RESEARCH ARTICLE

REVISED The impact of surveillance and other factors on detection of emergent and circulating vaccine derived polioviruses [version 2; peer review: 2 approved, 1 approved with reservations]

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Abstract

Background: Circulating vaccine derived poliovirus (cVDPV) outbreaks remain a threat to polio eradication. To reduce cases of polio from cVDPV of serotype 2, the serotype 2 component of the vaccine has been removed from the global vaccine supply, but outbreaks of cVDPV2 have continued. The objective of this work is to understand the factors associated with later detection in order to improve detection of these unwanted events.
Methods: The number of nucleotide differences between each cVDPV outbreak and the oral polio vaccine (OPV) strain was used to approximate the time from emergence to detection. Only independent emergences were included in the analysis. Variables such as serotype, surveillance quality, and World Health Organization (WHO) region were tested in a negative binomial regression model to ascertain whether these variables were associated with higher nucleotide differences upon detection.
Results: In total, 74 outbreaks were analysed from 24 countries between 2004-2019. For serotype 1 (n=10), the median time from seeding until outbreak detection was 284 (95% uncertainty interval (UI) 284-2008) days, for serotype 2 (n=59), 276 (95% UI 172-765) days, and for serotype 3 (n=5), 472 (95% UI 392-603) days. Significant improvement in the time to detection was found with increasing surveillance of non-polio acute flaccid paralysis (AFP) and adequate stool collection.
Conclusions: cVDPVs remain a risk; all WHO regions have reported at least one VDPV outbreak since the first outbreak in 2000 and outbreak

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response campaigns using monovalent OPV type 2 risk seeding future outbreaks. Maintaining surveillance for poliomyelitis after local elimination is essential to quickly respond to both emergence of VDPVs and potential importations as low-quality AFP surveillance causes outbreaks to continue undetected. Considerable variation in the time between emergence and detection of VDPVs were apparent, and other than surveillance quality and inclusion of environmental surveillance, the reasons for this remain unclear.

Keywords
polio, vaccination, eradication, cVDPVs, OPV

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REVISED **Amendments from Version 1**

The main revisions to the manuscript include: (1) a better explanation of the genetic sequencing protocols in place for polioviruses, (2) elaboration on why the data was split by serotypes 2 vs. 1 & 3, and (3) an update to the interpretation of Table 2 in order to highlight the importance of the relationship between type of surveillance via which the first isolate was detected (AFP vs. ES), despite the insignificant p-value. Since the article was first published, there was an importation of WPV1 into the African continent, so we have added commentary on the importance of maintaining high quality surveillance following this event.

Any further responses from the reviewers can be found at the end of the article

Introduction

Polio has been targeted for eradication since 1988 when countries represented within the World Health Assembly committed to eradication[1]. Whilst the initial goal to eradicate all poliovirus by 2000 was not achieved, two of the three wild serotypes have been eliminated, most recently type 3 in 2018[2–4]. The main driver in this reduction of cases has been vaccination achieved through both routine and supplementary immunisation activities (SIAs), largely with the oral polio vaccine (OPV), a live attenuated vaccine. OPV is important for polio eradication, as it provides both humoral and intestinal immunity. However, the genetic instability of the attenuated virus can result in mutations that increase transmissibility and neurovirulence of infections[5,6]. Consequently, circulating vaccine-derived polioviruses (cVDPVs) can arise and cause paralysis in affected individuals. Prior to 2000, these outbreaks had not been reported in any countries using OPV[7], and recent analysis has suggested that cVDPV emergence and spread is more common in populations with low to moderate mucosal immunity against poliovirus[8,9].

Since observing this unwanted effect of OPV vaccination, along with vaccine-associated paralytic polio (VAPP) and immunodeficiency-associated VDPVs (iVDPVs), removal of OPV from use has been prioritised within the Global Polio Eradication Initiative (GPEI)[10,11]. Especially for serotype 2, the risks of OPV have begun to outweigh the benefits because OPV use can seed additional outbreaks in susceptible populations, and the continued use of OPV2 was deemed unnecessary[12]. The Switch from trivalent OPV (tOPV) to bivalent OPV (bOPV), removing serotype 2, was accomplished globally in a two-week period at the end of April 2016[13]. Instead of the anticipated decrease in circulating VDPVs, in the third- and fourth-years post-Switch, outbreaks and geographic spread of outbreaks have increased.

The strategy for eradication described in the 2013–2018 GPEI Strategic Plan outlines that wild poliovirus should be interrupted whilst strengthening immunization systems, including the introduction of inactivated polio vaccine (IPV)[10]. Alongside, considerable investment has been made towards transition to a polio-free world that includes containment of all polioviruses, including minimising the risks of unintended release from laboratory facilities, and eventual removal of the OPV (known as cessation)[14]. This transition phase is needed to ensure that the chances of poliovirus transmission in a susceptible population would be as low as manageable, and that populations would remain protected from outbreaks. The Polio Post-Certification Strategy[14], describes the many facets of containing polioviruses, protecting populations, cessation of the OPV and detecting and responding to a polio threat. The Switch from tOPV to bOPV provided the first trial of removing one of the serotypes from the global vaccine supply. Within the Polio Post-Certification Strategy, the pre-cessation (zero-to-one-year post-certification) and immediate post-cessation (two to five years post-certification) were regarded as the time periods where VDPVs were most likely to emerge, where the risk was thought to be highest 12–18 months after (in the most recent example) bOPV withdrawal. The period of time until detection is based on modelling which suggests that the cumulative probability of detecting circulating poliovirus is over 99.9% by four years[15], but the modelling did not account for weaknesses in surveillance or include specific aspects of VDPV transmission.

cVDPVs are of particular concern in areas with low to moderate OPV induced immunity, as the virus is able to emerge and maintain transmission[9,16]. In (mostly high-income) countries with no OPV vaccination, there is minimal risk of VDPV emergence because the source is largely absent, transmission risk is lower, and vaccination coverage with the IPV is usually high. However, other risk factors for cVDPVs include: continued OPV use at low rates of coverage, prior elimination of the corresponding wild poliovirus serotype, insensitive acute flaccid paralysis (AFP) surveillance, and use of monovalent OPV (mOPV) and bOPV in SIAs due to the emergent risk of the live attenuated vaccine[6,8,17]. A novel, genetically stable OPV2 that is a modified version of the existing OPV2 but better retains attenuation is currently in development and has been approved and deployed for emergency use in 2021 in order to mitigate these risk factors[18,19].

Here we provide a retrospective analysis of cVDPV outbreaks between 2004 and 2019 and estimate the time from emergence to detection using publicly available data. We explore the differences in time to detection across VDPV serotypes and examine the effect of AFP surveillance and other factors on the time to detection. The aim is to provide useful information on the time to detection of VDPV outbreaks by serotype and the factors that affect this, in order to inform future cessation planning.

