science.sciencemag.org/cgi/content/full/science.aba1238/DC1

Supplementary Materials for

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

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Published 19 March 2020 on *Science* First Release
DOI: 10.1126/science.aba1238

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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 [4]. 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) [24, 25]. 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 [24]. 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 [7, 16]. 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 [26] (Supplementary Table 1). 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 [13].

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 [15]. 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 VP1 nucleotide changes of the isolate, and a scale parameter equal to the product of the number of VP1 nucleotides (901) and the average mutation rate (1.14×10^{-2} nucleotides per site per year). For isolates that were part of an emergence group that had > 1 isolate, we estimate the date of seeding for that emergence group by combining data from multiple isolates and then assigning this date of seeding to all isolates in the group (Supplementary Table 1). We selected the earliest three detected isolates of an outbreak and resampled each of their estimated dates of seeding 1000 times to produce a combined distribution with a median date and 95% CI. The analysis was restricted to the nucleotide differences of the first three isolates as using all isolates would have to account for the specific location of nucleotide mutations between isolates, which were not available for analysis. For sensitivity analysis, we repeated the procedure by selecting between one and up to ten of the earliest detected isolates, which did not result in any significant changes (Supplementary Figure 2). The limitations of this analysis are discussed below.

The probability that VDPV isolates were seeded after the switch (taken as 01 May 2016) was calculated using the cumulative probability of the empirical distribution of the estimated seeding date and determining what proportion of this distribution is greater than 01 May 2016. For VDPV isolates with a probability of seeding after the switch above 0.9, the database of mOPV2 campaigns was searched to identify mOPV2 campaigns occurring within the time-frame of the estimated date of seeding (95% CI), within the same state/province (Admin 1 level), country (Admin 0 level) or a neighbouring country. If more than one mOPV2 campaign was within the estimated date of seeding interval, the campaign closest in time (to the median estimated seeding date) was chosen in the nearest geographic area (i.e. 1st - Campaigns in the same Admin 1 level, 2nd - Campaigns from the same Admin 0 level, and 3rd - Campaigns from neighbouring countries).

Generalized linear models (GLMs) were used to quantify the patterns of VDPV emergences over time. For the GLMs, we computed univariate logistic regression (family = binomial, link = logit) on the index isolate of each genetic VDPV emergence. The predictor variable was the time in years between 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. 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.

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	23-Mar-16	26-Aug-16	1 (Nigeria: Borno)	Closed	5	0.29 (0.1, 0.47)	2	0	NaN (0)	32,37
SYR-1	Syrian Arab Republic	27-Aug-16	21-Sep-17	3 (Syrian Arab Republic: Deir Al Zour, Raqua, Homs)	Closed	13	0.31 (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	0.28 (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 Congo: Haut Katanga)	Closed	0	0.73 (0.6, 0.82)	2	2	80.5 (2)	7,8
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

[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. 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.

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

[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.

