ORIGINAL ARTICLE

Type 2 Poliovirus Detection after Global Withdrawal of Trivalent Oral Vaccine

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ABSTRACT

BACKGROUND

Mass campaigns with oral poliovirus vaccine (OPV) have brought the world close to the eradication of wild poliovirus. However, to complete eradication, OPV must itself be withdrawn to prevent outbreaks of vaccine-derived poliovirus (VDPV). Synchronized global withdrawal of OPV began with serotype 2 OPV (OPV2) in April 2016, which presented the first test of the feasibility of eradicating all polioviruses.

METHODS

We analyzed global surveillance data on the detection of serotype 2 Sabin vaccine (Sabin-2) poliovirus and serotype 2 vaccine–derived poliovirus (VDPV2, defined as vaccine strains that are at least 0.6% divergent from Sabin-2 poliovirus in the viral protein 1 genomic region) in stool samples from 495,035 children with acute flaccid paralysis in 118 countries and in 8528 sewage samples from four countries at high risk for transmission; the samples were collected from January 1, 2013, through July 11, 2018. We used Bayesian spatiotemporal smoothing and logistic regression to identify and map risk factors for persistent detection of Sabin-2 poliovirus and VDPV2.

RESULTS

The prevalence of Sabin-2 poliovirus in stool samples declined from 3.9% (95% confidence interval [CI], 3.5 to 4.3) at the time of OPV2 withdrawal to 0.2% (95% CI, 0.1 to 2.7) at 2 months after withdrawal, and the detection rate in sewage samples declined from 71.0% (95% CI, 61.0 to 80.0) to 13.0% (95% CI, 8.0 to 20.0) during the same period. However, 12 months after OPV2 withdrawal, Sabin-2 poliovirus continued to be detected in stool samples (<0.1%; 95% CI, <0.1 to 0.1) and sewage samples (8.0%; 95% CI, 5.0 to 13.0) because of the use of OPV2 in response to VDPV2 outbreaks. Nine outbreaks were reported after OPV2 withdrawal and were associated with low coverage of routine immunization (odds ratio, 1.64 [95% CI, 1.14 to 2.54] per 10% absolute decrease) and low levels of population immunity (odds ratio, 2.60 [95% CI, 1.35 to 5.59] per 10% absolute decrease) within affected countries.

CONCLUSIONS

High population immunity has facilitated the decline in the prevalence of Sabin-2 poliovirus after OPV2 withdrawal and restricted the circulation of VDPV2 to areas known to be at high risk for transmission. The prevention of VDPV2 outbreaks in these known areas before the accumulation of substantial cohorts of children susceptible to type 2 poliovirus remains a high priority. (Funded by the Bill and Melinda Gates Foundation and the World Health Organization.)

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The Global Polio Eradication Initiative has relied on oral poliovirus vaccine (OPV) to bring polio to the brink of eradication. Only 22 cases of poliomyelitis caused by wild poliovirus were reported in 2017 (all serotype 1). OPV is currently used in routine immunization and in mass campaigns among children younger than 5 years of age in more than 150 countries to ensure high levels of population immunity. It is a live-attenuated vaccine (containing Sabin poliovirus strains) that is inexpensive and easy to administer, and unlike the parenteral inactivated poliovirus vaccine (IPV), it replicates in the intestine to induce mucosal immunity that limits further infection and transmission. However, OPV is genetically unstable and can evolve during replication in the human intestine to regain the neurovirulence and replication characteristics of its parental wild-type strains.[1-3] In rare instances, OPV can cause vaccine-associated paralytic poliomyelitis (approximately one to two cases per million persons vaccinated) or lead to outbreaks of circulating vaccine-derived polioviruses (VDPV) that cause poliomyelitis (approximately one outbreak per 500 million persons vaccinated).[4]

The last naturally occurring case of poliomyelitis caused by serotype 2 wild poliovirus was reported in 1999 in India.[5,6] However, most cases (>90%) of circulating VDPV poliomyelitis that have been reported over the past decade have been caused by circulating serotype 2 VDPV (VDPV2, defined as vaccine strains that are at least 0.6% divergent from Sabin-2 poliovirus in the viral protein 1 genomic region; genetically linked isolates consistent with circulation are classified as circulating VDPV2[7]), in part because of a decline in immunity after the widespread use of bivalent and monovalent OPV containing serotypes 1 and 3 in supplemental immunization activities (i.e., mass campaigns).[8] The World Health Organization (WHO) therefore recommended the globally synchronized withdrawal of serotype 2 OPV (OPV2) by replacing trivalent OPV, which was still being used in many countries, with bivalent OPV during a 2-week period in April 2016 to prevent further emergence of circulating VDPV2.[9,10] To mitigate the risks associated with OPV2 withdrawal, the WHO recommended that at least one dose of trivalent IPV should be used in routine immunization in all countries.

A major risk associated with OPV2 withdrawal is the occurrence of further outbreaks of circulating VDPV2 that result from continued circulation of VDPV2 caused by the use of trivalent OPV before OPV2 withdrawal or by the accidental use of trivalent OPV after withdrawal of OPV2. The risk of an outbreak is likely to be highest during the first 12 months after OPV2 withdrawal.[11] However, if VDPV2 circulates after 12 months, the scale of an outbreak will most likely be greater owing to the accumulation of children who have not been immunized against serotype 2. Furthermore, the response to any outbreak of circulating VDPV2 will probably include the use of monovalent OPV2 because of the superior mucosal immunity induced by this vaccine as compared with IPV.[12] The use of monovalent OPV2 could cause more cases of circulating VDPV2, particularly as the time after OPV2 withdrawal increases, thus risking an escalation in the use of OPV2 and "cessation failure."[13]

The global withdrawal of OPV2 is therefore seen as a major test of the feasibility of eradication of all polioviruses, as envisaged by the Global Polio Eradication Initiative.[14] The detection rate of serotype 2 Sabin vaccine poliovirus (i.e., Sabin-2 poliovirus) has declined after the withdrawal of OPV2,[15] although an analysis of data from 17 countries showed some unexpected reports of detection during the first 8 months.[16] Here, we analyze the geographic distribution of Sabin-2 poliovirus and circulating VDPV2 detected in stool and sewage samples collected in 118 countries over the first 2 years after OPV2 withdrawal.

