Title: Evolving epidemiology of poliovirus serotype 2 following withdrawal of the type 2 oral poliovirus vaccine

Authors:

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Abstract:

While there have been no cases of type-2 wild poliovirus for over 20 years, transmission of type-2 vaccine-derived poliovirus (VDPV2) and associated paralytic cases in several continents represent a threat to eradication. The withdrawal of the type-2 component of oral poliovirus vaccine (OPV2) was implemented in April 2016 to stop VDPV2 emergence and secure eradication of all poliovirus type 2. Globally, children born after this date have limited immunity to prevent transmission. Using a statistical model, we estimate the emergence date and source of VDPV2s detected between May 2016 and November 2019. Outbreak response campaigns with monovalent OPV2 are the only available method to induce immunity to prevent transmission. Yet, our analysis shows that using monovalent OPV2 is generating more paralytic VDPV2 outbreaks with the potential for establishing endemic transmission. The novel OPV2 is urgently required, alongside a contingency strategy if this vaccine does not materialise or perform as anticipated.

One Sentence Summary: Outbreaks of vaccine-derived poliovirus (VDPV) serotype 2 can be traced to use of the oral poliovirus vaccine in outbreak response campaigns.

Main Text:

Ever since the oral poliovirus vaccine (OPV) was first identified in 2000 as the source of a paralytic poliomyelitis outbreak, vaccine-derived polioviruses (VDPV) have been a known obstacle to achieving polio eradication [1, 2]. Despite the global withdrawal of the serotype 2 component of OPV (OPV2), paralytic poliomyelitis cases associated with serotype 2 VDPV (VDPV2) have been reported in expanding global geographies. This is important as there is now a global cohort of children without immunity against serotype 2 that would prevent transmission, which could result in established endemicity of the virus. The inactivated poliovirus vaccine (IPV) can protect against

paralysis but provides limited intestinal immunity to stop transmission [5]. Therefore, the method to control VDPV2 transmission is through vaccination campaigns with the monovalent OPV2 (mOPV2) [3]. However, any use of mOPV2 carries the risk of seeding more VDPV2 [4].

After the eradication of the serotype 2 wild poliovirus (WPV), vaccination continued with OPV2 as part of the trivalent vaccine (tOPV, containing serotypes 1, 2 and 3) (Figure S1), resulting in periodic outbreaks of VDPV2 (as well as VDPV1 and VDPV3) and cases of vaccine-associated paralytic poliomyelitis (VAPP) [5]. This is because the attenuated virus strains contained in OPV can mutate and re-acquire factors associated with causing paralytic disease and transmission [6]. Populations with low immunisation coverage are particularly at risk of spread [6]. Once the eradication of the serotype 2 WPV was certified, it was decided to withdraw the OPV2 to prevent paralysis caused by type 2 poliovirus (Figure S1) [5]. In April 2016, the Global Polio Eradication Initiative (GPEI) coordinated a globally synchronised switch from tOPV to bivalent OPV (bOPV, containing Sabin 1 and 3) in all routine and supplemental immunization activities, commonly referred to as 'the Switch', (Figure S1) [7]. As a risk mitigation strategy, countries began to introduce a dose of inactivated poliovirus vaccine (IPV) into routine immunisation schedules to protect against paralysis from type 2 poliovirus [8]. However, an estimated 143 million children have not received IPV since April 2016 due to supply shortages (43 million) and poor routine immunisation coverage (100 million) [9]

It was predicted that after the Switch, circulation of type 2 polioviruses would steadily disappear. Some VDPV2 outbreaks were expected, largely from prior widespread tOPV use in immunisation campaigns (approximately 1.5 billion doses in the 12 months before the Switch) [10, 11]. The response to any outbreaks was to conduct campaigns with mOPV2, from a finite global stockpile of vaccine [3].While the virus disappeared from most geographies, eradication did not occur [12]. More recently, outbreaks of VDPV2 have been increasing in frequency and geographic spread (Figure 1). At present, WHO classifies circulating VDPV2 (cVDPV2) outbreaks as Public Health Emergencies of International Concern [13] . Here we investigate the epidemiology and source of

VDPV2 outbreaks through a retrospective analysis of poliovirus surveillance and mOPV2 campaign data between 01 May 2016 and 01 November 2019.

We obtained data on virus isolates from acute flaccid paralysis (AFP) cases and environmental samples through the surveillance network of the Global Polio Laboratory Network (GPLN), on 01 November 2019. Between 01 May 2016 and 01 November 2019, the GPLN had detected 859 isolates of VDPV2 and 325 cases of AFP across 26 countries (Figure 1). The AFP cases had a median age of 1.75 years (range 0.2-12 years) and 27.0% of cases reported receiving no previous polio vaccine doses.

We estimate the date of seeding interval (i.e. 95% confidence intervals for the date that the infectious OPV dose was administered) based on the date of detection and the number of nucleotides divergent from the OPV2 virus in the viral protein 1 (VP1) gene (Supplementary Methods). We assume that the first VP1 mutation is instantaneous and each subsequent mutation follows an average rate, previously estimated at 1.14 x 10-2 nucleotides per site per year, which corresponds to 1 nucleotide change observed after approximately 35 days [14]. The time to each independent mutation is modelled using an exponential distribution and the sum of waiting times as an Erlang distribution.

We calculate that 65.5% (548/837) of sequenced VDPV2 viruses detected since April 2016 have a $\geq$ 90% probability of being seeded after the Switch (Figure 2a). For isolates with a $\geq$90% probability of being seeded after the Switch, we identified whether a mOPV2 campaign was conducted within the same geographic region during the estimated seeding interval. We demonstrate that the source of 71.5% (392/548) of these isolates are consistent with mOPV2 outbreak response campaigns conducted within the country of emergence and 24.6% (135/548) consistent with mOPV2 campaigns conducted within a neighbouring country (Figure 2b).

VDPV isolates are classified as circulating VDPV2 (cVDPV2), when there is evidence of person-to-person transmission (isolates are genetically linked to a previously detected isolate) or ambiguous VDPV (aVDPV) events, when there is no evidence of transmission and after ruling out primary immunodeficiency in infected individuals [15, 16].

Since the Switch, we identify 62 aVDPV2 events and 41 independent cVDPV2 outbreaks (Figure 3, Table S1). A total of 126 post-Switch mOPV2 campaigns have been conducted in response to these outbreaks, utilising more than 300 million doses of the mOPV2 vaccine (Table S2), primarily in Nigeria (59%) and DRC (15%). These campaigns are consistent with seeding up to 28 of the 41 cVDPV2 outbreaks (Table S2).

The 41 cVDPV2 outbreaks emerged in Angola (n = 7), Central African Republic (CAR) (n=6), China (n=1), DRC (n = 10), Mozambique (n = 1), Nigeria (n = 9), Pakistan (n=3), Philippines (n=1), Somalia (n = 1), Syrian Arab Republic (Syria) (n = 1) and Zambia (n=1). International spread of cVDPV2s has led to transmission in Benin, Cameroon, Chad, Côte d'Ivoire, Ethiopia, Ghana, Kenya and Togo. The countries where these outbreaks occur are mainly characterized by suboptimal health systems with low routine immunisation coverage, inaccessible/active conflict affected areas and low sanitation and hygiene (Table S1).

In the first year after the Switch (May 2016- April 2017), our analysis shows that there were six cVDPV2 outbreaks, seeded before (n=5) or close to the time of the Switch (n=1), likely through immunisation with tOPV (Figure 3, Table S1). This was consistent with the predictions made, including from mathematical modelling groups [10, 17]. These outbreaks, which occurred in Nigeria (n=2), DRC (n=2), Pakistan (n=1) and Syria (n=1) were rapidly controlled through mOPV2 use (Table S1) mention [18].

