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

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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 materialize or perform as anticipated.

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 (3). Therefore, the method to control VDPV2 transmission is through vaccination campaigns with the monovalent OPV2 (mOPV2) (4). However, any use of mOPV2 carries the risk of seeding more VDPV2 (5).

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) (fig. S1), resulting in periodic outbreaks of VDPV2 (as well as VDPV1 and VDPV3) and cases of vaccine-associated paralytic poliomyelitis (VAPP) (6). This is because the attenuated

virus strains contained in OPV can mutate and re-acquire factors associated with causing paralytic disease and transmission (7). Populations with low immunization coverage are particularly at risk of spread (7). 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 (fig. S1) (6). 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', (fig. S1) (8). As a risk mitigation strategy, countries began to introduce a dose of inactivated poliovirus vaccine (IPV) into routine immunization schedules to protect against paralysis from type 2 poliovirus (9). However, an estimated 143 million children have not received IPV since April 2016 due to supply shortages (43 million) and poor routine immunization coverage (100 million) (10).

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 immunization campaigns (approximately 1.5 billion doses in the 12 months before the Switch) (11, 12).

The response to any outbreaks was to conduct campaigns with mOPV2, from a finite global stockpile of vaccine (4). While the virus disappeared from most geographies, eradication did not occur (13). More recently, outbreaks of VDPV2 have been increasing in frequency and geographic spread (Fig. 1). At present, WHO classifies circulating VDPV2 (cVDPV2) outbreaks as Public Health Emergencies of International Concern (14). 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. 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 materials). We assume 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 time to each independent mutation is modeled using an exponential distribution and the sum of waiting times as an Erlang distribution (supplementary materials).

Global VDPV2 detections and source

Between 01 May 2016 and 01 November 2019, the GPLN had detected 859 isolates of VDPV2 across 26 countries, including 325 cases of AFP (Fig. 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 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 (Fig. 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 neighboring country (Fig. 2B).

Circulating VDPV2 (cVDPV2) outbreaks

VDPV emergences are classified as cVDPV2, when there is evidence of person-to-person transmission (isolates are genetically linked to a previously detected isolate) or ambiguo-

us VDPV (aVDPV) events, when there is no evidence of transmission and after ruling out primary immunodeficiency in infected individuals (16, 17).

Since the Switch, we identify 62 aVDPV2 events and 41 independent cVDPV2 outbreaks (Fig. 3 and table S1). 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 immunization coverage, inaccessible/active conflict affected areas and low sanitation and hygiene (table S1).

A total of 126 post-Switch mOPV2 campaigns have been conducted in response to these outbreaks, utilizing more than 300 million doses of the mOPV2 vaccine (table S2), primarily in Nigeria (59%) and DRC (15%). These campaigns are consistent with seeding 27 of 41 outbreaks (table S2).

Evolving situation over time

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 immunization with tOPV (Fig. 3 and table S1). This was consistent with the predictions made, including from mathematical modelling groups (11, 18). 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) (19).

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 (13, 20).

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 (Fig. 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 neighboring 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 (18). 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 (Fig. 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 (Fig. 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 neighboring 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 (Fig. 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, 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 (Fig. 3). Subsequently, an individual with primary immunodeficiency was detected excreting virus genetically linked to the outbreak; however, the role of this case in the outbreak 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 emphasize the need for continuing high-quality surveillance and expanding environmental surveillance (21).

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. The risk of VDPV2 circulation is increasing over time, as the immunity of the global population rapidly decreases (5).

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, 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. The question that remains as to what the GPEI should do next?

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 through the Emergency Use Listing procedure (22).

A strategy for the response to cVDPV2s has been developed for 2020–2021. 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: 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 immunization, 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 Emergency of International Concern by the WHO (14). 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 (23).