Methods

Data Collection

We collected data from 495,035 children 0 to 14 years of age with acute flaccid paralysis, as reported through a network of health care providers and as recorded in the Polio Information System (maintained by the Global Polio Eradication Initiative) from clinical and epidemiologic investigations.[17] Two stool samples from each child with acute flaccid paralysis were analyzed for the presence of wild poliovirus, Sabin vaccine poliovirus, or vaccine-derived polioviruses according to standard WHO protocols.[18,19] Most cases (99%) of acute flaccid paralysis are not caused by poliovirus (nonpolio acute flaccid paralysis), and

the detection of Sabin vaccine poliovirus is usually a coincidental finding rather than an indicator of vaccine-associated paralytic poliomyelitis.[20] We analyzed epidemiologic and laboratory data from cases of acute flaccid paralysis reported in 118 countries in the African, eastern Mediterranean, Southeast Asian, and European regions; the stool samples were collected from January 1, 2013, through July 11, 2018.

Environmental surveillance (i.e., the systematic collection and testing of sewage samples to detect polioviruses) is performed in more than 30 countries to supplement surveillance of acute flaccid paralysis.[21,22] We analyzed environmental surveillance data from four high-risk countries (Afghanistan, Pakistan, Nigeria, and Kenya); 8528 sewage samples, collected between January 1, 2013, and July 11, 2018, were tested for polioviruses according to standard WHO protocols.[23] The number and spatial distribution of collection sites are shown in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