Interestingly, we observe that no virus was detected later than 6 months following the Switch in the American, European and South-East Asian Regions of WHO: no cVDPV2 outbreaks occurred and the rare detection of aVDPV2 in the first 6 months in these regions was limited likely because of generally high pre-switch intestinal mucosal immunity, good sanitation standards and post-switch IPV use [12, 19].

In the second year after the Switch (May 2017 to April 2018), 5 more outbreaks emerged (Table S1). We calculate that 1/5 were seeded before and 4/5 were seeded after the Switch (Figure 2). In two of these outbreaks (SOM-BAN-1 and NIE-JIG-1 emergences), failure to control the virus has resulted in spread across national borders to establish transmission in neighbouring countries: from Somalia to Kenya and Ethiopia, and from Nigeria to Niger, Cameroon, Ghana, Benin, Chad, Togo and Côte d'Ivoire (Table S1). These two outbreaks, which have not yet been controlled, are the longest in duration, with transmission detected for periods of 22 and 21 months, respectively (Table S1).

In the third and fourth years after the Switch (May 2018 to November 2019), it was expected (and planned) that there would be a substantial reduction in the number of outbreaks [17]. However, we demonstrate the highest frequency of outbreaks has been in this period: 10 outbreaks emerged between May 2018 and April 2019, and 20 in the period from May 2019 to November 2019 alone. Our analysis shows that all except one of these emergences were seeded after the Switch (Figure 1).

There has been a shift in epidemiology observed over this period, characterised by the emergence of several cVDPV2s in 2019 with low nucleotide divergence in geographies without preceding mOPV2 use (Figure 3). There have been six cVDPV outbreaks in the Central African Republic and seven in Angola (Table S1), which are consistent with seeding from mOPV2 responses in the neighbouring Democratic Republic of Congo. Additionally, two low divergence cVDPV2s have emerged in Pakistan, a country where mOPV2 had not been used in outbreak response for more than one year prior to the estimated seeding date (Table S1). On-going investigations are exploring hypotheses of

outbreak source, including multiple international importations from mOPV2-using areas and inadvertent mOPV2/tOPV use. However, established transmission of cVDPV2 now exists in these populations and as such, the geographic scope of detections is expanding rapidly (Figure 2).

The detection of two highly divergent cVDPV2s in China and the Philippines in 2019 confirms transmission in the Western Pacific Region (Table S1). In the Philippines, a the cVDPV2 was first detected in a AFP case in June 2019, with 64 nucleotides divergence from OPV2, suggesting the virus was seeded in 2014 (Figure 3). Subsequently, an individual with primary immunodeficiency was detected excreting virus genetically linked to the outbreak; however, whether this is the index or a secondary case, is not clear. It seems unlikely that the virus would circulate undetected for 5 years, although serotype 2 is thought to have approximately 2000 infections for every paralytic case, yet these examples emphasise the need for continuing high-quality surveillance and expanding environmental surveillance [20].

Using logistic regression, we demonstrate the probability that a new VDPV2 emergence: a) was seeded after the Switch, is increasing over time (logistic regression coefficient = 1.99, P-Value = <0.001, intercept = -1.66); and b) establishes person-to-person transmission, is increasing over time (logistic regression co-efficient estimate = 0.88, P-Value < 0.001, intercept = -2.27).

At this juncture, we show polio eradication is battling both the new emergences of cVDPV outbreaks seeded after the Switch, largely through outbreak response mOPV2 use, and outbreaks seeded before the Switch that had delayed detection. In 2019, we have observed the largest number of outbreaks and countries experiencing cVDPV2 transmission to date~~.~~. We conclude that the GPEI are in a paradoxical situation: on the one hand, it is not currently possible to control the outbreaks without inducing intestinal mucosal immunity through mOPV2 use, but on the other hand, the use of mOPV2 is generating VDPV2. This risk of VDPV2 circulation is increasing over time, as the immunity of the global population rapidly decreases [4].

Policy perspective

Since the switch over 4 years ago, the epidemiology of type 2 poliovirus has developed in directions that were neither expected or planned, which has policy implications for polio. Although the Switch has largely eliminated the incidence of type 2 vaccine-associated paralytic poliomyelitis (VAPP) and immunodeficiency-related VDPV cases [19], it has not achieved the major objective – that is the eradication of the last type 2 polioviruses (those originating from the oral poliovirus vaccine) in all populations. As discussed in the recent Science editorial, the question that remains as to what the GPEI should do next [20]?

Almost a decade ago, the GPEI initiated in 2010 the development of two candidates of serotype 2 novel oral poliovirus vaccine (nOPV2), which are currently completing Phase II clinical trials [21]. The nOPV2 are designed to provide similar intestinal immunity to the current OPV, while being more genetically stable. Therefore, the major advantage of nOPV2 use in outbreak control would be a lower risk of seeding new VDPV2 (and circulating VDPV outbreaks). In 2020, there are efforts to rapidly accelerate the clinical development of one candidate of this vaccine and pursue World Health Organisation regulatory approval though the Emergency Use Listing procedure [21].

A strategy for the response to cVDPV2s has been developed for 2020–2021 (unpublished). In the time before nOPV2 is available, the approach is to conduct enhanced outbreak response campaigns with the current OPV2 to contain cVDPV2 spread. Capacity to conduct aggressive, rapid and high-quality campaigns is essential, as persistent delays and pockets of low coverage will continually hinder the impact of outbreak responses with any vaccine, be it the nOPV2 or mOPV2.

Strengthening routine administration of IPV and strategic vaccination with remaining available IPV doses (to ensure missed children in areas at high risk are reached) will be employed as a paralysis prevention method.

When the nOPV2 vaccine becomes available in sufficient quantities, it will be rolled out to eventually replace mOPV2 in outbreak response. In the situation that nOPV2 does not materialize or perform as anticipated, or incurs substantial delays, the GPEI would have to implement a contingency plan (under preparation). The re-introduction of preventative vaccination with mOPV2 or tOPV, either through preventative campaigns or routine immunisation, would have to be considered. However, this approach would require quantities of mOPV2 or tOPV doses that are currently not available.

It is critical that cVDPV outbreaks be managed as national public health emergencies in line with the declaration of a Public Health Emergencies of International Concern by the WHO [13]. All GPEI partners, member state governments and agencies must fully operationalize their emergency frameworks to prevent the re-establishment of endemic transmission of type 2 poliovirus in the form of cVDPV2. It remains clear that OPV removal is essential to stop all cases of paralytic poliomyelitis. However, the epidemiology that has evolved since OPV2 removal has implications on existing strategies outlined for total OPV cessation, which need urgent attention [22].

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Competing Interests

Authors declare no competing interests.

Data and materials availability

Data used in this study is property of the individual countries and is available on the Polio Information System (PolIS). URL: https://extranet.who.int/polis/. Data access was provided through the Global Polio Eradication Initiative Data Sharing Agreement.

Disclaimer

The results and conclusions in this article are those of the authors and do not necessarily represent the official position or policies of the U.S. Centers for Disease Control and Prevention

List of Supplementary Materials:

Materials and Methods

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Figure S1

Figure S2

Fig. 1. Geographic location of vaccine-derived poliovirus type 2 isolates detected after the removal of type 2 oral poliovirus vaccine (OPV2), between 01 May 2016 and 01 November 2019. Data as of 01 November 2019. The colour of points illustrates the date of isolate detection.

