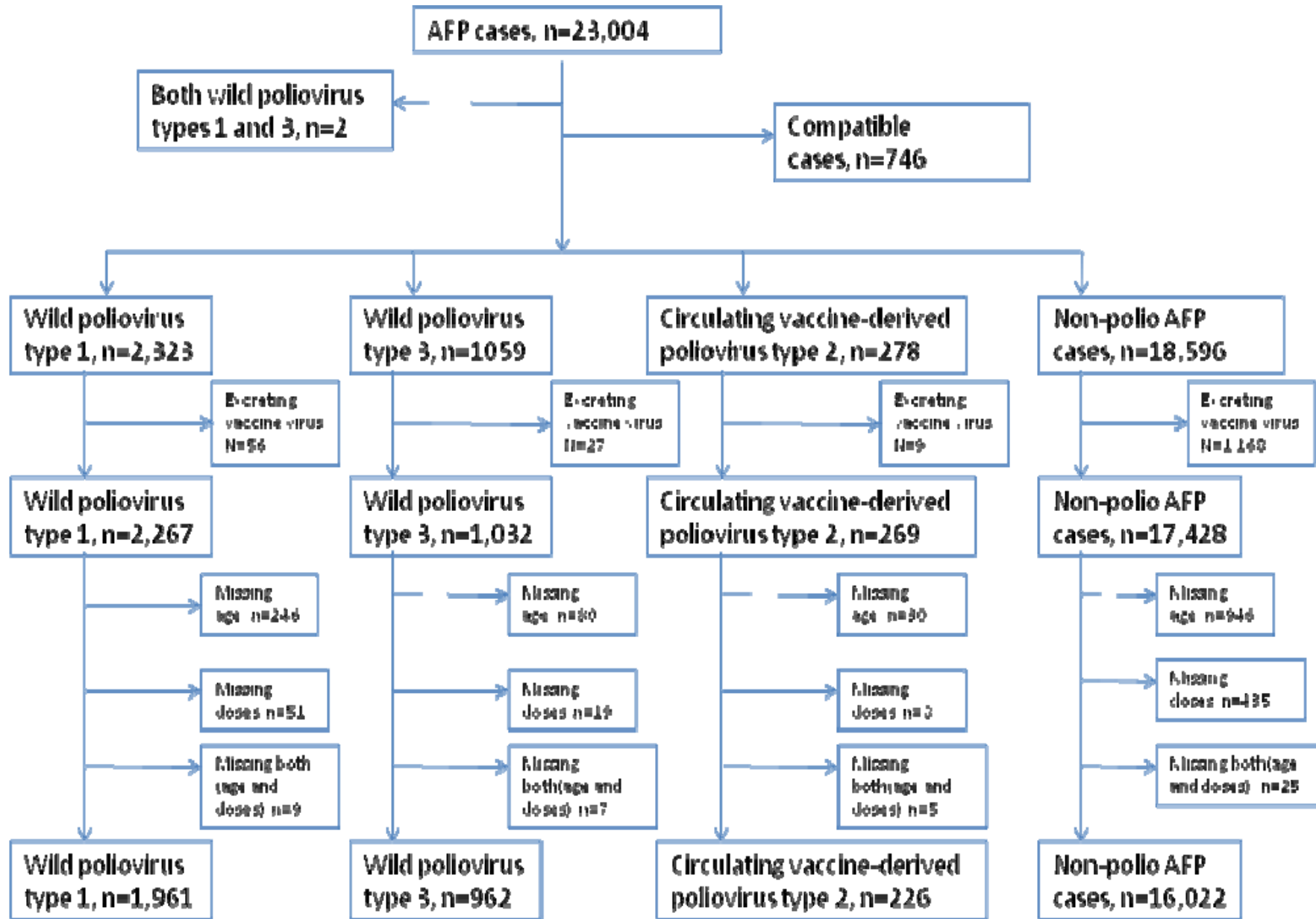
Zone	Year					Linear trend (average change per year)	P-value for linear trend
	2005	2006	2007	2008	2009*		
North West	0.31	0.32	0.34	0.33	0.33	0.006	0.006
<i>Sample size</i>	<i>912</i>	<i>858</i>	<i>730</i>	<i>932</i>	<i>548</i>		
North East	0.39	0.41	0.37	0.44	0.44	0.013	0.05
<i>Sample size</i>	<i>358</i>	<i>334</i>	<i>336</i>	<i>383</i>	<i>340</i>		
North Central	0.58	0.57	0.54	0.55	0.52	-0.014	<0.001
<i>Sample size</i>	<i>531</i>	<i>575</i>	<i>525</i>	<i>666</i>	<i>289</i>		
South West	0.65	0.63	0.57	0.63	0.61	-0.009	0.34
<i>Sample size</i>	<i>484</i>	<i>438</i>	<i>453</i>	<i>523</i>	<i>269</i>		
South South	0.62	0.60	0.47	0.53	0.54	-0.023	0.14
<i>Sample size</i>	<i>230</i>	<i>279</i>	<i>429</i>	<i>479</i>	<i>237</i>		
South East	0.59	0.54	0.43	0.48	0.48	-0.031	0.03
<i>Sample size</i>	<i>219</i>	<i>228</i>	<i>274</i>	<i>310</i>	<i>154</i>		
All	0.51	0.50	0.45	0.48	0.48	-0.008	0.18
<i>Sample size</i>	<i>2734</i>	<i>2712</i>	<i>2746</i>	<i>3290</i>	<i>1837</i>		