Methods

Detection of poliomyelitis outbreaks are dependent upon global surveillance for AFP and the Global Polio Laboratory Network where clinical specimens are investigated to identify poliovirus as the causative agent. To confirm poliovirus infection, at least two stool specimens should be collected 24–48 hours apart and within 14 days of the onset of AFP in affected individuals[20]. All samples undergo confirmatory testing and genetic sequencing at laboratories that are part of The Global Polio Laboratory Network (GPLN) following a standardised protocol to minimise contamination and maximise sensitivity[21]. Sequencing of the VP1 region of the viral genome is used to classify poliovirus; if the sample differs from the parental OPV strain

by 1–15% (or from 0.6% for serotype 2), the case is defined as a VDPV[9,22]. However, this definition changed in 2010 for serotype 2 only, such that prior to 2010, 10 nucleotide mutations in the VP1 region constituted a VDPV, but later on, the cut-off dropped to 6 nucleotide mutations. Therefore, we exclude type 2 outbreaks prior to 2010 (n=16) to account for this change as historic type 2 outbreaks where the isolate had <10 nucleotide mutations would not have been counted as a cVDPV.

By definition, cVDPV refers to VDPV isolates for which there is evidence of person-to-person transmission in the community and 'genetically linked VDPVs' are isolated from at least two individuals who do not live in the same household, or from one individual and ≥1 environmental surveillance (ES) sample reported through the comprehensive surveillance network[11]. Within the GPEI surveillance network, cVDPV outbreaks that spread across country borders are treated as separate outbreaks (requiring a response within each country). Here we are only interested in the emergence of new cVDPV outbreaks, and exclude outbreaks as a result of international spread. For example, an emergence first detected in Jigawa State, Nigeria, which has spread to several countries in West Africa is only included once in the dataset. Where possible, the lineage code for each cVDPV2 emergence is provided (extended data Table 1[23]).

Poliomyelitis is a notifiable disease, and as part of global surveillance for poliomyelitis, the GPEI and WHO laboratories report all confirmed outbreaks through the Morbidity and Mortality Weekly Reports (MMWR). Consequently, we use these reports to compile a spreadsheet of all cVDPV outbreaks from 2000 to February 2020. Outbreaks were first identified using MMWR reports and then country and year(s) of the outbreak were searched using the search terms: 'vaccine-derived poliovirus* OR VDPV OR circulating vaccine-derived poliovirus* OR cVDPV'. This search criteria is not a systematic review of all literature for polio outbreaks within the time period, but due to the nature of disease surveillance for poliomyelitis, this resulted in a comprehensive list of outbreaks. The number of nucleotide sequences that are different to the Sabin 2 strain at first detection (referred to as 'VP1 divergence') and the dates of the first and last isolates of the outbreak were also collated through the literature search. As per exclusion criteria, we did not include outbreaks that did not meet the aforementioned cVDPV definition or were the result of international spread. The annual country-level non-polio acute flaccid paralysis (AFP) rate and percentage of adequate stool specimens collected, both indicators of surveillance quality, were extracted for each outbreak and year corresponding to the start of the outbreak. In order examine the effect of environmental sampling as a supplement to AFP surveillance, the mechanism via which the first isolate was detected (AFP or ES) was ascertained for each outbreak. Additionally, we included WHO region, Diphtheria-Pertussis-Tetanus vaccine dose 3 (DPT3) coverage (which is often used as a marker for routine immunisation coverage), and whether the outbreak was detected before/after 2016. Multiple independent emergences observed within the same country-year unit of observation were treated as multiple observations even if the associated surveillance data and outbreak response remained the same. HF was responsible for initial database creation while MA independently cross-checked the data.

Variables associated with the number of nucleotide differences were explored using a negative binomial model. A negative binomial model was selected because the variance of the reported number of nucleotide differences was larger than the mean and the data was highly dispersed. The minimum number of mutations was 9 for serotypes 1 and 3, and 6 for serotype 2, and the outcome variable was shifted-left so that the minimum number was 0. Separate datasets were created for serotype 2 and serotypes 1 and 3 to account for the small sample size of types 1 and 3 outbreaks and because of the similar case to infection ratio for serotypes 1 and 3[24]. The data set for types 1 and 3 retained a covariate for serotype. Preliminary analysis illustrated that outbreaks with nucleotide mutations ≥30 (n=4) affected the fit of the model to the data (due to over-dispersion that could not fully be accounted for) and were removed from the dataset as outliers. A multivariate regression model was built using stepwise removal by comparing differences in the Akaike information criteria (AIC) between candidate models and assessing the negative binomial dispersion parameter (θ). Interactions between variables were also examined.

For every VDPV outbreak, we estimate the time to detection using the following methods. Each VDPV outbreak has included with it the number of VP1 mutations associated with the first case(s), and is used to estimate the time to detection. The first VP1 mutation of the Sabin strain is assumed to be instantaneous and each subsequent mutation follows an average rate of 1.14×10^{-2} nucleotides per site per year[25,26]. The VP1 RNA gene consists of 906 nucleotides, so we would expect approximately 1 nucleotide change every 35 days under a constant clock model. We assume that the viral evolution rate is the same across all serotypes[27,28]. Each independent mutation was modelled using an exponential distribution and the sum of waiting times as an Erlang distribution, as done for a previous analysis of cVDPVs[26]. By treating each VDPV detection as a random sample of the population parameter for the time to detection, we use bootstrapping of the sample estimates of time to detection to provide robust estimates for serotype 2 and serotypes 1 and 3. The empirical distribution function of the bootstrapped samples were used to calculate the probability of VDPV outbreaks being detected within one and four years. All analyses were carried out in R version 4.0.3.

This work was completed between June 2020 and April 2021 and revised following peer review in April 2022. This project received ethical approval from the London School of Hygiene & Tropical Medicine (LSHTM) on 29th June 2020: project ID 21929.

Results

Independent cVDPV outbreaks

Review of MMWR reports identified a total of 96 outbreaks in 28 countries. However, once outliers were excluded and the change of cVDPV2 definition was accounted for and cVDPV2 outbreaks pre-2010 were removed, a total of 74 cVDPV outbreaks as a result of independent emergences were analysed from 24 countries (Table 1). cVDPV type 2 was the most frequent serotype isolated, accounting for 80% of outbreaks, followed by serotypes 1 and 3, accounting for 13% and 7% of outbreaks, respectively. Of the 74 outbreaks, 18 (24%) were first detected via ES.

Table 1. Summary of all circulating vaccine derived polioviruses (cVDPVs) included in the analysis split by serotype.
WHO=World Health Organization; NPAFP= non-polio acute flaccid paralysis; CI=confidence interval.