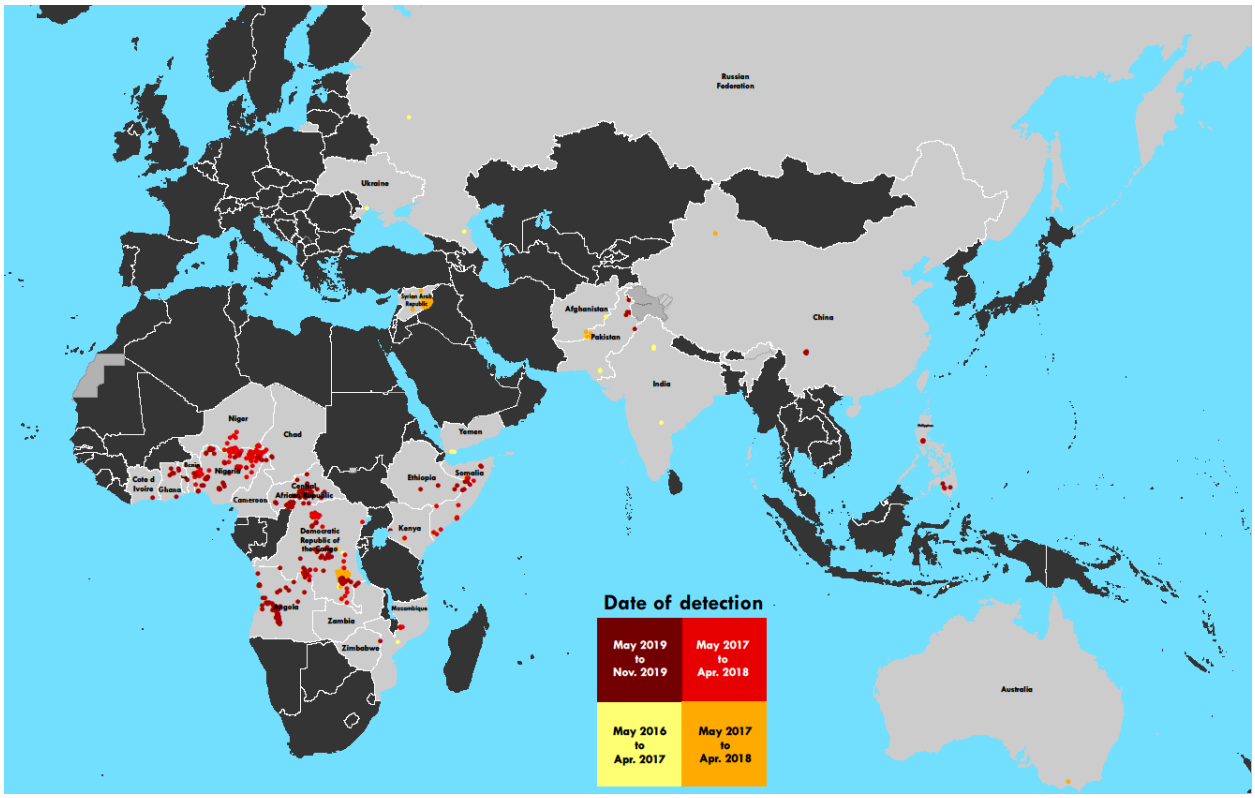
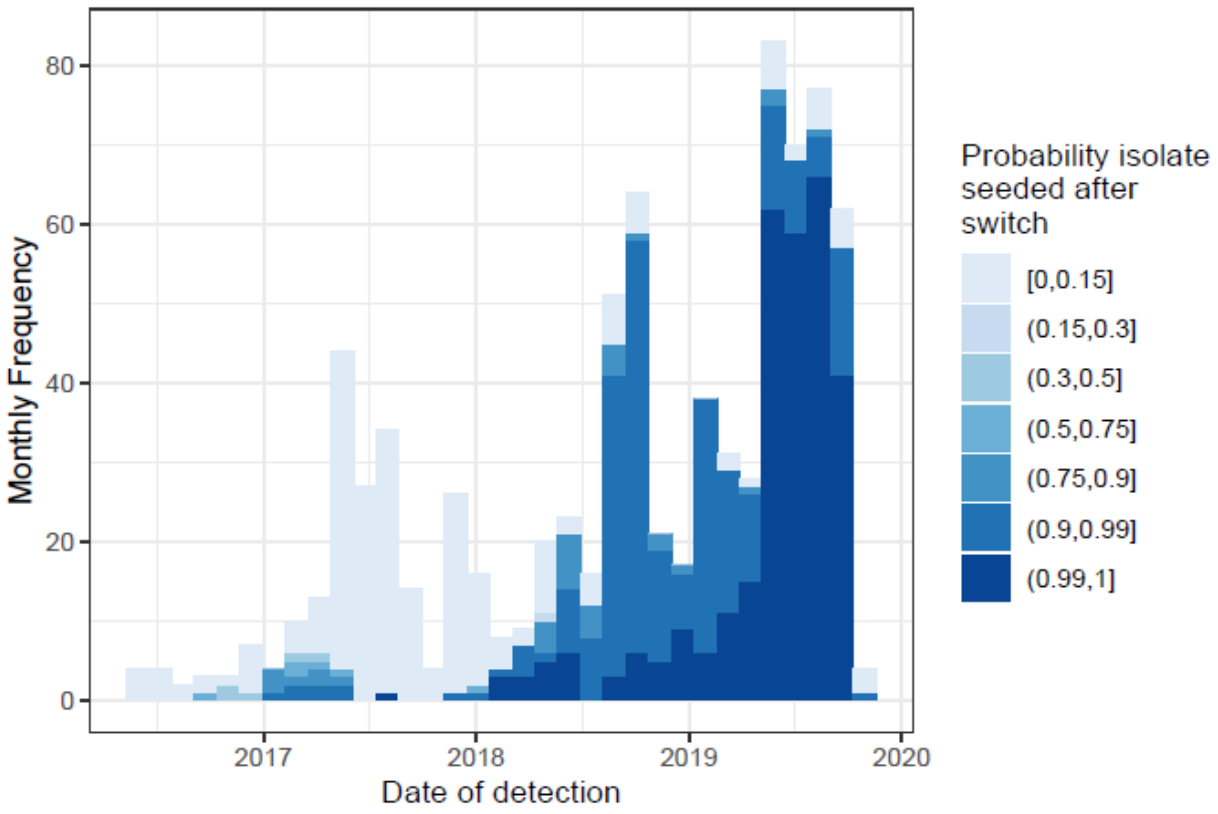


Fig.2. Incidence of detected global vaccine-derived poliovirus type 2 isolates between 01 May 2016 and 01 November 2019. In Figure A, the probability that isolate was seeded after the Switch (01 May 2016) was calculated based on the 95% CI of the estimated seeding date, estimated by the number of nucleotides divergence from the poliovirus vaccine strain, in the viral protein 1 gene of the position, assuming a model for the mutation rate (See Supplementary Material for Methods). In Figure B. for all isolates with >0.9 probability of post-switch seeding, the colour demonstrates whether there was a corresponding mOPV2 campaign within estimated dates of seeding and the same or adjacent country.