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Tables S1 and S2

Figs. S1 and S2

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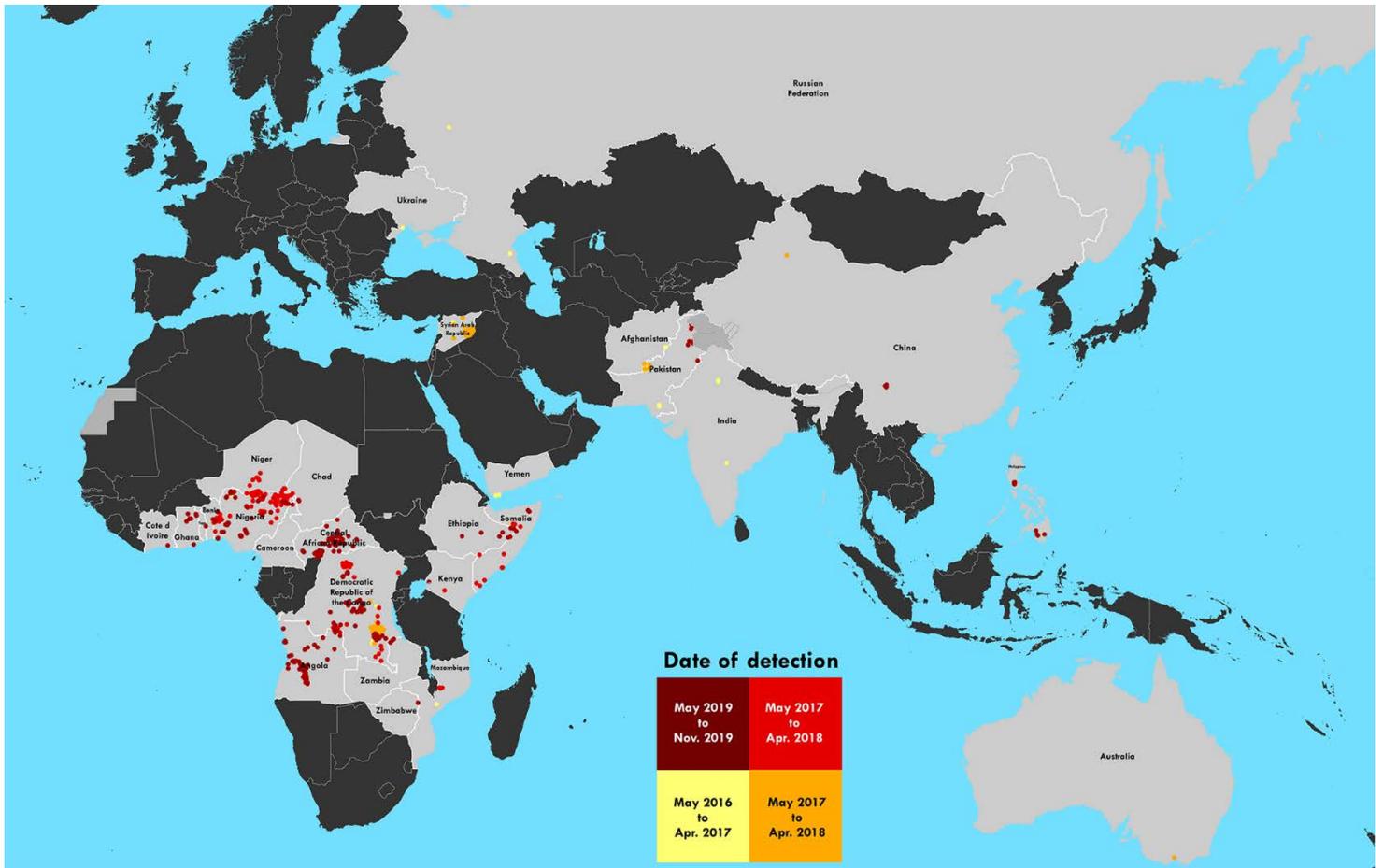


Fig. 1. Geographic location of vaccine-derived poliovirus type 2 isolates detected after the removal of type 2 oral poliovirus vaccine (OPV2), between 01 May 2016 and 01 November 2019. The color of points illustrates the date of isolate detection. Data as of 01 November 2019.