WHO Region	Country	Number of outbreaks	Median* duration days (range**)	Median* nucleotide difference from Sabin strain of the first isolate (range**)	Mean NPAFP rate (per 100,000 children <15) (95% CI)	Mean % adequate stool samples (95% CI)
Serotype 1						
AFR	MADAGASCAR	1	338	20	4.2	85.6
AFR	MOZAMBIQUE	1	112	27	2.7	87.2
AMR	DOMINICAN REPUBLIC	1	190	17	-	-
EUR	UKRAINE	1	7	20	2.7	97.4
SEAR	INDONESIA	1	139	10	2.4	85.5
SEAR	MYANMAR	2	258 (59, 458)	19.5 (14, 25)	2.8	92.7
WPR	CHINA	2	55 (51, 59)	11 (9, 13)	1.9	92.2
WPR	LAOS	1	269	21	2.6	57.1
WPR	PAPUA NEW GUINEA	1	193	14	7.9	44.7
Global Type 1 total		10	125.5 (7, 458)	17 (9, 27)	3.2 (1.9, 4.5)	82.7 (70.2, 95.2)
Serotype 2						
AFR	ANGOLA	5	195 (39, 288)	7 (6, 10)	5.0	85.1
AFR	CENTRAL AFRICAN REPUBLIC	7	99 (0, 275)	7 (6, 10)	9.2	71.1
AFR	CHAD	2	184 (97, 270)	6 (6)	10.2	84.6
AFR	DRC	12	173 (1, 473)	8 (6, 19)	7.7	84.2
AFR	ETHIOPIA	4	94 (41, 151)	12 (10, 18)	2.9	90.8
AFR	GUINEA	1	475	12	2.6	96.6
AFR	MOZAMBIQUE	1	57	6	3.4	88.5
AFR	NIGERIA	9	84 (0, 637)	10 (6, 16)	11.9	95.4
AFR	SOUTH SUDAN	1	3	9	4.2	94.4
AFR	TOGO	1	78	13	4.6	70.2
AFR	ZAMBIA	1	71	9	3.8	84.3
EMR	AFGHANISTAN	1	1295	8	11.0	92.6
EMR	PAKISTAN	9	58 (8, 654)	6 (6, 9)	17.7	87.1
EMR	SYRIA	1	202	22	3.6	80.4
EMR	YEMEN	1	179	6	3.4	91.5
SEAR	MYANMAR	1	172	13	2.5	93.2
WPR	CHINA	2	300 (113, 487)	10 (6, 13)	2.0	92.3
Global Type 2 total		59	105 (0, 1295)	8 (6, 22)	8.9 (7.3, 10.4)	86.2 (84.2, 88.2)
Serotype 3						
AFR	ETHIOPIA	1	556	12	2.6	79.0
AFR	MADAGASCAR	1	32	13	1.3	89.4
EMR	SOMALIA	1	183	14	4.8	97.7
EMR	YEMEN	1	454	18	4.3	93.2
WPR	CAMBODIA	1	50	17	2.0	95.8
Global Type 3 total		5	255	14 (12, 18)	3.0 (1.2, 4.8)	91.0 (81.3, 100)
Total Outbreaks		74	109 (0, 1295)	9 (6, 27)	7.7 (6.3, 9.0)	86.0 (83.8, 88.2)

*Median and **range provided if more than 1 outbreak, otherwise single value provided

For serotype 1 (n=10), the median nucleotide divergence for the first isolate of the outbreak was 17 (range: 9, 27) and the mean non-polio AFP rate was 3.2 cases per 100,000 of the population under 15 years of age (95% confidence interval (CI): 1.9-4.5) (Table 1). Half (50%) of type 1 outbreaks were contained or closed within 120 days. For serotype 2 (n=59), the median nucleotide divergence for the first isolate of the outbreak was 8 (range: 6, 22) and the mean non-polio AFP rate was 8.9 cases per 100,000 of the population under 15 years of age (95% CI: 7.3, 10.4). The majority of type 2 outbreaks (54%) were contained within 120 days. For serotype 3 (n=5), the median nucleotide divergence for the first isolate of the outbreak was 14 (range: 12, 18) and the mean non-polio AFP rate was 3.0 (95% CI: 1.2, 4.8) cases per 100,000 of the population under 15 years of age. In total, 40% of type 3 outbreaks were contained within 120 days.

For serotype 2, a regression model of the number of nucleotide differences of the first isolate for each outbreak suggests a decrease in nucleotide difference with increasing non-polio AFP rate and percentage of adequate stool samples collected (incidence rate ratio (IRR) 0.18, 95% CI 0.06-0.49, $p<0.01$ and IRR 0.91 95% CI 0.84-0.99, $p=0.05$, respectively), but no significant difference between classification (AFP or ES) ($p=0.07$), Table 2. Despite the non-significant p-value and wide confidence interval that crosses 1.00, the IRR (2.15 95% CI: 0.93, 5.4) provides weak evidence that rate of nucleotide mutations of outbreaks identified via ES is greater when compared to outbreaks first identified through AFP surveillance. Interaction between non-polio AFP rate and percentage of adequate stool samples was significant for both serotype 2 and serotypes 1 and 3 (IRR 1.02 95% CI 1.01-1.04, $p<0.01$ and IRR 1.01 95% CI 1.0-1.03, $p=0.03$, respectively). A regression model was attempted for the 15 outbreaks that were either type 1 or 3, but low sample size prevents meaningful interpretation (extended data Table 2[23]). The mean estimates of the regression terms for serotypes 1 and 3 were similar in value to serotype 2 estimates, for example, there was no significant difference in surveillance classification for serotypes 1 and 3 (IRR 0.22, 95% CI 0.04-1.28, $p=0.08$), but the confidence intervals of the regression estimates were wide, likely due to low sample size.

The effects of non-polio AFP rate on nucleotide differences are shown in Figure 1, where the negative binomial regression model for serotype 2 is used to predict counts of nucleotide differences. To illustrate the interaction between non-polio AFP rate and percentage of adequate stool samples, Figure 1a illustrates that as both non-polio AFP rate and percentage of adequate stool increases, predicted nucleotide differences decline. Although the type of surveillance via which the first isolate was detected (AFP case or ES) was not significant in the final model and could act as a confounder, in Figure 1b, predicted nucleotide differences decrease as non-polio AFP rate increases for both surveillance mechanisms, but to a greater extent for AFP at low rates of non-polio AFP surveillance.

Model residuals (Figure 2a) for the serotype 2 model support an appropriate model structure as the plot illustrates homoscedasticity of the residuals. The Q-Q plot (Figure 2b) further supports the assumed theoretical distribution for the final models as most values are centred along the Q-Q line, but the extreme values illustrate deviation from the assumed normal distribution of residuals. Figure 2c provides a visual comparison of expected vs. observed frequencies of nucleotide mutations. For serotype 2, outbreak frequencies corresponding to 6, 13, 19 and 22 nucleotide mutations are under-estimated by the model.

Table 2. Final regression model of factors associated with the number of nucleotide differences of the first isolate of vaccine derived poliovirus (VDPV) outbreaks. Sample size and dispersion parameter (θ) for the serotype 2 model are reported. AFP=acute flaccid paralysis; ES=environmental surveillance; IRR=incidence rate ratio; CI=confidence interval.