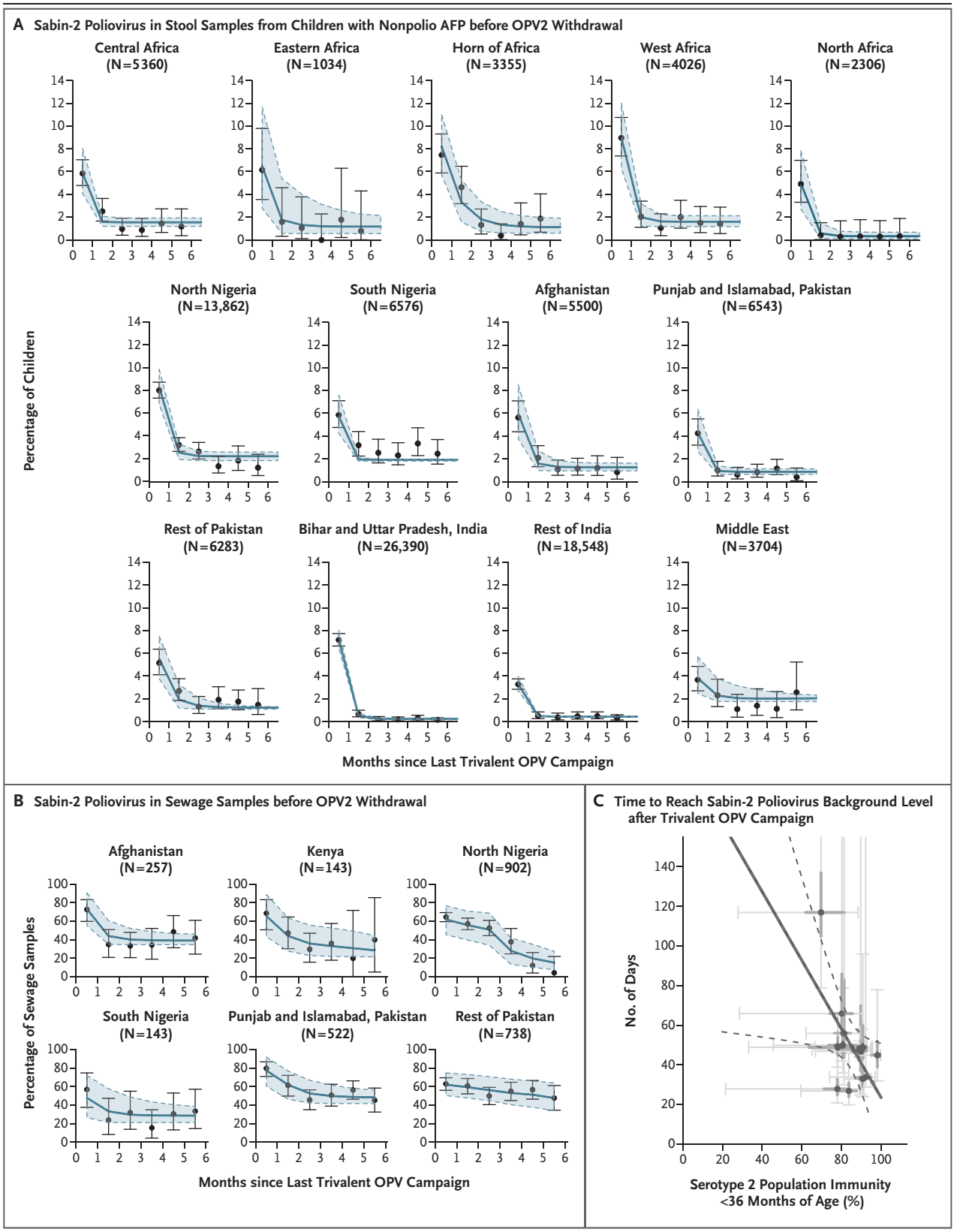
STATISTICAL ANALYSIS

We fit logistic-regression models to data on the prevalence of Sabin-2 poliovirus isolated from persons with nonpolio acute flaccid paralysis before the withdrawal of OPV2. We assumed that the odds of detection of Sabin-2 poliovirus decline as an exponential function of time since the last trivalent OPV campaign in that province. Detection of Sabin-2 poliovirus asymptotically approaches a low constant background level, resulting from either routine vaccination with trivalent OPV or the migration of recently vaccinated children from other provinces; the low constant background level was estimated with an offset variable (independent of time), and the decline was estimated with a logit-link function. Countries were grouped according to region in the analysis except for India and the three countries in which wild poliovirus is endemic, which were analyzed at the national (Afghanistan) or subnational (India, Pakistan, Nigeria) level (Table S1 in the Supplementary Appendix). Fixed effects determining the decline in the rate of Sabin-2 poliovirus and the background level were estimated for each population. Data were censored at the time of the next campaign or at 6 months after the last campaign, whichever was sooner. We used the same approach for environmental surveillance data, but with a mixed-effects model to account for repeated observations at each environmental surveillance site and site-specific variation in sensitivity to detect poliovirus. The models were fitted under a Bayesian framework with the use of integrated nested Laplace approximation through the R-INLA package[24] and the R programming language.[25] We used the fitted models to predict the prevalence of Sabin-2 poliovirus after OPV2 withdrawal and accounted for the use of monovalent OPV2 in subsequent outbreak-response campaigns by assuming that the decline in prevalence after a monovalent OPV2 campaign is similar to that after a trivalent OPV campaign (see the Supplementary Appendix).

We also tested the correlation between serotype 2 population immunity among children younger than 36 months of age and the estimated

Figure 1 (facing page). Detection of Sabin-2 Poliovirus over Time since the Last Trivalent Oral Poliovirus Vaccine (OPV) Campaign and Relationship between Decline in Detection and Serotype 2 Population Immunity in Young Children.

Panel A shows the percentage of children with nonpolio acute flaccid paralysis (AFP) who tested positive for serotype 2 Sabin vaccine (Sabin-2) poliovirus in stool samples, and Panel B the percentage of sewage samples positive for Sabin-2 poliovirus, before withdrawal of the serotype 2 oral poliovirus vaccine (OPV2), according to country of analysis. All samples were collected before OPV2 withdrawal between January 1, 2013, and April 15, 2016; the number of children (Panel A) or sewage samples (Panel B) are shown above each plot. The "rest of Pakistan" corresponds to Pakistan provinces other than Punjab and Islamabad, and the "rest of India" corresponds to Indian states other than Uttar Pradesh and Bihar. The observed prevalence of detection is indicated by solid circles; I bars indicate 95% binomial confidence intervals. The blue lines represent the fit of the statistical model of Sabin-2 detection, and the blue shading inside the dashed lines indicates the 95% credible interval. Panel C shows the estimated time for the prevalence of Sabin-2 poliovirus to reach within 0.1% of background levels (solid circles), according to the estimated serotype 2 population immunity (median estimate across the given population). The horizontal dark gray bars represent the interquartile range of serotype 2 population immunity, and the vertical dark gray bars the 50% credible interval for the number of days to reach background levels. The horizontal light gray I bars represent the 95% range of serotype 2 population immunity, and the vertical light gray I bars the 95% credible interval for the number of days to reach background levels. The dark diagonal line represents the linear trend between immunity and time to reach background levels, and the dashed lines the 95% confidence interval of this trend.



time for the prevalence of Sabin-2 poliovirus to reach within 0.1% of background levels after a trivalent OPV campaign. Population immunity was estimated at subnational levels over 6-month periods from the vaccination histories of children with nonpolio acute flaccid paralysis (<36 months of age) and from estimates of OPV efficacy against serotype 2 poliomyelitis, with the use of a spatiotemporal random-effects model as described previously.[26]

We performed univariable and multivariable mixed-effects logistic regression to identify risk factors for a province having one or more cases of circulating VDPV2 after OPV2 withdrawal. The most parsimonious yet adequate model was identified with the use of the "widely applicable information criteria."[27] Full details of the statistical methods and data sources are provided in the Supplementary Appendix.