Monthly Frequency
0
20
40
60
80
2017
2018
2019
2020
Date of detection
Probability isolate seeded after switch
[0,0.15]
(0.15,0.3]
(0.3,0.5]
(0.5,0.75]
(0.75,0.9]
(0.9,0.99]
(0.99,1]

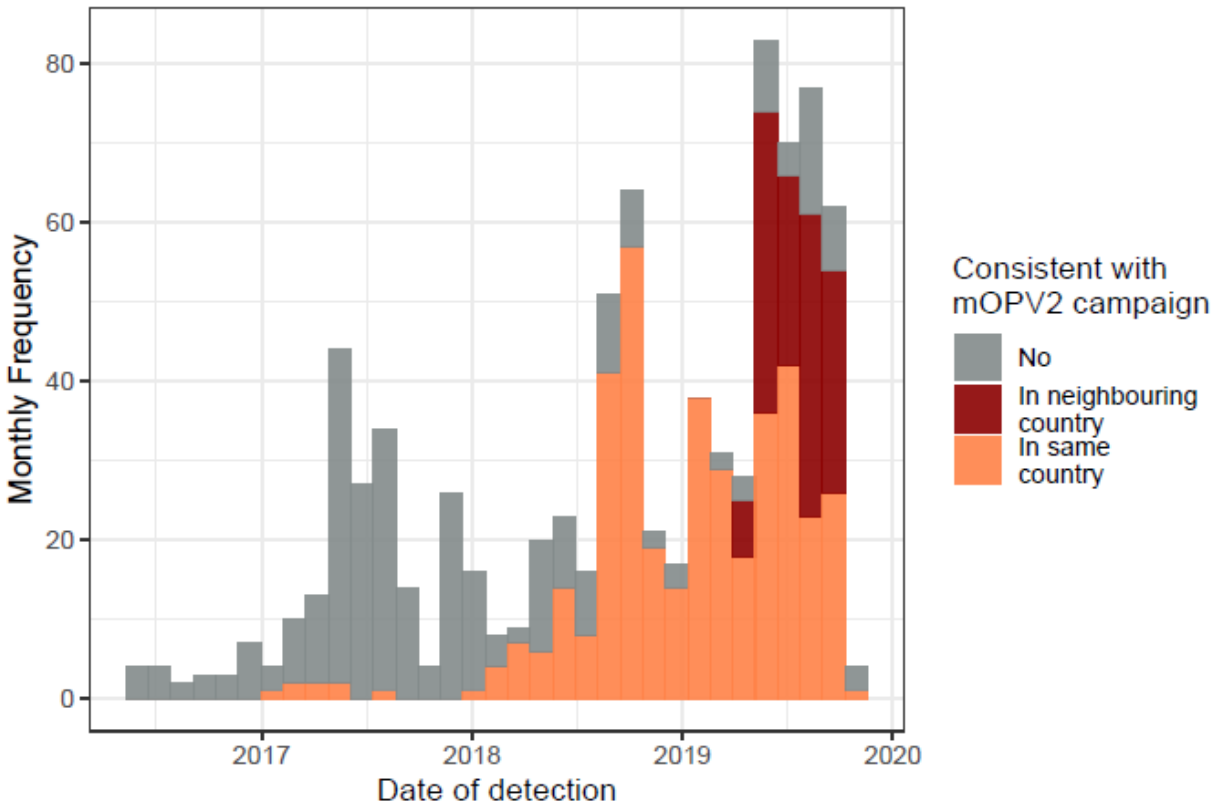
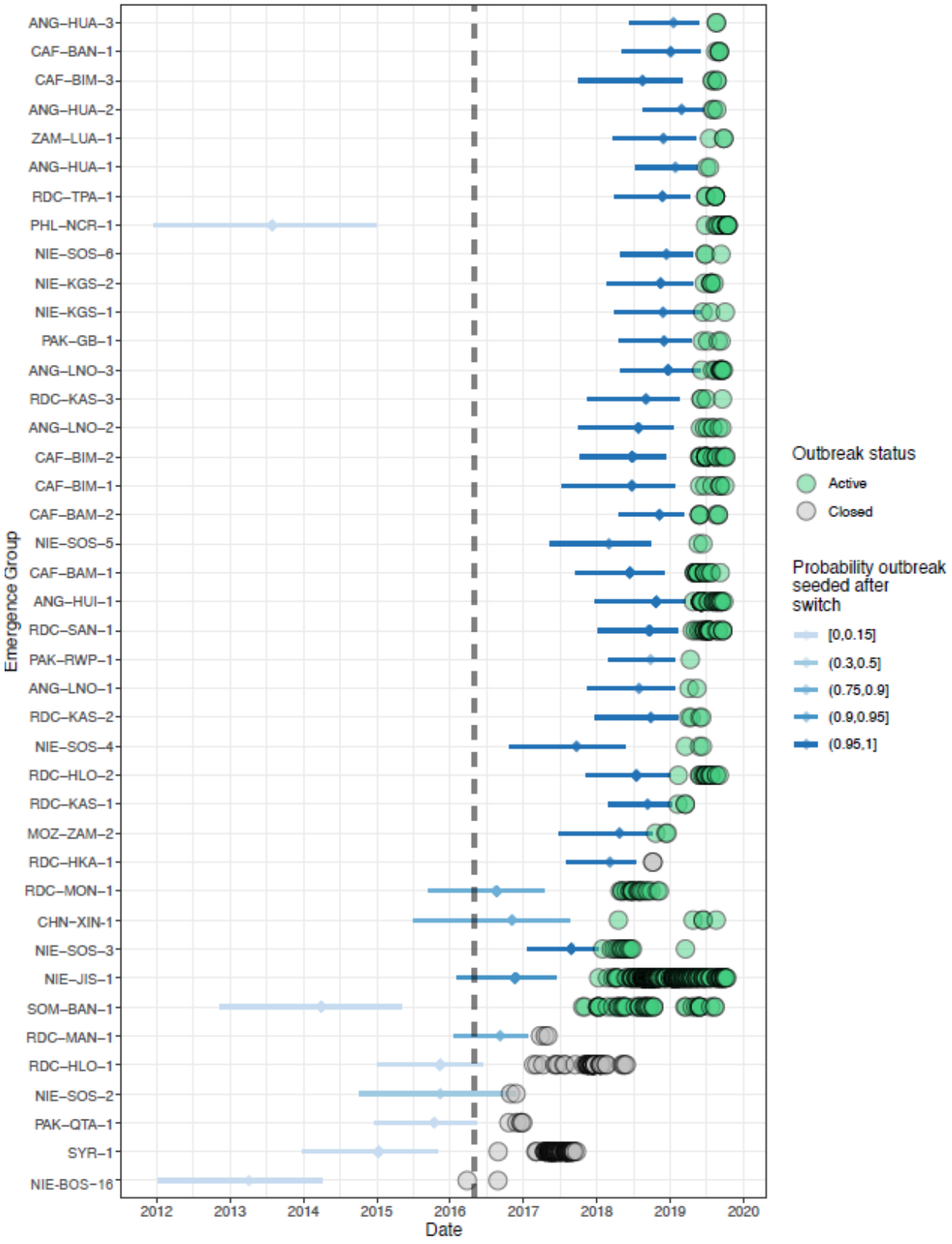

Monthly Frequency
0
20
40
60
80
2017
2018
2019
2020
Date of detection
Consistent with mOPV2 campaign
No
In neighbouring country
In same country

Fig. 3. Timeline of cVDPV2 outbreaks reported between 01 May 2016 and 01 November 2019, ordered by the date of first isolate detection. The estimated seeding date (i.e. the date that infectious OPV dose was administered) and 95% confidence intervals are given by horizontal bars, coloured by the probability that date of seeding was after the removal of tOPV on the 01 May 2016 (date of switch illustrated by a dashed black line). Detected virus isolates shown by coloured circles, with the colour indicating whether the outbreak is assumed active (detection within previous 12 months) or closed (no detection in previous 12 months). All as of 01 November 2019.