Serotype 2 (n = 59) θ = 0.99			
Variable	**Factor**	**IRR, multivariable (95% CI)**	**P-value**
Intercept	-	-	
Unit increase of non-polio AFP rate (cases per 100,000 children aged <15 years old) Mean (95% CI): 8.9 (7.3, 10.4)	Linear term	0.18 (0.06, 0.49)	<0.01
Percent of stool samples adequately collected Mean (95% CI): 86.2 (84.2, 88.2) <80%: n = 9 (15%)	Linear term	0.91 (0.84, 0.99)	0.047
Unit increase of non-polio AFP rate * Percent of stool samples adequately collected	Interaction term	1.02 (1.01, 1.04)	<0.01
Type of surveillance via which first isolate was detected (AFP case or ES) AFP: n = 42 (71.1%) ES: n = 17 (28.8%)	ES (vs. AFP)	2.15 (0.93, 5.4)	0.069

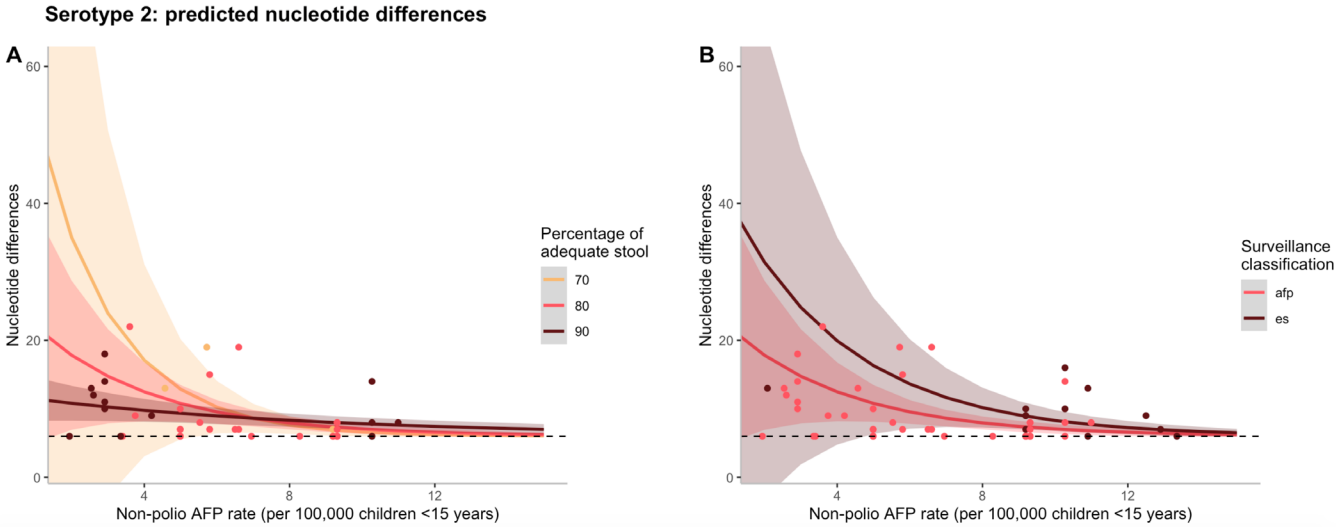

Figure 1. (**A**) Predicted counts of nucleotide differences for serotype 2 based on the final negative binomial regression model vs. non-polio AFP rate (per 100,00 children <15 years of age). The different colour lines correspond to varying percentages of adequate stool samples collected and the shaded regions represent a 95% confidence interval of model predictions. The different colour points also correspond to varying percentages of adequate stool samples collected, but represent data from a particular cVDPV2 outbreak. (**B**) Predicted counts of nucleotide differences for serotype 2 based on the final negative binomial regression model vs. non-polio AFP rate (per 100,00 children <15 years of age). The different colour lines correspond to the type of surveillance via which the first isolate was detected and the shaded regions represent a 95% confidence interval of model predictions. The different colour points also correspond to the type of surveillance via which the first isolate was detected, but represent data from a particular cVDPV2 outbreak. In both figures, the black dashed line represents the minimum threshold cut-off of nucleotide differences (n=6) to be considered a cVDPV2.

Similar figures for serotypes 1 and 3 can be found in extended data Figure 1[23].

Estimating the time to outbreak detection

The time to detection was estimated for each outbreak, including uncertainty intervals (Figure 3). Using the bootstrap method, the median time from seeding until outbreak detection for serotype 1 (n=10), was 284.3 (95% UI 284.3-2007.8) days and it was estimated that 91.5% of outbreaks would be detected within four years. The median time from seeding until outbreak detection for serotype 2 (n=59) was 276.1 (95% UI 172.3-764.8) days and 99.7% of outbreaks are estimated to be detected within four years. For serotype 3 (n=5), the median time from seeding until outbreak detection was 472.4 (95% UI 392.1-603.1) days and it was estimated that 100% of outbreaks would be detected within four years. Using the full uncertainty of the estimated time to detection, 20 of the 59 (34%) outbreaks of serotype 2 were detected under one year, whereas no serotype 1 or 3 outbreaks were detected within one year.

Discussion

Polio eradication has been deemed an achievable undertaking, but with timeline and budget pressures ever present, it is importance to better understand the risks associated with cessation strategies and how to better plan for unwanted events. Emerging and circulating VDPVs are one of many threats to eradication, and detecting cVDPVs early in order to respond and limit transmission in communities will be important throughout the final stages of eradication.

This analysis illustrates several observations about cVDPV outbreaks. cVDPVs caused by serotype 2 have been more commonly detected than outbreaks caused by serotypes 1 and 3. This observation was apparent between 2000–2015 when the trivalent OPV was in use, as well as in subsequent years. When children are vaccinated with the OPV, the serotype 2 strain is more competitive in the gut mucosa[29,30], resulting in increased 'take' by vaccinated individuals and subsequently a higher rate of secondary spread. The increased rate of spread was exacerbated post-Switch as a larger proportion of populations were not vaccinated with the serotype 2 strain due to the strategy of cessation. Additionally, a recent modelling study using inference from data on several clinical trials suggests that the order of transmissibility within equivalent populations is in the descending order of serotype 2, 1, and 3, which would further explain the observed frequency of each serotype-specific VDPV outbreak[31].

The number of nucleotide differences at the time of detection did not significantly vary between serotypes. For serotype 1, it has between estimated that there are approximately 200 infections for every case, 2000 infections for a serotype 2 case, and 1000 infections for a serotype 3 case[32]. Based on differences in the