RESULTS

DECLINE IN THE PREVALENCE OF SABIN-2 POLIOVIRUS BEFORE OPV2 WITHDRAWAL

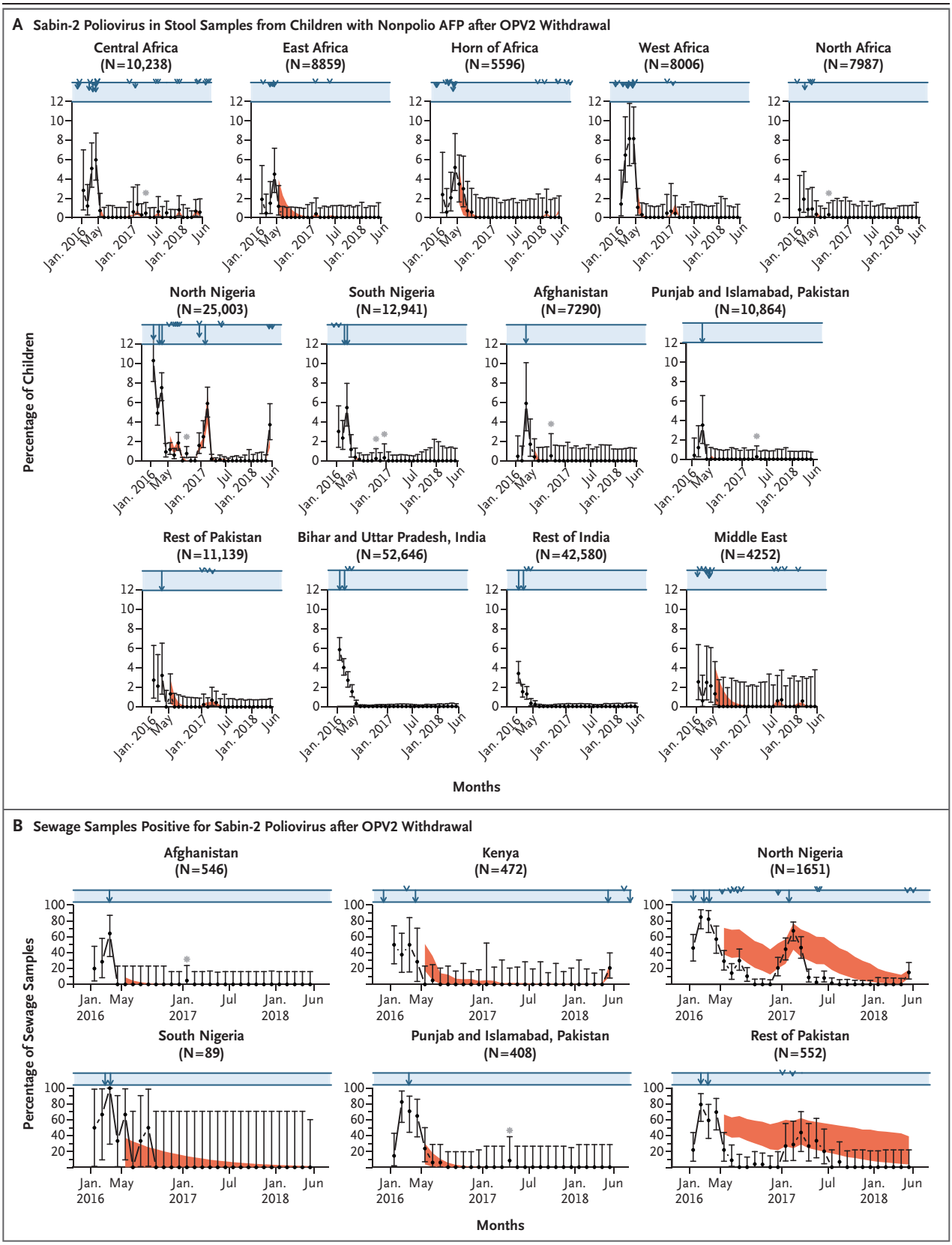
The percentage of persons with nonpolio acute flaccid paralysis who tested positive for Sabin-2 poliovirus in stool samples was highest within the first month after a trivalent OPV campaign and declined rapidly to a lower background level (<3%) within 1 to 2 months after the campaign (Fig. 1A). Background levels varied from 0.3 to 2.2% and were highest in Nigeria. The decline in prevalence was slower in the Horn of Africa, North Nigeria, West Africa, Afghanistan, and Pakistan (outside of Punjab and Islamabad provinces), such that the odds ratios for the detection of Sabin-2 poliovirus 30 days after the last trivalent OPV campaign, as compared with the beginning of the campaign, were significantly larger in these populations than in the other populations we analyzed (Table S2 in the Supplementary Appendix). Low serotype 2 population immunity appeared to be a risk factor for persistent detection; the time for the prevalence of Sabin-2 poliovirus to reach background levels increased with lower population immunity (r^2=0.34, P=0.04) (Fig. 1C). The estimated serotype 2 population immunity increased in the majority of countries until April 2016 — from 81.5% on average in July through December 2015 to 88.4% in January through April 2016 (Fig. S2 in the Supplementary Appendix). The percentage of sewage samples positive for Sabin-2 poliovirus also decreased after trivalent OPV campaigns, albeit at a significantly slower rate and to a higher background level than were observed in stool samples (Fig. 1B, and Table S2 in the Supplementary Appendix).

Figure 2 (facing page). Detection of Sabin-2 Poliovirus over Time after Global OPV2 Withdrawal.

Panel A shows the percentage of children with nonpolio AFP who tested positive for Sabin-2 poliovirus in stool samples, and Panel B the percentage of sewage samples positive for Sabin-2 poliovirus according to country of analysis. The observed prevalence of detection is indicated by solid circles. I bars indicate 95% binomial confidence intervals, and the red shading the 95% model prediction intervals of the change in Sabin-2 detection over time. The prediction interval accounts for the effect of trivalent OPV campaigns before OPV2 withdrawal and the monovalent OPV2 campaigns after withdrawal. The blue arrows within the blue-shaded areas above the graphs indicate when the campaigns occurred. The length of the bars of the arrows is proportional to the fraction of the population (Panel A) or sewage collection sites (Panel B) targeted at each campaign, with an arrow bar that spans the full height of the blue-shaded area indicating that 100% of the population or all districts with sewage collection sites were targeted. The monthly prevalence of Sabin-2 poliovirus that was greater than the prediction interval and considered unexpected are marked by gray asterisks. Data from the sewage collection sites that commenced sampling only after OPV2 withdrawal are not shown (see Fig. S11 in the Supplementary Appendix).