NIE-BOS-16: This outbreak was genetically linked to a cVDPV2 emergence originating in Chad in 2012.


ANG–HUA–3
CAF–BAN–1
CAF–BIM–3
ANG–HUA–2
ZAM–LUA–1
ANG–HUA–1
RDC–TPA–1
PHL–NCR–1
NIE–SOS–6
NIE–KGS–2
NIE–KGS–1
PAK–GB–1
ANG–LNO–3
RDC–KAS–3
ANG–LNO–2
CAF–BIM–2
CAF–BIM–1
CAF–BAM–2
NIE–SOS–5
CAF–BAM–1
ANG–HUI–1
RDC–SAN–1
PAK–RWP–1
ANG–LNO–1
RDC–KAS–2
NIE–SOS–4
RDC–HLO–2
RDC–KAS–1
MOZ–ZAM–2
RDC–HKA–1
RDC–MON–1
CHN–XIN–1
NIE–SOS–3
NIE–JIS–1
SOM–BAN–1
RDC–MAN–1
RDC–HLO–1
NIE–SOS–2
PAK–QTA–1
SYR–1
NIE-BOS-16
Emergence Group
2012
2013
2014
2015
2016
2017
2018
2019
2020
Date
Outbreak status
Active
Closed
Probability outbreak seeded after switch
[0,0.15]
(0.3,0.5]
(0.75,0.9]
(0.9,0.95]
(0.95,1]

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Supplementary Materials for

Evolving epidemiology of poliovirus serotype 2 following withdrawal of the type 2 oral poliovirus vaccine

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This PDF file includes:

Materials and Methods

Materials

The primary surveillance sources of the GPEI are cases of acute flaccid paralysis (AFP) among children aged <15 years. As part of the case investigation detailed case histories and stool samples are collected to determine poliovirus infection. Environmental surveillance has been established within more than 30 countries where wastewater samples are collected and tested for polioviruses. Additional surveillance includes outbreak response contact sampling and community sampling [3, 16]. All collected samples are tested in Global Polio Laboratory Network (GPLN) laboratories per WHO protocols with virus isolation, intratypic differentiation (ITD) and genomic sequencing, to identify WPV, Sabin-like (derived from oral poliovirus vaccine) poliovirus, and vaccine-derived polioviruses (VDPV) [23, 24]. Poliovirus isolates are classified by comparing the nucleotide sequence of the coding region of the viral capsid protein 1 (VP1) with the corresponding vaccine strain: for serotype 2, Sabin-like virus are $\geq$ 0 and < 6 nucleotides divergent and VDPV2s are $\geq$ 6 nucleotides divergent from the 903 nucleotide VP1 [23].[23]. VDPVs are further classified as 1) cVDPV, when evidence of person-to-person transmission in the community exists; 2) immunodeficiency-related VDPV (iVDPV), when they are isolated from persons with primary immunodeficiencies; and 3) ambiguous VDPV (aVDPV), when they are clinical isolates from persons with no known immunodeficiency and no evidence of transmission, or they are sewage isolates that are unrelated to other known VDPVs and whose source is unknown [6, 15]. cVDPV2 outbreaks are coded and tracked by a designation of the country, the state or province, and a sequential count of the emergence from that geography (e.g. the third cVDPV2 outbreak occurring in Sokoto State of Nigeria is coded NIE-SOS-3). The iVDPV cases are excluded from this analysis.

All mOPV2 supplemental immunisation activities conducted between 01 May 2016 and 01 August 2019 were exported from Polio Information System (polIS) database. The exported data included the start and end date of campaign activity, administrative area (Admin 0, Admin 1 and Admin

2 levels) and the number of doses distributed. Geographical information system data for boundaries of administrative areas (Admin levels 0, 1 and 2) were obtained from the World Health Organization. The Admin 0 level is referred to as country. All Sabin-like and VDPV2 poliovirus isolates with date of sample collection between 01 May 2016 and 01 November 2019 were exported from the polIS line list. Extracted data for each isolate included the date of detection (or sample collection), virus classification, surveillance method, and VP1 nucleotide divergence from the Sabin 2 vaccine. The Admin 1 level routine immunisation coverage estimates for all African countries were taken as the estimated coverage of three doses of Diphtheria-tetanus-pertussis (DTP3) in 2016, from Mosser et al [25]. For countries outside the African continent, routine immunisation coverage was defined as the proportion of non-polio AFP cases in the given Admin 1 region who reported receiving 3 OPV doses through routine immunisation aged between 12-24 months from 2016 to 2019, as used previously [12].

All data was exported as of 01 November 2019.

Methods

For all VDPV2 isolates and outbreaks we estimate the seeding date and likely source from which the virus was seeded after the withdrawal of OPV2 using the following methods. We define the date of seeding of VDPV2 as the date that the infectious OPV2 dose was administered which subsequently evolved into VDPV2. First, the date of seeding for each isolate was estimated with 95% confidence intervals (CI) by back-calculating from the date of detection (either AFP case or ENV sample) based on the number of nucleotide differences in the VP1 sequence from the Sabin 2 strain. We assumed that the first VP1 mutation is instantaneous and each subsequent mutation follows an average rate, previously estimated at 1.14×10^{-2} nucleotides per site per year, which corresponds to 1 nucleotide change observed after approximately 35 days [14]. The waiting time to each independent mutation is modelled using an exponential distribution that assumes a constant evolution rate, and the Erlang distribution is the sum of the waiting times. The Erlang distribution had a shape parameter equal to n-1, where n is the number of

418 VP1 nucleotide changes of the isolate, and a scale parameter equal to the product of the number of VP1
419 nucleotides (901) and the average mutation rate (1.14×10^{-2} nucleotides per site per year). For isolates
420 that were part of an emergence group that had > 1 isolate, we estimate the date of seeding for that
421 emergence group by combining data from multiple isolates and then assigning this date of seeding to all
422 isolates in the group. We selected the earliest three detected isolates of an outbreak and resampled each
423 of their estimated dates of seeding 1000 times to produce a combined distribution with a median date
424 and 95% CI. The analysis was restricted to the nucleotide differences of the first three isolates as using
425 all isolates would have to account for the specific location of nucleotide mutations between isolates,
426 which were not available for analysis. For sensitivity analysis, we repeated the procedure by selecting
427 between one and up to ten of the earliest detected isolates, which did not result in any significant
428 changes (Supplementary Figure 2). The limitations of this analysis are discussed below.
429 The probability that VDPV isolates were seeded after the switch (taken as 01 May 2016) was
430 calculated using the cumulative probability of the empirical distribution of the estimated seeding date
431 and determining what proportion of this distribution is greater than 01 May 2016. For VDPV isolates
432 with a probability of seeding after the switch above 0.9, the database of mOPV2 campaigns was
433 searched to identify mOPV2 campaigns occurring within the time-frame of the estimated date of seeding
434 (95% CI), within the same state/province (Admin 1 level), country (Admin 0 level) or a neighbouring
435 country. If more than one mOPV2 campaign was within the estimated date of seeding interval, the
436 campaign closest in time (to the median estimated seeding date) was chosen in the nearest geographic
437 area (i.e. 1st - Campaigns in the same Admin 1 level, 2nd - Campaigns from the same Admin 0 level, and
438 3rd - Campaigns from neighbouring countries).
439 Generalized linear models (GLMs) were used to quantify the patterns of VDPV emergences over
440 time. For the GLMs, we computed univariate logistic regression (family = binomial, link = logit) on the
441 index isolate of each genetic VDPV emergence. The predictor variable was the time in years between
442 the Switch (taken as 01 May 2016) and date of detection. The binary response variables were: estimated

seeding date is post-switch (yes or no); and emergence evolved into a cVDPV2 outbreak (yes or no). For all GLMs we report co-efficient estimates and accompanying P-value.