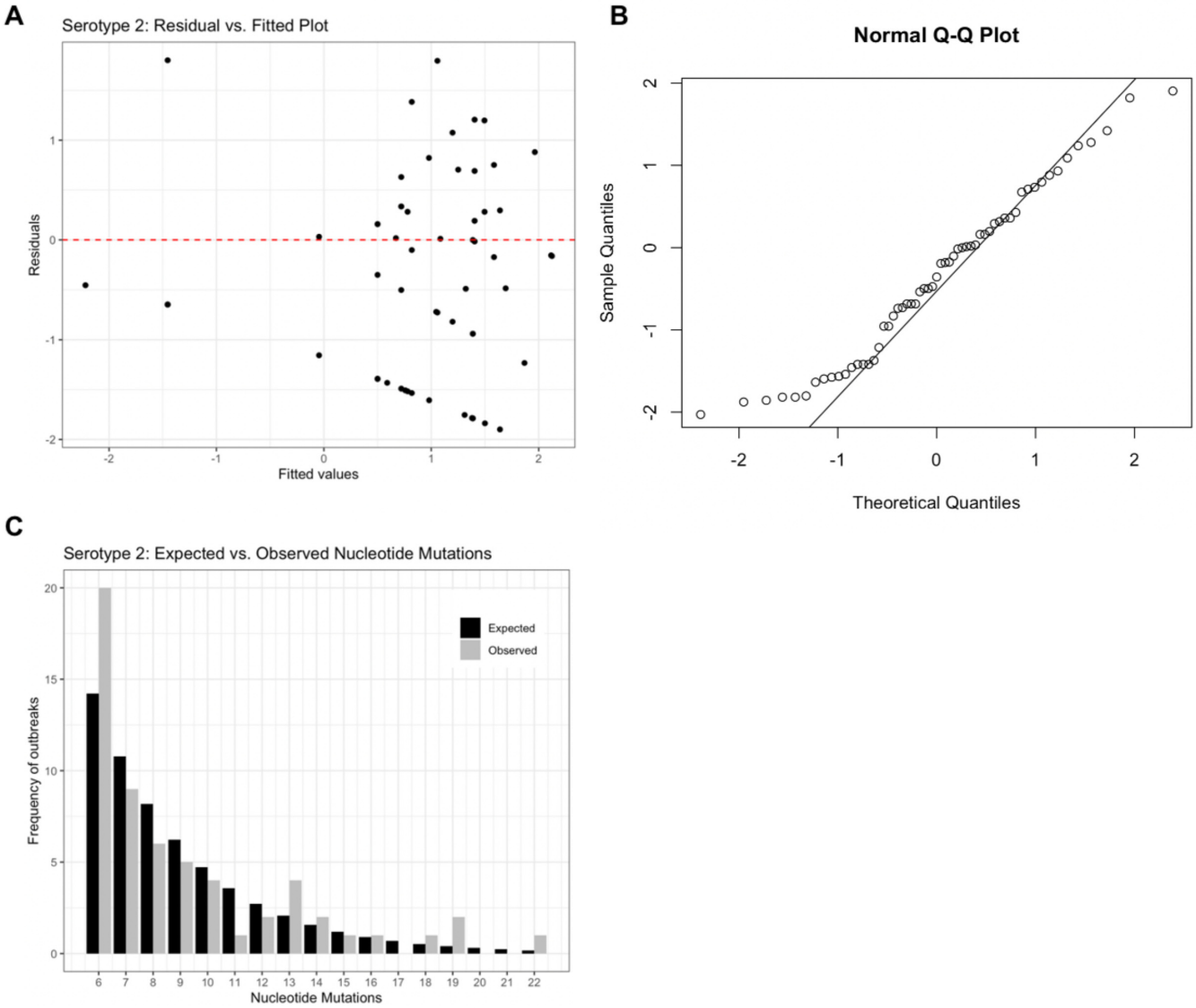

Figure 2. Serotype 2 diagnostic plots. (**A**) residual vs. fitted values, (**B**) Normal Q-Q plot and (**C**) Expected vs. observed frequencies of nucleotide mutations assuming a negative binomial distribution. Figure 2A shows how far the fitted values vary from the residual values, the closer to the red dashed line, the better fit. Figure 2B is used to analyse the distribution of the data. Because several points at the bottom left of the figure deviate from the Q-Q line, the data is positively skewed towards lower nucleotide mutations.

asymptomatic rate, one might expect nucleotide differences of type 1 and 3 to be lower than serotype 2 when first detected, which was not observed. Based on the data from reported outbreaks, detection of cVDPVs does not seem sensitive to differences in symptomatic reporting that is associated with serotype, but may be influenced by unknown differences in where serotype specific detections emerge, which in-turn are affected by surveillance efforts within these countries.

In countries where ES is present, detection of emergent cVDPVs has previously been shown to be quicker than if surveillance relied on AFP alone[33]. Here, we identified weak evidence that outbreaks detected through ES had higher nucleotide divergence, which is contradictory. However, ES is likely placed in locations with known risks of poliovirus transmission and potential challenges in AFP reporting, which may potentially bias findings. Although WHO region did not account for differences in detection time, ES is more commonly implemented across the AFR and EMR regions in comparison to other WHO regions. The total number of active ES sites across AFR, EMR and SEAR WHO regions was 620 in 2020, a 15% increase in the number of reported active ES sites in

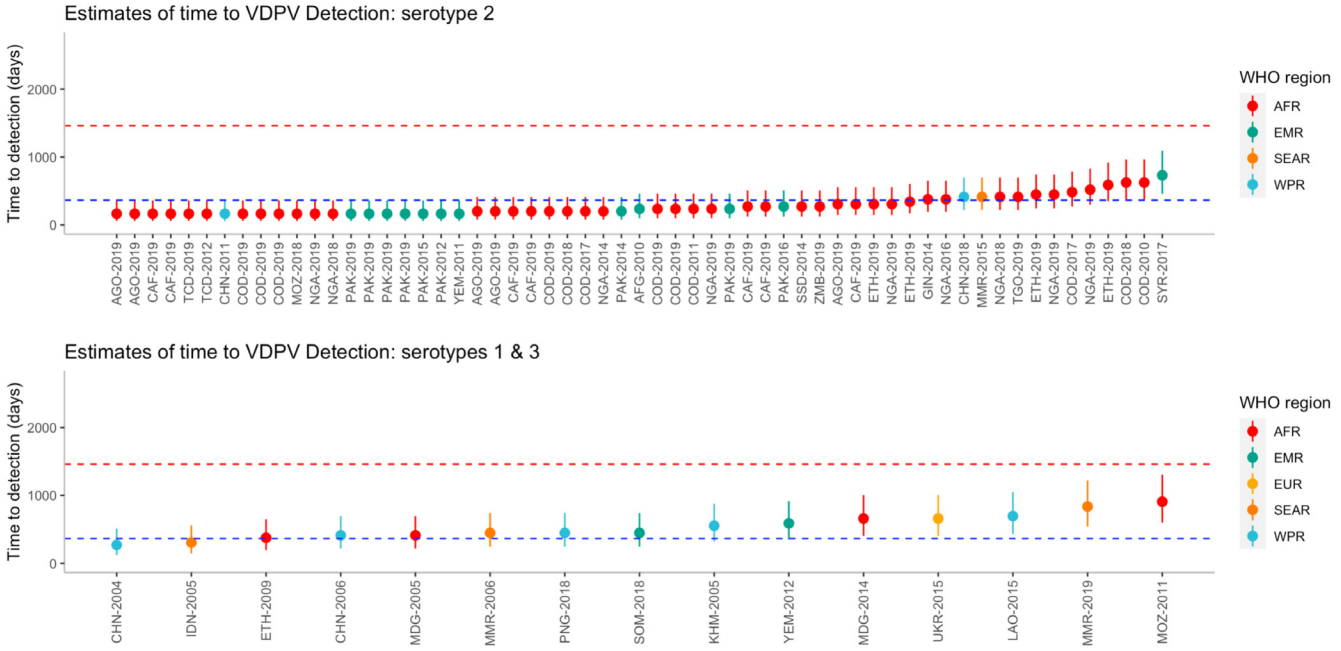

Figure 3. Estimated time to detection of each outbreak from the reported number of nucleotide differences from the Sabin strain, by serotype and region. Outbreaks are ordered on the x-axis by increasing time to detection, where uncertainty in the estimates are shown using 95% uncertainty intervals. Dashed lines represent one year (blue) and four years (red). Country names along the x-axis have been abbreviated using a country's corresponding United Nations ISO 3166-1 alpha-3 code and year of first detection.