DECLINE IN THE PREVALENCE OF SABIN-2 POLIOVIRUS AFTER OPV2 WITHDRAWAL

The prevalence of Sabin-2 poliovirus in stool samples from children with nonpolio acute flaccid paralysis declined in all countries after OPV2 withdrawal in April 2016 — from 3.9% (95% confidence interval [CI], 3.5 to 4.3) in March to 0.2% (95% CI, 0.1 to 2.7) in June 2016 (P<0.001 by a chi-square test) (Fig. 2). The geographic distribution became more localized over time, and in June 2016, the virus was detected in children with nonpolio acute flaccid paralysis only in Nigeria, West Africa, and the Horn of Africa (Fig. 3) (the detection rates of Sabin-2 poliovirus according to country are shown in Figs. S3 through S6 in the Supplementary Appendix). These declines in the prevalence of poliovirus and the persistence of poliovirus in populations with lower levels of serotype 2 immunity were consistent with the statistical model of Sabin-2 poliovirus detection (Fig. 2). However, there were four



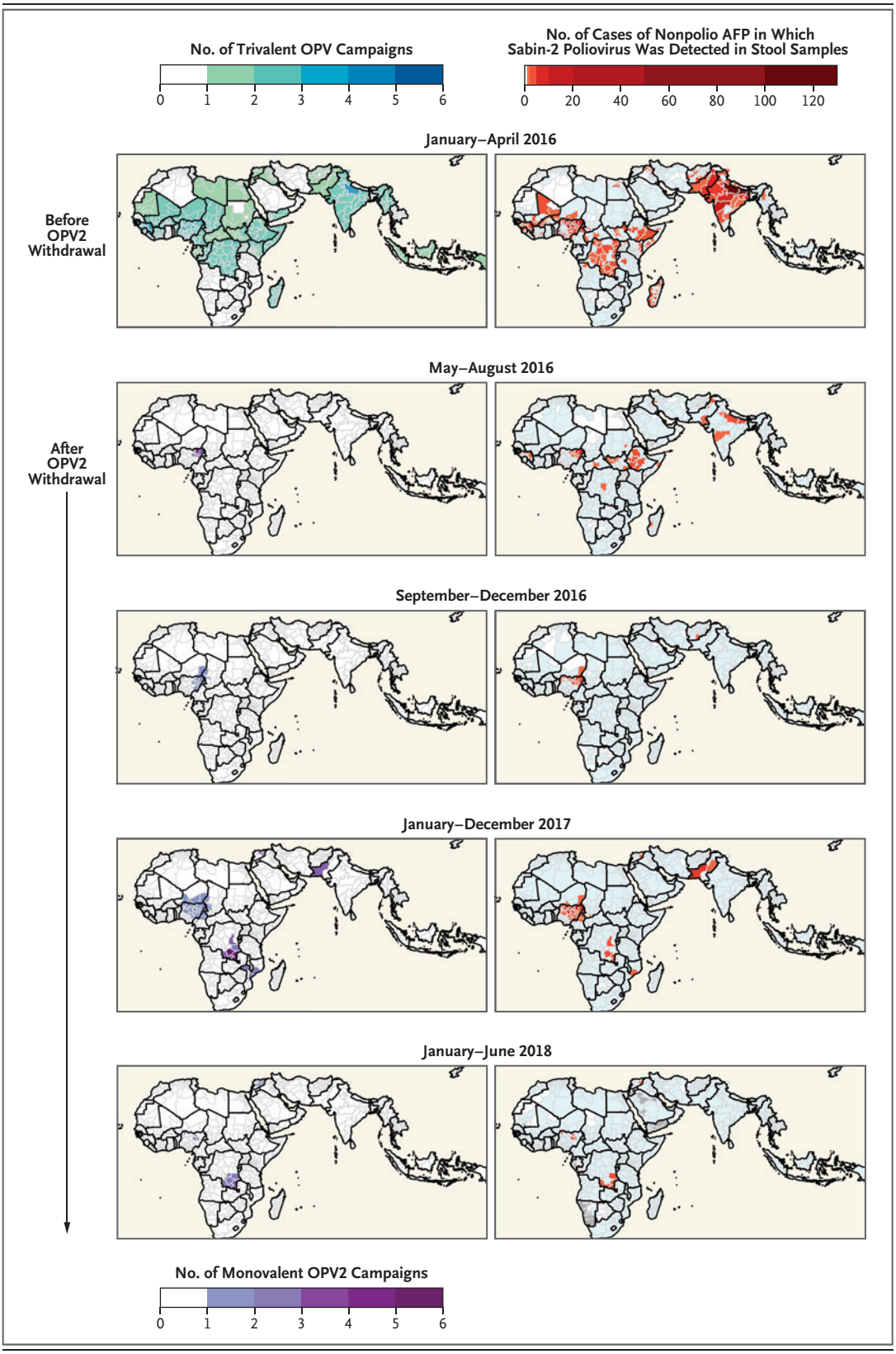


Figure 3 (facing page). Locations of Trivalent OPV or Monovalent OPV2 Campaigns in African, Eastern Mediterranean, and Southeast Asian Regions and the Number of Nonpolio AFP Cases with Sabin-2 Poliovirus Detected in Stool Samples in Those Regions.