The limitations of our analysis include the absence of genetic sequencing data from VDPV isolates to inform the estimated date of sequencing. The genetic information available for each isolate was the genetic cluster (emergence group) the virus was associated with and the number of nucleotides divergent from Sabin 2 in the VP1 gene. The ability to construct a phylogenetic tree using genetic sequences would provide more accurate inference. In this analysis, we have not considered the time between the most recent mutation and time of detection, as this short time is not programmatically significant compared to the uncertainty in the time of seeding (range of 304-1100 days) captured by the 95% confidence intervals.

Table S1.

Outbreak Code	Country	Date detected	Date of most recent isolate	Number of impacted states (country: states)	Assumed status[1]	Observed duration, months	RI coverage[2], mean estimate (95% CI)	Isolates (n)	AFP cases (n)	Mean case age, months (n)	VP1 nucleotide divergence (range)[3]
NIE-BOS-16	Nigeria	26-Mar-16	26-Aug-16	1 (Nigeria: Borno)	Closed	5	0.29 (0.1, 0.47)	2	0	NaN (0)	37,37
SYR-1	Syrian Arab Republic	27-Aug-16	21-Sep-17	3 (Syrian Arab Republic: Deir Al Zour, Raqua, Homs)	Closed	13	(0.14, 0.5)	117	74	18.6 (74)	22,34
PAK-QTA-1	Pakistan	20-Oct-16	28-Dec-16	1 (Pakistan: Balochistan)	Closed	2	(0.19, 0.39)	5	1	16 (1)	10,18
NIE-SOS-2	Nigeria	28-Oct-16	02-Mar-17	1 (Nigeria: Sokoto)	Closed	4	0.04 (0, 0.08)	3	1	30 (1)	7,17
RDC-HLO-1	Democratic Republic of the Congo	20-Feb-17	27-May-18	4 (Democratic Republic of the Congo: Haut Lomami, Tanganika, Haut Katanga, Ituri)	Closed	15	0.62 (0.5, 0.74)	50	27	25.5 (27)	14,29

RDC-MAN-1	Democratic Republic of the Congo	26-Mar-17	02-May-17	1 (Democratic Republic of the Congo: Maniema)	Closed	1	0.51 (0.3, 0.7)	3	2	30 (2)	7,9
SOM-BAN-1	Somalia	22-Oct-17	13-Aug-19	9 (Somalia: Banadir Irobi, Hiran, Gedo, Lower Juba, Sool)	Ongoing	22	0.58 (0.2, 0.88)	44	12	40.6 (10)	37,55
NIE-JIS-1	Nigeria	10-Jan-18	10-Oct-19	24 (Nigeria: Jigawa, Gombe, Yobe, Borno, Katsina, Zinder)	Ongoing	21	0.09 (0, 0.17)	239	65	30.5 (62)	13,35
NIE-SOS-3	Nigeria	30-Jan-18	18-Mar-19	2 (Nigeria: Sokoto, Niger)	Ongoing	14	0.04 (0, 0.08)	15	1	19 (1)	6,14
CHN-XIN-1	China	18-Apr-18	18-Aug-19	2 (China: Xinjiang, Sichuan)	Ongoing	16	1 (0.15, 1.0)[5]	5	1	53 (1)	13,33
RDC-MON-1	Democratic Republic of the Congo	26-Apr-18	08-Nov-18	1 (Democratic Republic of the Congo: Mongala)	Ongoing	6	0.45 (0.3, 0.59)	21	11	14.1 (11)	18,26
RDC-HKA-1	Democratic Republic of the Congo	06-Oct-18	07-Oct-18	1 (Democratic Republic of the	Closed	0	0.73 (0.6, 0.82)	2	2	80.5 (2)	7,8

				Congo: Haut Katanga)							
MOZ-ZAM-2	Mozambique	21-Oct-18	17-Dec-18	1 (Mozambique: Zambezia)	Ongoing	2	0.91 (0.8, 0.97)	3	1	75 (1)	6,10
RDC-KAS-1	Democratic Republic of the Congo	08-Feb-19	17-Mar-19	1 (Democratic Republic of the Congo: Kasai)	Ongoing	1	0.68 (0.5, 0.81)	3	1	24 (1)	6,7
RDC-HLO-2	Democratic Republic of the Congo	10-Feb-19	02-Sep-19	2 (Democratic Republic of the Congo: Haut Lomami, Haut Katanga)	Ongoing	7	0.62 (0.5, 0.74)	16	11	16.5 (11)	8,12
NIE-SOS-4	Nigeria	18-Mar-19	10-Jun-19	1 (Nigeria: Sokoto)	Ongoing	3	0.04 (0, 0.08)	3	0	NaN (0)	16,20
RDC-KAS-2	Democratic Republic of the Congo	03-Apr-19	07-Jun-19	1 (Democratic Republic of the Congo: Kasai)	Ongoing	2	0.68 (0.5, 0.81)	4	4	35 (4)	6,11
ANG-LNO-1	Angola	05-Apr-19	14-May-19	1 (Angola: Lunda Norte)	Ongoing	1	0.22 (0.1, 0.35)	2	1	16 (1)	8,10
PAK-RWP-1	Pakistan	11-Apr-19	11-Apr-19	1 (Pakistan: Punjab)	Ongoing	0	0.85 (0.82, 0.88)	1	0	NaN (0)	7,7

RDC-SAN-1	Democratic Republic of the Congo	21-Apr-19	20-Sep-19	2 (Democratic Republic of the Congo: Sankuru, Kasai Oriental)	Ongoing	5	0.46 (0.3, 0.61)	23	19	21.5 (15)	6,16
ANG-HUI-1	Angola	27-Apr-19	25-Sep-19	5 (Angola: Huila, Cuanza Sul, Kwanza Sul, Huambo)	Ongoing	5	0.33 (0.21, 0.48)	29	15	35 (1)	6,13
CAF-BAM-1	Central African Republic	01-May-19	07-Sep-19	3 (Central African Republic: RS1, RS4, RS7)	Ongoing	4	0.36 (0.1, 0.63)	17	4	33.7 (3)	10,17
NIE-SOS-5	Nigeria	20-May-19	13-Jun-19	1 (Nigeria: Sokoto)	Ongoing	1	0.04 (0, 0.08)	2	1	48 (1)	14,15
CAF-BAM-2	Central African Republic	27-May-19	29-Aug-19	2 (Central African Republic: RS4, RS5)	Ongoing	3	0.44 (0.2, 0.73)	6	1	30 (1)	7,12
CAF-BIM-1	Central African Republic	28-May-19	30-Sep-19	3 (Central African Republic: RS1, RS4, RS7)	Ongoing	4	0.36 (0.1, 0.63)	7	4	33 (1)	6,16