2019[34], but the percentage of the population within a catchment area remains comparatively low and poorly measured. While ES remains a useful source for detecting circulating viruses, its low coverage will mean that ES can only supplement AFP surveillance to enable rapid detection of VDPVs.

The relationship between non-polio AFP rate and time to detection illustrates that in order to detect VDPVs early, a country needs to maintain a high rate of non-polio AFP surveillance. Now that wild poliovirus has been eliminated from the African continent, there may be incentive to reduce the intensity of non-polio AFP surveillance in the region. However, in line with the Global Polio Eradication Initiative Strategic Plan 2019–2023, which calls for closing gaps and strengthening global surveillance, this analysis has illustrated the importance of maintaining a high rate of non-polio AFP surveillance, especially for timely detection of cVDPVs[11]. While higher NPAFP rates well beyond the minimal threshold for quality are more predictive of earlier cVDPV detection, this does not necessarily mean that the surveillance standard is too low. Instead, this suggests that while standards are in place, they perhaps do not accurately capture localised issues that may mitigate surveillance sensitivity. Accurate rates of clinical syndrome that are not associated with poliovirus (i.e., Guillain-Barré syndrome) would need to be detected with greater sensitivity to ensure true cases of poliovirus are not missed[35]. The most recent GPEI protocol for responding to poliovirus outbreaks describes NPAFP goals and how recommended levels of surveillance may vary across high-risk areas versus smaller areas with fewer children under 15 years of age[36]. Therefore, as cVDPVs remain a threat, AFP surveillance must remain high in all areas with OPV use and/or suboptimal IPV coverage. Low rates of NPAFP surveillance that persist across many settings coupled with the low case to infection rate for polio means undetected transmission is possible in many areas, jeopardising the attainment of polio eradication. As the risk of importation of infection across the African continent increases following the 2021 WPV1 importation in Malawi[37], adopting strategies to improve surveillance are increasingly important.

Adequate stool describes both the timeliness and quality of the samples (i.e., collected within 14 days of paralysis onset, 24–48 hours apart, and arrival at the laboratory in "good" condition) and current WHO guidelines state that at least 80% of AFP cases should have stool collection described as adequate, which this analysis further supports[38]. However, while the mean percentage of adequate stool specimens in this analysis exceeds 80% for all serotypes, 15% and 20% of outbreaks of serotypes 2 and serotypes 1 and 3, respectively, fall below this targeted 80%. Also, this indicator is often reported at the national level while research suggests that percentage of adequate stool specimens is not only disparate at subnational levels, but particular age groups are not well-covered by the surveillance system and some countries report inaccurate rates of adequate stool specimen collection[39]. After accounting for factors other than WHO regions, WHO region did not remain a significant explanatory variable, suggesting region specific differences do not account for nucleotide divergences as much as surveillance

quality (both non-polio AFP rate and percentage of adequate stool samples collected).

Of the cVDPV2 outbreaks that were seeded post-Switch, the source of about 95% of isolates was found to be consistent with mOPV2 outbreak response campaigns[26]. This has been due to the inherent nature of mOPV2, and likely poorly implemented campaigns, and also because children recently vaccinated with mOPV2, or their contacts, travelled outside the response zones to areas where children born after the Switch were fully susceptible to infection[40]. The need to improve these response campaigns has been recognised with an addendum to the Polio Endgame Strategy 2019–2023, whereby the strategy is to implement actions such as enhanced outbreak response campaigns and ensure sufficient supply of mOPV2 to diminish immunisation gaps[10]. The novel OPV2 vaccine is expected to replace the mOPV in 2021–2022 (subject to findings during emergency use licensure), reducing the risk of cVDPV2 emergence. As illustrated in this analysis, emergences of cVDPV2 from mOPV2 are likely to continue for up to four years after the last mOPV2 campaign, meaning that nOPV2 use in outbreak response will be required for at least this period of time.

A weakness of our approach is that we assume that VDPV mutations occur at a constant and independent rate. In reality, multiple mutations may result in a reduction in nucleotide divergence (through back mutations). Consequently, our estimates may under-estimate the time to detection. Additionally, we have not used data on ambiguous (aVDPVs – progenitors to cVDPVs) to observe the frequency of detection across WHO regions. Inclusion of this data may provide further insight on factors associated with detection, but is reliant on consistent laboratory reporting of aVDPVs across WHO regions. Additionally, this analysis was a retrospective analysis of cVDPV outbreaks where few countries have included IPV into routine immunisation, meaning that we were unable to explore any effects of IPV on VDPV detection. Furthermore, this analysis was done at the national level, where no relationship between RI coverage and time to detection was observed. We recognise that at a smaller geographical level, the relationship between RI coverage may have a stronger relationship with time to detection, highlighting a potential type 1 error and limitation to this analysis.

In conclusion, this analysis of cVDPV outbreaks illustrates that surveillance for AFP—ensuring a high non-polio AFP rate with adequate stool collection—can result in quick detection of cVDPV outbreaks, having the potential to prevent transmission and subsequent cases in populations. In all regions, undetected circulation of poliovirus will remain an issue until the current OPV vaccines are no longer necessary.

Data availability

Underlying data

Zenodo: mauzenbergs/polio_vdpv: VDPV Extended Data. https://doi.org/10.5281/zenodo.4776357[23].

This project contains the following underlying data:

- VDPV_dat.csv

Extended data

Zenodo: mauzenbergs/polio_vdpv: VDPV Extended Data. https://doi.org/10.5281/zenodo.4776357[23].

This project contains the following underlying data:

- VDPV_Extended_Data.pdf

Software availability

Source code available from: https://github.com/mauzenbergs/polio_vdpv

Archived source code at time of publication:

https://doi.org/10.5281/zenodo.4776357[23]

Acknowledgements

We thank members of the GPEI Risk Assessment Working Group, where discussions have been helpful in developing this analysis. We also thank Stephanie Kovacs from the Centers for Disease Control and Prevention who provided valuable insight on methodology and manuscript edits. Original database creation was completed as part fulfilment of HF's MSc degree at the London School of Hygiene and Tropical Medicine. Scientists from the Institute for Disease Modeling at the Foundation are co-authors and were involved in the analysis of data, preparation of the manuscript, and the decision to submit for publication.