Monovalent OPV2 campaigns were conducted after OPV2 withdrawal in response to the detection of circulating or ambiguous serotype 2 vaccine–derived poliovirus (VDPV2, defined as vaccine strains that are at least 0.6% divergent from Sabin-2 poliovirus in the viral protein 1 genomic region; genetically linked isolates consistent with circulation are classified as circulating VDPV2, and VDPV2 without evidence of circulation or VDPV2 isolated from persons with no known immunodeficiency is classified as ambiguous VDPV2). In the maps on the right, the light blue shading indicates that all nonpolio AFP cases in the unit were negative, the gray shading that all stool samples from the unit have not yet been linked to laboratory results, and the white shading that no cases of nonpolio AFP were reported. The publication of this map does not imply the expression of any opinion on the part of World Health Organization (WHO) about the legal status of any territory, city, or area or of its authorities or about the delimitation of its frontiers or boundaries.

cases of detection of Sabin-2 poliovirus in Sudan, South Nigeria, and Afghanistan between August and December 2016 that were not expected from the statistical model of Sabin-2 poliovirus detection (Fig. 2).

From January 2016 through June 2018, the number of sewage samples collected by month increased over time (Fig. S7 in the Supplementary Appendix). The percentage of monthly samples in which Sabin-2 poliovirus was detected in each of the four countries (Afghanistan, Kenya, Nigeria, and Pakistan) was relatively high (≥20%) before the withdrawal of OPV2 and declined after the last trivalent OPV campaign in each country (Fig. 2). The prevalence of Sabin-2 poliovirus in the sewage samples was 71% (95% CI, 61.0 to 80.0) at the time of withdrawal and 13% (95% CI, 8.0 to 20.0) at 2 months after withdrawal. The rate of decline was faster than expected from the statistical model of Sabin-2 poliovirus detection in northern Nigeria and Pakistan (excluding Punjab and Islamabad provinces).

DETECTION OF VDPV2 AFTER OPV2 WITHDRAWAL

From May 1, 2016, to July 11, 2018, a total of 108 cases of circulating VDPV2 poliomyelitis were reported (Fig. 4) and were linked to eight different outbreaks in five countries (Nigeria [two separate outbreaks], Pakistan, Democratic Republic of the Congo [three separate outbreaks[28]], Somalia, and Syria). The majority of cases (74 of the 108 cases) were reported in Syria. One case in Somalia involved coinfection with circulating type 3 VDPV. Circulating VDPV2 was also detected in sewage samples from Nigeria (including an additional outbreak without reported cases in Sokoto state), Pakistan, Somalia, and Kenya; the isolate in Kenya was linked to the outbreak in Somalia. In univariable analyses, low routine immunization coverage, low serotype 2 population immunity, and low population density were within-country risk factors for the detection of circulating VDPV2 cases in a province (Table 1). There was no association between cases of circulating VDPV2 and the number or timing of trivalent OPV campaigns before OPV2 withdrawal. In the final multivariable model, provinces with low routine immunization coverage and low population immunity were more likely to report cases of circulating VDPV2, such that an absolute decrease of 10% in these variables resulted in odds of reporting a case of circulating VDPV2 in a province that were increased by a factor of 1.6 and 2.6, respectively (Table 1).

Ambiguous VDPV2 (i.e., VDPV2 without evidence of circulation or VDPV2 isolated from persons with no known immunodeficiency) was isolated in stool samples from six patients with poliomyelitis. In the countries that we analyzed sewage sample data, ambiguous VDPV2 was isolated in 20 sewage samples obtained after OPV2 withdrawal; 16 of the 20 isolations of ambiguous VDPV2 in the sewage samples occurred within 4 months after monovalent OPV2 campaigns (Fig. S8 in the Supplementary Appendix; and Videos 1 and 2, available at NEJM.org). In addition, the Global Polio Eradication Initiative reported four isolations of ambiguous VDPV2 in sewage samples collected in India from April through June 2016, two isolations in sewage samples collected in India and Australia in 2017, and one isolation in sewage samples collected in Somalia in 2018 (within 4 months after a monovalent OPV2 campaign in Somalia).

Videos showing maps of type 2 poliovirus detection are available at NEJM.org

DETECTION OF SABIN-2 POLIOVIRUS AFTER MONOVALENT OPV2 CAMPAIGNS

Monovalent OPV2 campaigns were implemented in several states in northern Nigeria, in adjacent

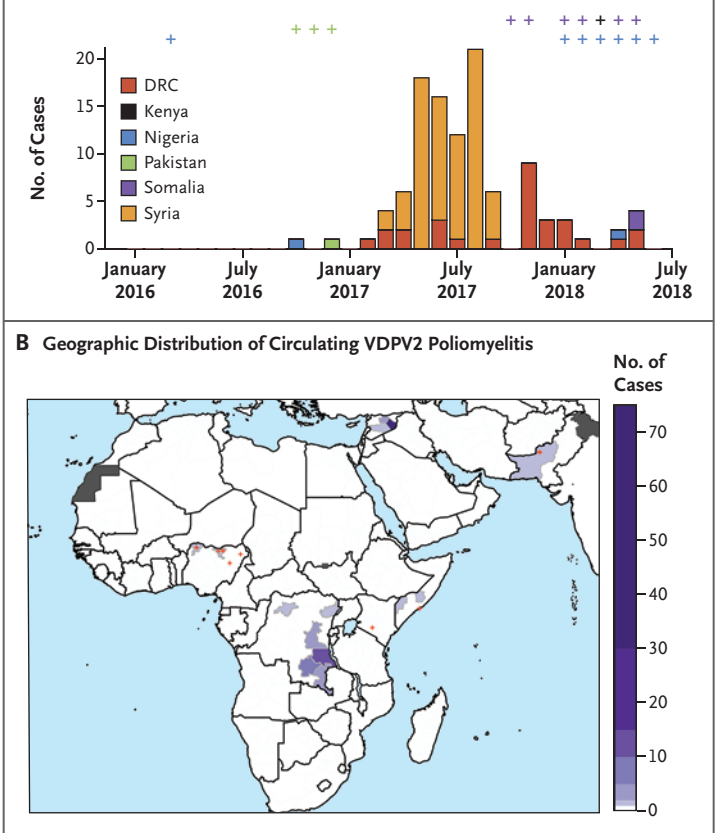


Figure 4. Incidence of Circulating VDPV2 between January 2016 and June 2018 According to Time and Location.