CAF-BIM-2	Central African Republic	28-May-19	05-Oct-19	3 (Central African Republic: RS1, RS7, RS6)	Ongoing	4	0.36 (0.1, 0.63)	21	2	NaN (0)	7,18
ANG-LNO-2	Angola	01-Jun-19	15-Sep-19	5 (Angola: Lunda Norte, Lunda Sul, Malanje, Kwanza Sul, Moxico)	Ongoing	3	0.22 (0.1, 0.35)	7	6	15 (2)	9,15
RDC-KAS-3	Democratic Republic of the Congo	03-Jun-19	18-Sep-19	2 (Democratic Republic of the Congo: Kasai, Kwilu)	Ongoing	4	0.68 (0.5, 0.81)	4	4	22.7 (3)	8,16
ANG-LNO-3	Angola	07-Jun-19	23-Sep-19	3 (Angola: Lunda Norte, Uíge, Luanda)	Ongoing	4	0.22 (0.1, 0.35)	11	8	NaN (0)	6,11
PAK-GB-1	Pakistan	10-Jun-19	11-Sep-19	3 (Pakistan: Punjab, Gilgit Baltistan, Islamabad)	Ongoing	3	0.85 (0.82, 0.88)	6	3	NaN (0)	7,11
NIE-KGS-1	Nigeria	13-Jun-19	02-Oct-19	1 (Nigeria: Kogi)	Ongoing	4	0.46 (0.3, 0.62)	3	2	29 (1)	8,9
NIE-KGS-2	Nigeria	20-Jun-19	08-Aug-19	1 (Nigeria: Kogi)	Ongoing	2	0.46 (0.3, 0.62)	6	2	34.5 (2)	7,10
NIE-SOS-6	Nigeria	24-Jun-19	11-Sep-19	1 (Nigeria: Sokoto)	Ongoing	3	0.04 (0, 0.08)	3	0	NaN (0)	6,10

PHL-NCR-1	Philippines	26-Jun-19	15-Oct-19	3 (Philippines: Armm, Ncr, Southern Mindanao)	Ongoing	4	0.32 (0.16, 0.52)	12	3	NaN (0)	63,71
RDC-TPA-1	Democratic Republic of the Congo	27-Jun-19	14-Aug-19	1 (Democratic Republic of the Congo: Tshuapa)	Ongoing	2	0.41 (0.3, 0.55)	6	0	NaN (0)	7,11
ANG-HUA-1	Angola	02-Jul-19	16-Jul-19	1 (Angola: Huambo)	Ongoing	0	0.45 (0.3, 0.58)	2	2	NaN (0)	6,6
ZAM-LUA-1	Zambia	16-Jul-19	25-Sep-19	1 (Zambia: Luapula)	Ongoing	2	0.84 (0.7, 0.93)	3	1	NaN (0)	9,10
ANG-HUA-2	Angola	30-Jul-19	21-Aug-19	1 (Angola: Huambo)	Ongoing	1	0.45 (0.3, 0.58)	3	2	NaN (0)	6,6
CAF-BIM-3	Central African Republic	30-Jul-19	22-Aug-19	1 (Central African Republic: RS1)	Ongoing	1	0.36 (0.1, 0.63)	4	2	30 (2)	9,15
CAF-BAN-1	Central African Republic	16-Aug-19	03-Sep-19	2 (Central African Republic: RS7, RS2)	Ongoing	1	0.45 (0.2, 0.73)	4	1	NaN (0)	7,9
ANG-HUA-3	Angola	19-Aug-19	19-Aug-19	2 (Angola: Benguela, Huambo)	Ongoing	0	0.31 (0.2, 0.45)	2	2	NaN (0)	7,8

Summary and demography of classified circulating vaccine-derived poliovirus (cVDPV) outbreaks detected between May 2016 and 01 November 2019, data as of 01 November 2019.

[1]Status is dependent on whether there has been detection of the cVDPV virus in the past 12 months, as of 01 November 2019.

[2]Routine immunisation coverage estimate from the Admin 1 area in which emergence was first detected; see supplementary methods.

[3]Number of nucleotides differences in the viral protein 1 gene (VP1) of the detected poliovirus compared to the Sabin 2 virus in oral poliovirus vaccine.

[4]This outbreak was identified to be genetically linked to a cVDPV2 emergence originating in Chad in 2012.

[5]Routine immunisation coverage estimate provided as a country estimate for China.

Abbreviation: AFP, Acute Flaccid Paralysis; RI, Routine Immunisation; VP1, Viral Protein 1.

Table S2.

Country	Number of outbreaks detected since 01 May 2016	Number of rounds	Total mOPV doses (million)	Doses per round (million), median (range)	Number aVDPV events consistent with time of mOPV2 campaign[1]			Number cVDPV outbreaks consistent with time of mOPV2 campaign[1]		
					In the OBRA	In the country	Neighbouring country	In the OBRA	In the country	Outside country
Angola	7	8	4.1	0.35 (0.1-1.18)	0	0	0	0	0	0
Benin	1	1	0.3	0.3 (0.3-0.3)	0	0	0	0	0	0
Cameroon	1	5	4.3	0.24 (0.02-3.68)	0	0	0	0	0	0
Central African Republic	6	2	0.9	0.45 (0.07-0.83)	0	0	0	0	0	0
Chad	1	4	2.3	0.2 (0.19-1.75)	0	0	0	0	0	0
Democratic Republic of the Congo	10	25	35.3	0.72 (0-7.92)	0	1	0	2	5	13[2]
Ethiopia	1	5	2.4	0.52 (0.19-0.59)	0	0	0	0	0	0
Ghana	1	2	2.1	1.05 (0.18-1.92)	0	0	0	0	0	0
Kenya	1	3	6.1	2.42 (0.82-2.88)	1	0	0	0	0	0
Mozambique	1	6	5.3	0.65 (0.5-1.48)	0	0	0	0[3]	0	0

Niger	1	9	17.2	2.52 (0.15-4.63)	0	0	0	0	0	0
Nigeria	9	37	170.6	1.96 (0-38.3)	26	6	0	5	2	0
Pakistan	3	3	3	0.79 (0.51-1.66)	3	0	0	0	0	0
Somalia	1	11	7.6	0.73 (0.05-1.6)	3	0	0	0	0	0
Syrian Arab Republic	1	4	1.6	0.45 (0.15-0.59)	0	0	0	0	0	0
Togo	1	1	0.1	0.14 (0.14-0.14)	0	0	0	0	0	0

Outbreak response to circulating vaccine-derived poliovirus serotype 2 (cVDPV2) outbreaks and subsequent isolation of type 2 poliovirus by country, between 01 May 2016 and 01 November 2019.

[1]We define a VDPV consistent with time of mOPV2 campaigns as a VDPV where the estimated date of seeding 95% confidence interval spans an mOPV2 campaign in a similar geographic region. The geographic region is classified as within outbreak response area (OBRA), within the country (but outside OBRA) or within a neighbouring country to the mOPV2 campaign.

[2]There are 7 cVDPV2 in Angola and 6 in Central African Republic with estimated dates of seeding spanning mOPV2 campaigns conducted in the neighbouring country of Democratic Republic of Congo.

[3]The cVDPV outbreak in Mozambique, Zambezia (MOZ-ZAM-2) is estimated to have been seeded at least 4 months after the mOPV2 campaign in Zambezia.

Fig. S1. Roadmap of the key timepoints in the Global Polio Eradication Initiative Endgame Strategic Plan.