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Open Peer Review

Current Peer Review Status: ? ✓ ✓

Version 1

Reviewer Report 10 March 2022

https://doi.org/10.21956/gatesopenres.14511.r31648

✓ **Svea Closser**
Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

This is a very clearly written and well presented paper about the critically important issue of cVDPV outbreaks, with the conclusions presented logically and reasonably. Although I am not an expert in quantitative methods, the methods used appear logical and appropriate, and the authors understand well the nature of the dataset they are working with. The information and analysis presented are informative and practically useful. The discussion is a clear and helpful review of the available information on cVDPV outbreaks, and articulates well what this paper adds.

A few suggestions for further strengthening an excellent and informative paper:

Some of the main practical take-aways (that ES may be less immediately useful than high quality AFP surveillance; that lower quality AFP surveillance means that outbreaks are likely to continue undetected for a significant period of time; and that mop up campaigns using mOPV2 carry risks of seeding cVDPV outbreaks) could be highlighted more in the abstract.

The implications could be pulled out a bit more in the Discussion—there could be some more courageous discussion here. Some questions that came up for me included: Given that surveillance across much of the world is not good enough to detect outbreaks on the timescale we all would like, what level of undetected transmission might we need to assume is ongoing globally, and what are the implications of this? What strategies might the authors suggest instead of mOPV2 mop ups? What is known about the extent to which nOPV, or IPV, would alleviate the cVDPV problem, and what might this paper add to discussions about prioritizing one vaccine over another?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: In the past five years, I have received grant funding from the Bill and Melinda Gates Foundation, and have worked closely with other GPEI partner institutions including WHO and UNICEF. I confirm that this potential conflict of interest did not affect my ability to write an objective and unbiased review of the article.

Reviewer Expertise: I am an anthropologist who has been studying the polio eradication program for more than 15 years.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 26 Apr 2022

Megan Auzenbergs, London School of Hygiene & Tropical Medicine, London, UK

Thank you for your favourable critique of this manuscript. We have taken your comments into consideration and offer the following replies and changes:

1. Some of the main practical take-aways (that ES may be less immediately useful than high quality AFP surveillance; that lower quality AFP surveillance means that outbreaks are likely to continue undetected for a significant period of time; and that mop up campaigns using mOPV2 carry risks of seeding cVDPV outbreaks) could be highlighted more in the abstract.

- These are very helpful take-away points. Several changes have been made to strengthen messaging in the abstract, lines 28-31. As word count is limited for the abstract, we have tried to incorporate your feedback in the most concise, yet meaningful, way possible.

2. The implications could be pulled out a bit more in the Discussion—there could be some more courageous discussion here. Some questions that came up for me included: Given that surveillance across much of the world is not good enough to detect outbreaks on the timescale we all would like, what level of undetected transmission might we need to assume is ongoing globally, and what are the implications of this? What strategies might the authors suggest instead of mOPV2 mop ups? What is known about the extent to which nOPV, or IPV, would

alleviate the cVDPV problem, and what might this paper add to discussions about prioritizing one vaccine over another?

- Several of your points have now been incorporated into the discussion section, specifically, your points around persistent low rates of AFP surveillance and ongoing undetected transmission:
  - "Low rates of non-polio AFP surveillance that persist across many settings coupled with the low case to infection rate for polio means undetected transmission is possible in many areas, jeopardising the attainment of polio eradication. As the risk of importation of infection across the African continent increases following the 2021 WPV1 importation in Malawi, adopting strategies to improve surveillance are increasingly important."

Competing Interests: No competing interests were disclosed.

Reviewer Report 06 August 2021

https://doi.org/10.21956/gatesopenres.14511.r30931

Walter A. Orenstein
Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

This is an important study which provides modeling data showing earlier detection of cVDPV polio outbreaks at sites with better non-polio acute flaccid paralysis (NPAFP) reporting and adequate stool collections. This information can play a critical role in assuring if cVDPV outbreaks were occurring, they would be detected quickly, making containment easier.

The article could benefit with some discussion of why higher NPAFP rates well beyond the minimal threshold for quality are more predictive of earlier cVDPV detection. Does this mean that the standard is too low and are there data the authors can reference regarding what would represent accurate rates of a clinical syndrome not associated with polioviruses? Also, for Table 1, can the authors clarify what the time frame is for the NPAFP rate compared to 1st detection of the outbreak?

Table 2 is important in showing the relationship between various factors and detection of cVDPVs at an earlier time. The IRR is unclear. It would be helpful to add a footnote to the table describing what an IRR of 2.15 in Environmental versus versus AFP surveillance means.

The relationship of AFP versus ES for early detection is, as noted by the authors, not significant (p value 0.069). But this is really borderline non-significant and this reviewer feels the authors need to be cautious in dismissing the relationship.

Figure 2 A and B are difficult for this non-statistician to understand. It would be helpful if more description of the graphs for a non-statistical audience was added.

In the abstract, the authors mention the first outbreak in 2001 of cVDPV1. In actuality, the outbreak started in 2000 and continued into 2001. See MMWR 50(39) 855-6, October 5, 2001.

On page 3, left column, 3rd paragraph, line 11, there is a typo: "a low" should be "as low".

There is another typo on page 4, left column, line 10. The authors say "systemtic". Should it be "systematic"?

Also in that same paragraph, there are some asterisks. This reviewer did not see what the asterisks referred to.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I have a career as a public health physician. I was Director of the US Immunization Program at the CDC for 16 years. For 3 years I was in charge of the polio efforts at the Bill & Melinda Gates Foundation (2008-2011)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 26 Apr 2022

Megan Auzenbergs, London School of Hygiene & Tropical Medicine, London, UK

We thank the reviewer for their insightful and positive critique. We have taken your

comments into consideration and offer the following responses and changes to the manuscript:

1. The article could benefit with some discussion of why higher NPAFP rates well beyond the minimal threshold for quality are more predictive of earlier cVDPV detection. Does this mean that the standard is too low and are there data the authors can reference regarding what would represent accurate rates of a clinical syndrome not associated with polioviruses?

- Thank you for this useful question, this is a great point regarding the standards in place for AFP surveillance. As Tangermann et al. 2017 states: "high rates of AFP reporting do not necessarily imply highly sensitive surveillance, because, in the absence of sufficient supervision, there may be considerable over-reporting of children as AFP cases who actually do not have AFP, while true AFP cases."
    - This suggests that while standards are in place, they perhaps do not accurately capture localised issues that may mitigate surveillance sensitivity. Accurate rates of clinical syndrome that are not associated with poliovirus (i.e., Guillain-Barré syndrome) would need to be detected with greater sensitivity to ensure true poliovirus cases are not missed. A change has been made to add this important point to the discussion, lines 345-351.
- Additionally, the most recent GPEI protocol for responding to poliovirus outbreaks describes NPAFP goals and how recommended levels of surveillance may vary across high-risk areas versus smaller areas with fewer children under 15 years of age. This is now included in the manuscript lines 355-360.

2. Also, for Table 1, can the authors clarify what the time frame is for the NPAFP rate compared to 1st detection of the outbreak?

- The mean NPAFP rate that is listed in Table 1 is the annual rate reported during the year of the first detection of the outbreak. This information is provided in line 136:
    - "The annual country-level non-polio acute flaccid paralysis (AFP) rate and percentage of adequate stool specimens collected, both indicators of surveillance quality, were extracted for each outbreak and year corresponding to the start of the outbreak".