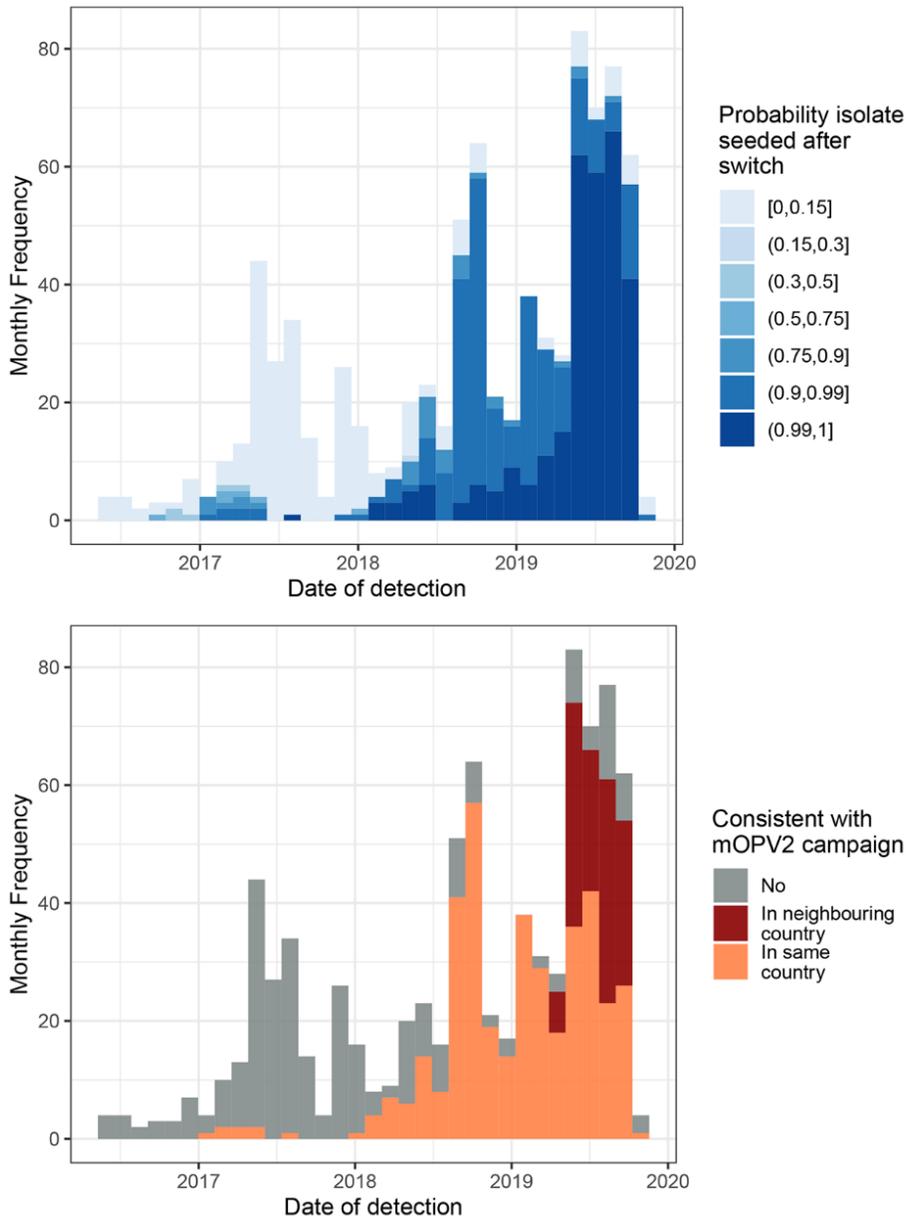


Fig. 2. Incidence of detected vaccine-derived poliovirus type 2 isolates between 01 May 2016 and 01 November 2019. (A) The probability that isolate was seeded after the Switch (01 May 2016) was calculated based on the 95% CI of the estimated seeding date, estimated by the number of nucleotides divergence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