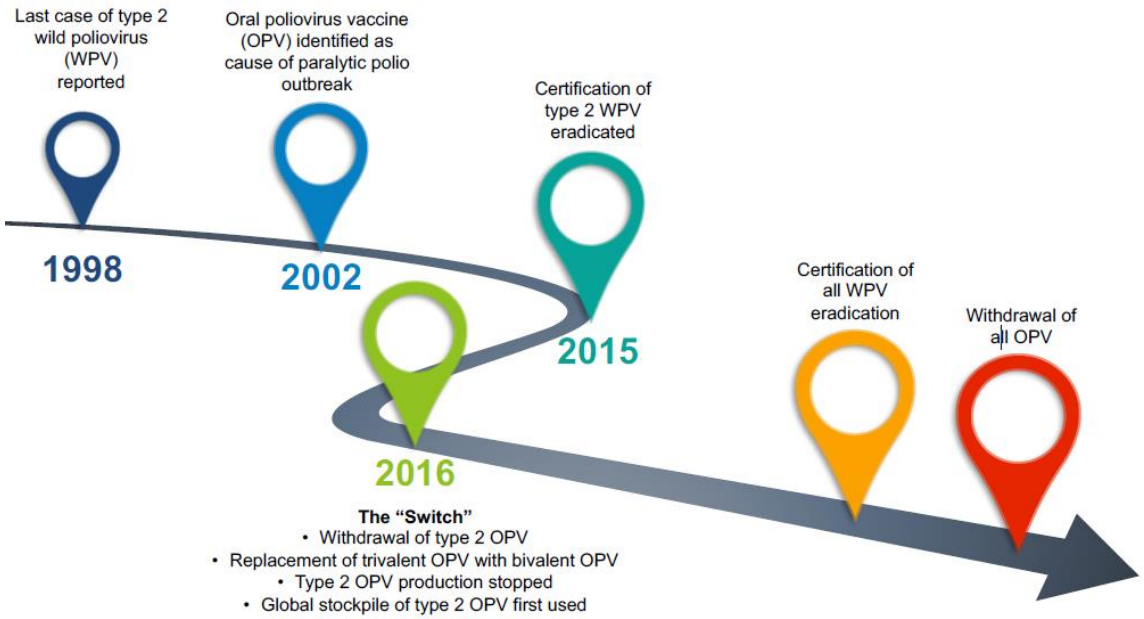
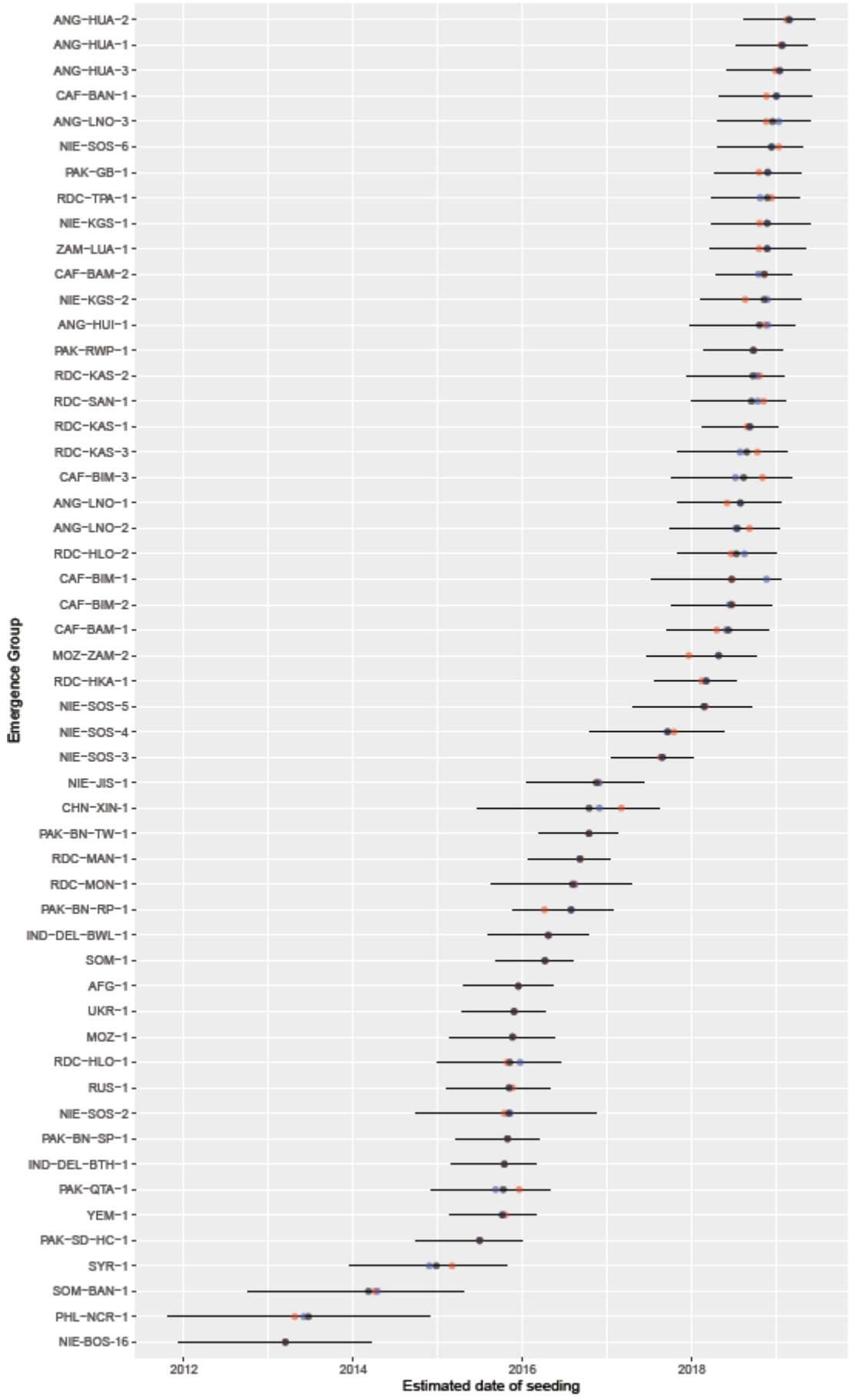


Fig. S2: Sensitivity analysis on the number of isolates selected into generating the estimated date of seeding for a VDPV emergence group. Black circles and horizontal lines indicate the median date of seeding with 95% CI that were used in this manuscript, calculated

using from the nucleotide divergence of the first three isolates detected of an emergence group. Coloured circles show the median date of seeding calculated when one (red) or up to ten (blue) of the first detected isolates of an emergence group were used.


ANG-HUA-2
ANG-HUA-1
ANG-HUA-3
CAF-BAN-1
ANG-LNO-3
NIE-SOS-6
PAK-GB-1
RDC-TPA-1
NIE-KGS-1
ZAM-LUA-1
CAF-BAM-2
NIE-KGS-2
ANG-HUI-1
PAK-RWP-1
RDC-KAS-2
RDC-SAN-1
RDC-KAS-1
RDC-KAS-3
CAF-BIM-3
ANG-LNO-1
ANG-LNO-2
RDC-HLO-2
CAF-BIM-1
CAF-BIM-2
CAF-BAM-1
MOZ-ZAM-2
RDC-HKA-1
NIE-SOS-5
NIE-SOS-4
NIE-SOS-3
NIE-JIS-1
CHN-XIN-1
PAK-BN-TW-1
RDC-MAN-1
RDC-MON-1
PAK-BN-RP-1
IND-DEL-BWL-1
SOM-1
AFG-1
UKR-1
MOZ-1
RDC-HLO-1
RUS-1
NIE-SOS-2
PAK-BN-SP-1
IND-DEL-BTH-1
PAK-QTA-1
YEM-1
PAK-SD-HC-1
SYR-1
SOM-BAN-1
PHL-NCR-1
NIE-BOS-16
Emergence Group
2012
2014
2016
2018
Estimated date of seeding