3. Table 2 is important in showing the relationship between various factors and detection of cVDPVs at an earlier time. The IRR is unclear. It would be helpful to add a footnote to the table describing what an IRR of 2.15 in Environmental versus AFP surveillance means.

- In the amended version, a footnote has been added to table 2 further explaining the interpretation this IRR and how the IRR can be used to predict what the nucleotide changes would be of an isolated virus under specific circumstances (AFP vs. ES).

4. The relationship of AFP versus ES for early detection is, as noted by the authors, not significant (p value 0.069). But this is really borderline non-significant and this reviewer feels the authors need to be cautious in dismissing the relationship.

- Thank you for this important point. We agree that this relationship may have been incorrectly dismissed and we now make a point to mention the IRR despite the borderline non-significant p-value. Note that we have retained the finding in the model presented for this reason, but also that the IRR is positive, which points towards ES being implemented in high-risk areas with concerns for AFP rates.
- We made a change in the manuscript to address your point, lines: 254-257 (or paragraph 3 of the results section).

5. Figure 2 A and B are difficult for this non-statistician to understand. It would be helpful if

more description of the graphs for a non-statistical audience was added.
- Thank you for this consideration, the caption for figure 2 A and B has now been updated with more explanation of how to best interpret the plots for a non-statistical audience.

6. In the abstract, the authors mention the first outbreak in 2001 of cVDPV1. In actuality, the outbreak started in 2000 and continued into 2001. See MMWR 50(39) 855-6, October 5, 2001.
- This is a correct statement. The abstract and corresponding relevant text have been corrected to align with MMWR reports.

7. On page 3, left column, 3rd paragraph, line 11, there is a typo: "a low" should be "as low".
- Thank you for noting this, it has now been changed in the manuscript.

8. There is another typo on page 4, left column, line 10. The authors say "systemtic". Should it be "systematic"?
- Thank you for noting this, it has now been changed in the manuscript.

9. Also in that same paragraph, there are some asterisks. This reviewer did not see what the asterisks referred to.
- Thank you for noting this, when conducting literature searches in large databases, an asterisk is used to include variations of the same word within the search criteria. For example, “poliovirus*” would include all versions of the word in the search criteria, such as: “polioviruses”. This is standard best practice for systematic reviews, especially when words such as “immunisation” can be spelled differently in the English language. Such a word should be included as “immuni*ation” in searches to include articles that use “immunization” and “immunisation”.
- For this reason, no changes have been made to the manuscript text regarding search terms.

Competing Interests: No competing interests were disclosed.

Reviewer Report 07 July 2021

https://doi.org/10.21956/gatesopenres.14511.r30747

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Yvonne Maldonado
Department of Pediatrics, Stanford University, Stanford, CA, USA

Thank you for the opportunity to read an interesting paper on the importance of ongoing surveillance for the detection of cVDPVs and the impact of surveillance methodology on the timely detection of mutated vaccine virus. The statistical analyses were sound as described for the

research questions and have brought up a number of interesting points for the GPEI to consider, especially in light of the decline in reported cases of AFP in the last year.

1. I would have liked to see more description in the methods regarding the source of the genetic sequences used in this analysis and the measures put into place to assess the validity of these sequences. Would the authors be able to expand further in the main text?

2. In the third paragraph of the methods, the authors note, “Separate datasets were created for serotype 2 and serotypes 1 and 3, and the latter retained a covariate for serotype.” While the authors noted that a covariate for serotype exists in the shared dataset, I was wondering why different datasets were not created for each serotype?

3. Given the impact of vaccination on the emergence of cVDPVs, were the authors able to look at vaccination schemes or vaccination coverage as a covariate for the countries where outbreaks were detected? Or to look at vaccination coverage in these outbreaks in relation to neighboring countries where outbreaks were not detected?

4. Paragraph 6 in the discussion brings up a great point on the value of environmental surveillance as a tool for earlier detection of cVDPVs. I would suggest moving that higher in the discussion.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious Disease Epidemiology, Polio Epidemiology, Oral Poliovirus Vaccine Transmission, Environmental Surveillance for Oral Poliovirus Vaccine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Apr 2022

Megan Auzenbergs, London School of Hygiene & Tropical Medicine, London, UK

Thank you for your important comments on this analysis. We have taken your questions into consideration and offer the following responses and changes to the manuscript:

1. I would have liked to see more description in the methods regarding the source of the genetic sequences used in this analysis and the measures put into place to assess the validity of these sequences. Would the authors be able to expand further in the main text?

- We have provided further clarification of the sequencing protocol, which is carried out by CDC, in the text (line number 103):
  - "All samples undergo confirmatory testing and genetic sequencing at laboratories that are part of the Global Polio Laboratory Network (GPLN) following a standardised protocol to minimise contamination and maximise sensitivity."

2. In the third paragraph of the methods, the authors note, "Separate datasets were created for serotype 2 and serotypes 1 and 3, and the latter retained a covariate for serotype." While the authors noted that a covariate for serotype exists in the shared dataset, I was wondering why different datasets were not created for each serotype?

- Thank you for the clarifying question. The reason was statistically motivated. The sample size for types 1 and 3 were too small to ascertain meaningful summary statistics. Further the case: infection ratio is similar for serotypes 1 and 3, whereas serotype 2 has a larger case to infection ratio.
- Both of these reasons have now been added to the methods section of the manuscript, lines 153-154:
  - "Separate datasets were created for serotype 2 and serotypes 1 and 3, to account for the small sample size of types 1 and 3 outbreaks and because of the similar case to infection ratio for serotypes 1 and 3. The data set for types 1 and 3 retained a covariate for serotype."

3. Given the impact of vaccination on the emergence of cVDPVs, were the authors able to look at vaccination schemes or vaccination coverage as a covariate for the countries where outbreaks were detected? Or to look at vaccination coverage in these outbreaks in relation to neighboring countries where outbreaks were not detected?

- Routine immunisation coverage was assessed as a potential covariate as we recognised the importance of vaccination schemes. However, the covariate for RI coverage was dropped as inclusion did not result in a model of best fit, as determined by Akaike information criterion (AIC).
- A proposed mechanism by which RI may affect the time from seeding to detection of a VDPV is that in areas of lower RI coverage, there may be an increase in virus circulation, subsequent higher levels of infection and cases, and therefore decreased time to detection. It is possible that RI coverage has more of an impact at a smaller geographical level than at the national level, the level at which this analysis was carried out. In this case, the analysis at the national level may not detect a relationship for RI coverage and time to detection that may exist at a smaller geographical level. We recognise this as a limitation and potential source of a type 1 error.
- This limitation has now been included in the discussion section about limitations,

lines: 349-352.

4. Paragraph 6 in the discussion brings up a great point on the value of environmental surveillance as a tool for earlier detection of cVDPVs. I would suggest moving that higher in the discussion.

- Thank you for this suggestion. This paragraph has now been moved up higher so it is one of the first points in the discussion, line 282 onwards.

Competing Interests: No competing interests were disclosed.