*January – June

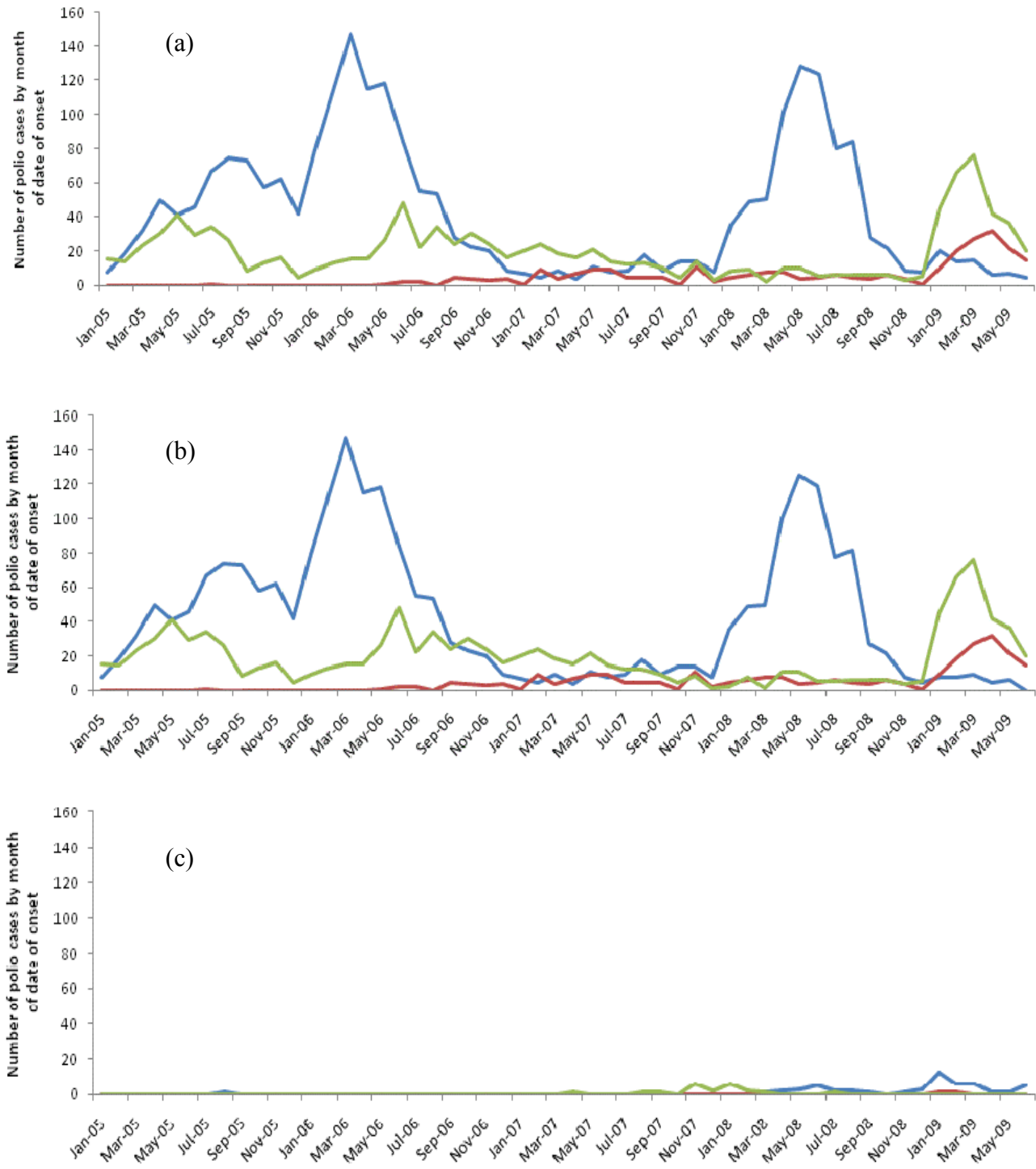
Supplementary Table 6 Predictors for a district reporting its first case of serotype 2 cVDPV