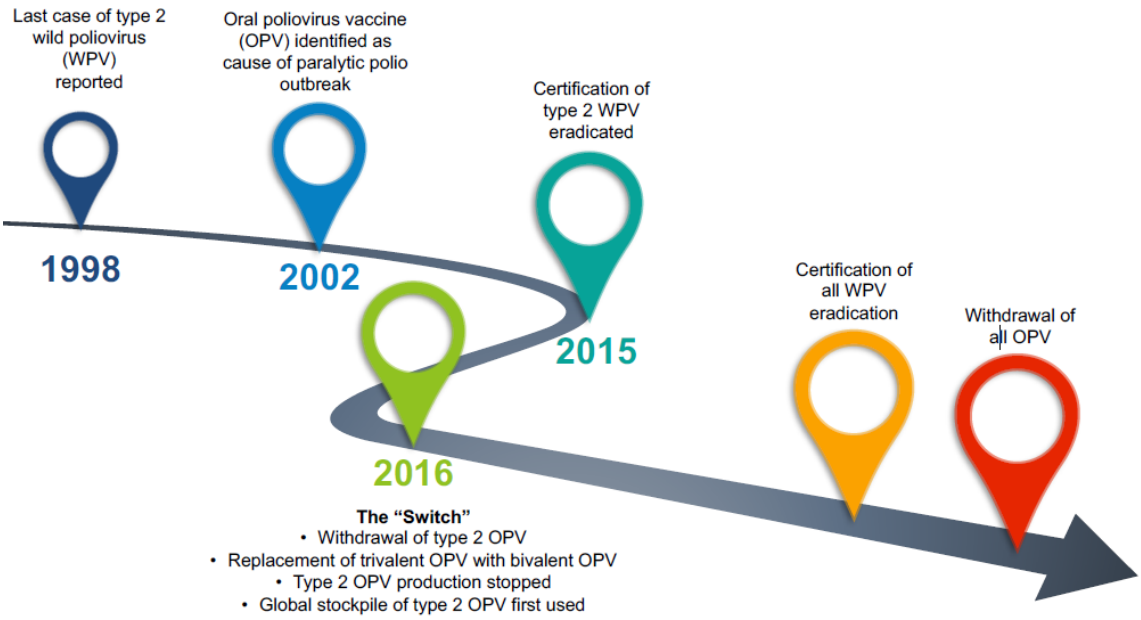
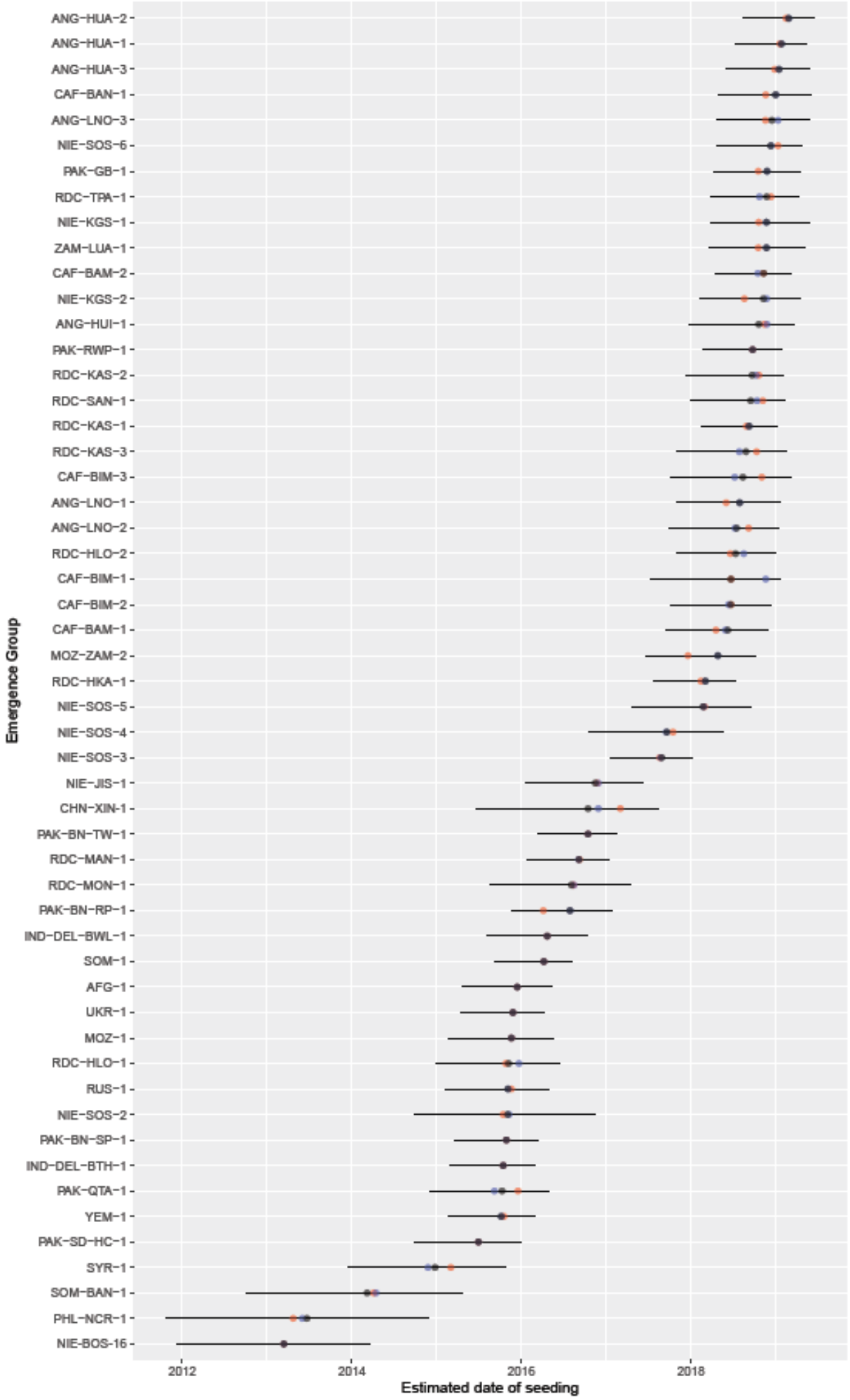


Fig. S2: Sensitivity analysis on the number of isolates selected into generating the estimated date of seeding for a VDPV emergence group. Black circles and horizontal lines indicate the median date of seeding with 95% CI that were used in this manuscript, calculated using from the nucleotide divergence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

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