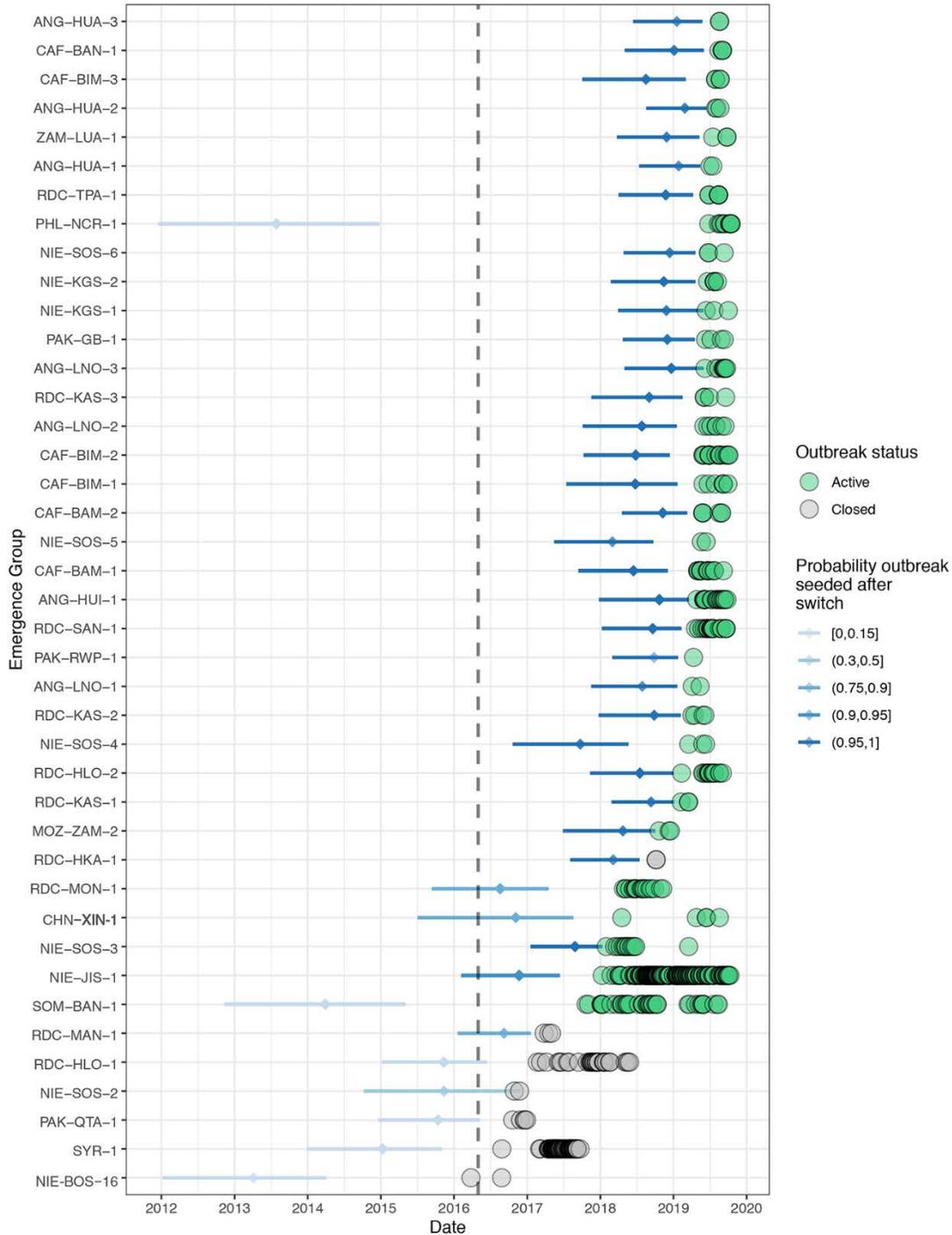


Fig. 3. Timeline of circulating VDPV2 outbreaks reported between 01 May 2016 and 01 November 2019, ordered by the date of first isolate detection. The estimated seeding date (i.e., the date that infectious OPV dose was administered) and 95% confidence intervals are given by horizontal bars, colored by the probability that date of seeding was after the Switch on the 01 May 2016 (date of switch illustrated by a dashed black line). Detected virus isolates shown by colored circles, with the color indicating whether the outbreak is assumed active (detection within previous 12 months) or closed (no detection in previous 12 months). Data as of 01 November 2019. NIE-BOS-16: This outbreak was genetically linked to a cVDPV2 emergence originating in Chad in 2012.

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