Variable	Relative hazard (95% CI)	z-statistic	P-value
Square of the median distance from cases reported in the previous six months / 1000	0.0022 (-0.0042, 0.0086)	0.69	0.49
Immunity level across the state in the previous six months	-0.103 (-2.34, 2.13)	-0.09	0.93
Interaction between the above two variables	-0.019 (-0.033, -0.006)	-2.85	0.004

Supplementary Figure 1 Flow chart illustrating the total number of Acute Flaccid Paralysis (AFP) cases used in the analysis (Jan 2005-June 2009)

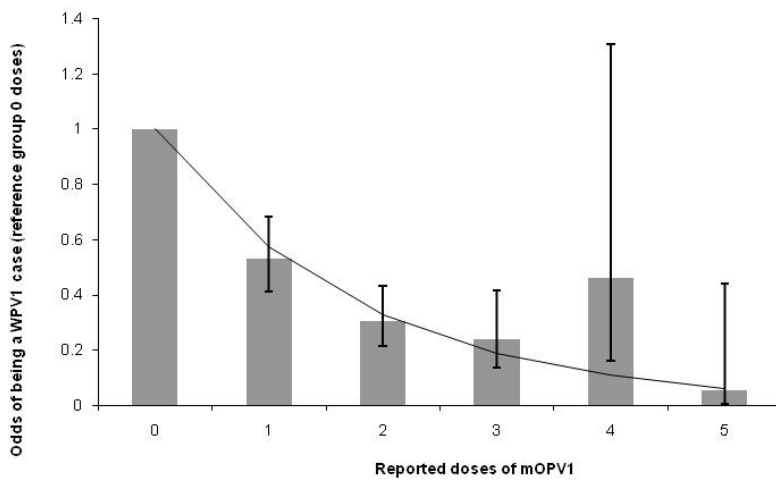


Supplementary Figure 2 Number of cases of all three types of polio currently circulating in Nigeria by month of date of onset (January 2001 – June 2009 shown). Blue indicates wild poliovirus type 1, green, wild poliovirus type 3 and red, circulating vaccine-derived poliovirus. Graph (a) data for the whole of Nigeria, (b) northern states only and (c) southern states only.

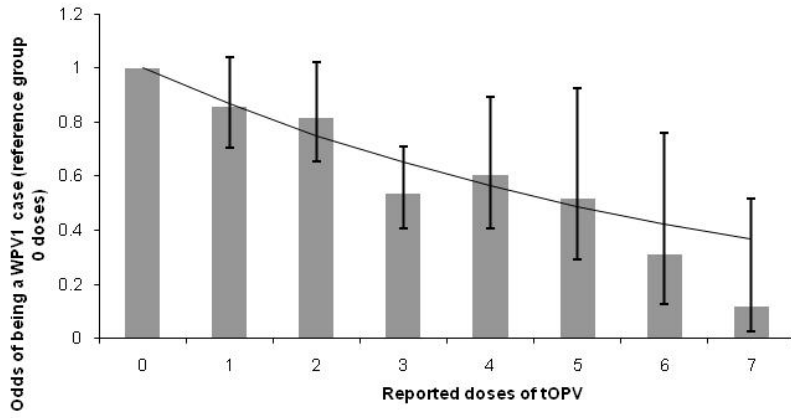


Supplementary Figure 3 Relative odds of being a paralytic polio case by estimated number of OPV doses received. The estimate relative odds are given by the bars, with error bars indicating 95% confidence intervals, and the curved line represents the relationship between the relative odds of being a case and number of doses based on a constant vaccine effectiveness per dose received. (a) Relative odds of AFP associated with WPV1 by estimated number of mOPV1 doses received (up to 5 doses shown), (b) relative odds of AFP associated with WPV1 by estimated number of tOPV doses received (up to 7 doses shown), (c) relative odds of AFP associated with cVDPV2 by estimated number of tOPV doses received (due to small numbers of doses received, half doses are shown, up to 2.5 doses), (d) relative odds of AFP associated with WPV3 by estimated number of mOPV3 doses received (due to small numbers of doses received, half doses are shown, up to 2 doses), (e) relative odds of AFP associated with WPV3 by estimated number of tOPV doses received (up to 5 doses shown)