Shown is the incidence of circulating VDPV2 poliomyelitis between January 2016 and June 2018 according to time (Panel A) and location (Panel B). Globally synchronized withdrawal of OPV2 occurred during a 2-week period in April 2016. The plus signs in Panel A (with colors based on country) indicate the detection of circulating VDPV2 in sewage samples by month of collection, and the red plus sign in Panel B indicate the detection of circulating VDPV2 in sewage samples by location. The publication of this map does not imply the expression of any opinion on the part of WHO about the legal status of any territory, city, or area or of its authorities or about the delimitation of its frontiers or boundaries. DRC denotes Democratic Republic of the Congo.

areas of Niger, Chad, and Cameroon, in Balochistan, Pakistan, in multiple provinces of Democratic Republic of the Congo, in several provinces of Syria, and in the Banadir and Shabelle provinces of Somalia, when circulating VDPV2 was detected in stool or sewage samples after OPV2 withdrawal (or shortly before in the state of Borno, Nigeria[31]); in addition, a monovalent OPV2 campaign was implemented in central Mozambique after the detection of ambiguous VDPV2 (Fig. 3). All these campaigns resulted in subsequent detection of Sabin-2 poliovirus in stool samples from children with nonpolio acute flaccid paralysis, which was expected from the statistical model of Sabin-2 poliovirus detection (Figs. 2 and 3, and Videos 1 and 2). The virus was also detected in a cluster of samples collected from northern Nigeria in September 2016 (>1.5 months after a monovalent OPV2 campaign), from southern Chad in April 2017, and from Punjab, Pakistan, in June 2017, which were not expected from the statistical model of Sabin-2 poliovirus detection (Fig. 2). The prevalence of Sabin-2 poliovirus in stool samples was less than 0.1% (95% CI, <0.1 to 0.1) at both 12 and 24 months after OPV2 withdrawal. The virus was detected for a longer time after monovalent OPV2 campaigns in sewage samples than in stool samples from children with nonpolio acute flaccid paralysis (Videos 1 and 2), as predicted by the statistical model of Sabin-2 poliovirus detection (Table S2 in the Supplementary Appendix). The prevalence of Sabin-2 poliovirus in sewage samples was 8.0% (95% CI, 5.0 to 13.0) at 12 months after withdrawal and 0% (95% CI, 0 to 1.7%) at 24 months after withdrawal. In general, the detection of Sabin-2 poliovirus in sewage samples obtained in Nigeria occurred within the outbreak-response zones in which monovalent OPV2 campaigns were performed (Fig. 2 and Video 2), but in Pakistan, the virus was also detected in sewage samples collected from sites outside the outbreak-response zone and across the border in Kandahar, Afghanistan (Fig. 2 and Video 1). Monovalent OPV2 campaigns in response to outbreaks of VDPV2 were conducted in late June and July 2018 in Democratic Republic of the Congo, Somalia, Ethiopia, and Kenya, but as of July 11, 2018, laboratory testing of stool samples from children with nonpolio acute flaccid paralysis had not been completed in these areas. Further monovalent OPV2 campaigns are planned in Nigeria, Democratic Republic of the Congo, Somalia, and Ethiopia.

DISCUSSION

The success of global polio eradication depends not only on the eradication of wild polioviruses but also on the eradication of all live polioviruses, including the live-attenuated oral vaccine strains. Although many wealthier countries have successfully switched from OPV to IPV in their

Table 1. Risk Factors Associated with Report of at Least One Case of Circulating VDPV2 in a Province after OPV2 Withdrawal.*

Variable	Data Source	Odds Ratio for ≥1 Case of Circulating VDPV2 (95% Credible Interval)	
		Univariable	Multivariable
Routine immunization coverage	Estimated from OPV doses received through routine immunization reported in case reports of nonpolio AFP among children from Pakistan and Syria 12 to 23 months of age (Polio Information System) or data from DPT3 immunization campaigns in Nigeria and the Democratic Republic of the Congo[29]	1.53 (1.14–2.16)†	1.64 (1.14–2.54)†
Population level of serotype 2 immunity in the first half of 2016	Estimated from OPV doses reported in case reports of nonpolio AFP among children <36 months of age (Polio Information System)	2.64 (1.39–5.53)‡	2.60 (1.35–5.59)‡
Number of trivalent OPV campaigns during the 6 months before OPV2 withdrawal	Vaccination campaign calendar (Polio Information System)	0.78 (0.39–1.40)§	NA
Days since the last trivalent OPV campaign before April 2016	Vaccination campaign calendar (Polio Information System)	0.96 (0.82–1.12)¶	NA
Population size	Worldpop[30]	0.53 (0.11–2.45)‖	NA
Population density	Worldpop[30] and WHO geodata	0.16 (0.04–0.55)**	NA