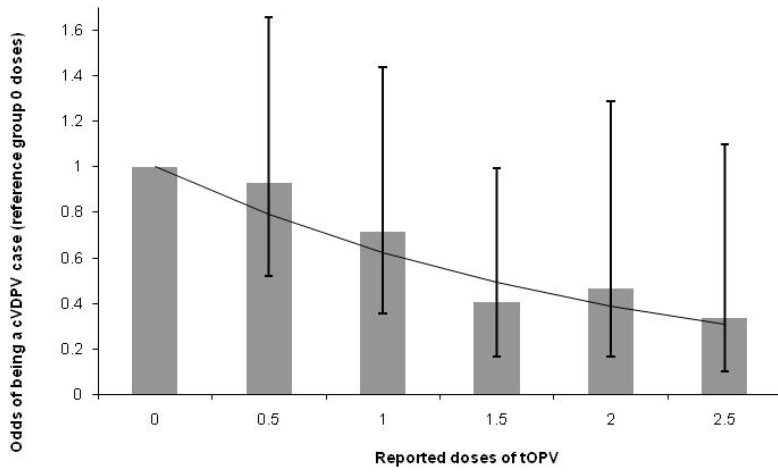
(a)



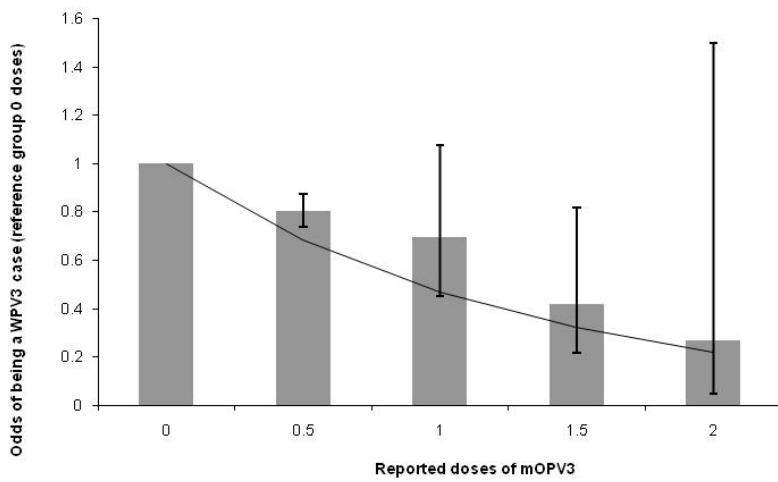
(b)



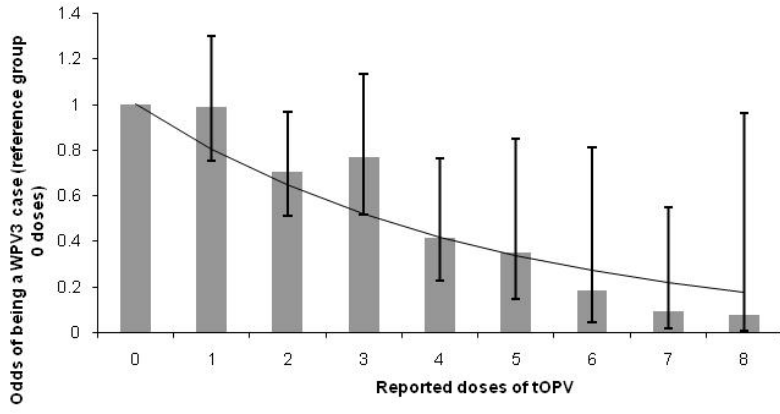
(c)



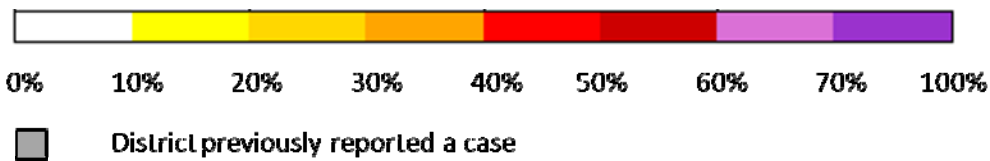
(d)



(e)



Supplementary Figure 4 An animation showing the evolution over time of the spatial distribution of the hazard of reporting a type 2 cVDPV2 among the districts in Nigeria can be found at <http://www1.imperial.ac.uk/resources/E4B07B06-03BD-4638-A802-99D62FF48C8D/cvdpv2.swf>. The animation can be opened in any web browser with the Adobe Flash Player plug-in or in the Windows Media Player. The estimated hazard of a district reporting its first cVDPV2 case by month from October 2006 through June 2009 is shown based on the fit of the proportional hazards model. Black dots indicate cases of cVDPV2 reported during that month. Legend for hazards shown is as follows:



Relative hazard of a district reporting its first case of serotype 2 cVDPV compared to a district that is 0km from all cases reported in the previous 6 months and has 0% population immunity

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