* OPV2 was withdrawn between April 17 and May 1, 2016. Data are for all provinces in Nigeria, Pakistan, Syria, and Democratic Republic of the Congo as of August 8, 2017. Results are shown from univariable and multivariable mixed-effects logistic regression. Odds ratios for some variables are not shown (not applicable [NA]), because the variables were not included in the best-fitting multivariable model. DPT3 denotes diphtheria–pertussis–tetanus, OPV oral poliovirus vaccine, OPV2 OPV serotype 2, VDPV2 serotype 2 vaccine–derived poliovirus, and WHO World Health Organization.
† The odds ratio is for a 10% absolute decrease in routine immunization coverage.
‡ The odds ratio is for a 10% absolute decrease in the population level of serotype 2 immunity.
§ The odds ratio is for a unit increase in the number of trivalent OPV campaigns.
¶ The odds ratio is for a unit increase in the number of days between April 1, 2016, and the previous trivalent OPV campaign.
‖ The odds ratio is for a $\log_{10}$ increase in population size.
** The odds ratio is for a $\log_{10}$ increase in population size per square kilometer.

routine immunization schedules,[32,33] the synchronized withdrawal of OPV2 in April 2016 in all countries in which OPV was used was a major test of the feasibility of poliovirus eradication. We show here that serotype 2 vaccine poliovirus disappeared rapidly after OPV2 withdrawal, but in a small number of high-risk locations it has persisted because of the use of monovalent OPV2 in response to VDPV outbreaks or unplanned administration of trivalent OPV from old stocks.[15] We also show that variation in the rate of decline can be explained in part by differences in the level of population immunity, which is likely to affect the duration of shedding of the virus in individual persons and the extent of secondary transmission of vaccine-derived poliovirus.

Outbreaks of circulating VDPV2 were reported in Nigeria, Pakistan, Syria, Somalia, Kenya, and Democratic Republic of the Congo in the 24 months after OPV2 withdrawal. These outbreaks occurred in populations with low coverage of routine immunization and low population immunity against serotype 2 poliomyelitis, an observation that is consistent with the findings from analyses of reports of emergence and spread of VDPV2 in Nigeria.[34] Although these findings highlight the challenges facing the program, the clear association with known risk factors and the absence of more widespread circulating VDPV2 outbreaks offer support for the Global Polio Eradication Initiative strategy of synchronized OPV withdrawal.

The Global Polio Eradication Initiative currently recommends that the response to circulating VDPV2 outbreaks should be at least two high-quality immunization campaigns with monovalent OPV2, given its superior ability to induce mucosal immunity as compared with IPV.[12] There is concern that the use of monovalent OPV2 threatens the eradication of this serotype of poliovirus, given the risk of creating further cases of circulating VDPV2 in populations with limited routine

IPV coverage and growing susceptibility to serotype 2 poliomyelitis.[35] Since the withdrawal of OPV2, multiple monovalent OPV2 campaigns have been implemented in response to circulating VDPV2 outbreaks, and we show that the decline in the prevalence of Sabin-2 poliovirus after these campaigns has been rapid and in line with predictions from estimates made before OPV2 withdrawal. In terms of geographic spread, in Nigeria there were few detections in stool samples or in sewage samples obtained from areas outside the outbreak-response zone after multiple large-scale monovalent OPV2 campaigns in northern states. In contrast, Sabin-2 poliovirus was frequently detected in areas outside the outbreak-response zone in Pakistan, where the monovalent OPV2 campaigns were initially small (600,000 doses of monovalent OPV2 administered across 2700 km^2), as compared with the majority of campaigns in Nigeria (2 million to 50 million doses across 32,000 to 661,000 km^2). This may reflect differences in campaign quality, scale, or population movement (or combinations thereof). Ambiguous VDPV2 have been detected in sewage samples after monovalent OPV2 campaigns in Nigeria, Pakistan, and Somalia. However, the results of genetic sequence analysis suggest that all but two outbreaks (in 2018 in Sokoto, Nigeria) of circulating VDPV2 that we report here represent continued transmission of lineages that emerged before OPV2 withdrawal.[28] Only the 2018 outbreak in Sokoto, Nigeria, has probably emerged from the use of monovalent OPV2 after global OPV2 withdrawal. However, as of July 11, 2018, no cases of poliomyelitis had been reported from this outbreak, and the virus has been detected only in sewage samples. Further investigation is required to establish whether these outbreaks were caused by outbreak response campaigns with monovalent OPV2 or the illicit use of either this vaccine or trivalent OPV.

Our study has several limitations. First, we do not report isolations of Sabin-2 poliovirus from the Americas or the western Pacific region because these data were not available through the Polio Information System. Second, the rate of reporting of acute flaccid paralysis varies across populations, and our findings are more uncertain in areas with few cases of this condition.[36] Environmental surveillance provides important additional data — showing a more sustained detection of Sabin-2 poliovirus, a finding that is consistent with the greater sensitivity of this surveillance method. Expansion of environmental surveillance is an important component of the long-term polio eradication strategy.[22] Finally, we did not consider the association of seasonality with the detection of Sabin-2 poliovirus, which may have affected the accuracy of our projections because of the effects of season on virus survival and transmission.[20]

In summary, high levels of population immunity at the time of OPV2 withdrawal have facilitated the disappearance of Sabin-2 poliovirus and restricted circulating VDPV2 to areas known to be at high risk for transmission. The withdrawal of OPV2 is a test of the Global Polio Eradication Initiative strategy to eradicate all polioviruses, including the live vaccine–derived virus. Our findings provide evidence that supports the planned withdrawal of bivalent OPV after eradication of wild polioviruses is confirmed, provided that a high level of immunity and effective surveillance is maintained in high-risk areas. Nonetheless, in 2017, the number of poliomyelitis cases associated with circulating VDPV2 (96 cases) exceeded those caused by wild poliovirus (22 cases) for the first time, and outbreak-response campaigns with monovalent OPV2 are continuing in several countries. Timely control of these outbreaks in the context of a growing cohort of children who do not have immunity to type 2 poliovirus is critical to the success of polio eradication.

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