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Evaluation of the Switch from trivalent Oral Poliovirus Vaccine (tOPV) to bivalent Oral Poliovirus Vaccine (bOPV) in 2016: Lessons Learned and Implications for an Anticipated Cessation of bOPV

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- i) Abbreviations
- ii) Definitions
- iii) Brief biographic sketch of authors
- iv) Sounding board members and affiliations
- v) Potential Conflict-of-Interest

## Executive Summary

### Report:

1. Background and Rationale
2. Objective and Methods (Mandate, TORs, Peer review and Public comment)
3. Findings from the evaluation of OPV2 withdrawal (Quantitative & Qualitative)
4. Recommendations for the anticipated bOPV Cessation
5. Conclusions
6. Way Forward (Proposed Priorities)

## Annexes

A. Table summarizing the evaluation of prerequisites and readiness criteria for OPV2 withdrawal.

B. Table summarizing analyses underpinning the findings from evaluation of OPV2 withdrawal.

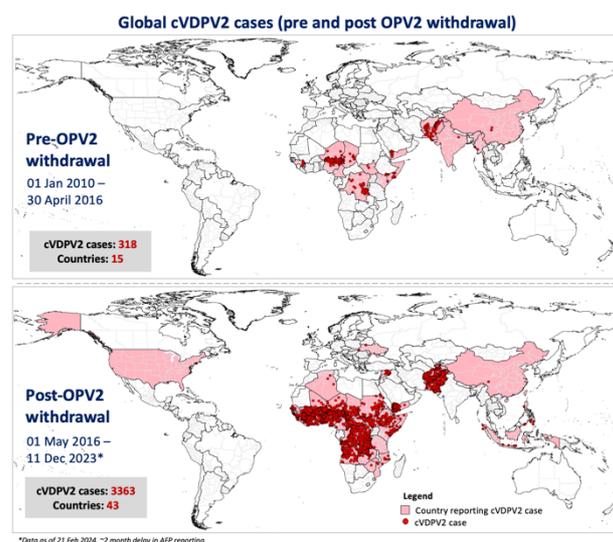
Disclaimer: This draft report represents the views of the switch evaluation team.

## EXECUTIVE SUMMARY

Background and Rationale: To achieve global polio eradication, poliovirus must be removed from populations everywhere, including the Sabin viruses contained in the oral poliovirus vaccine (OPV). While OPV has played a key role in eradication (and reduced the global paralytic case burden by >99.9%), its continued use poses a constant risk of re-establishing poliovirus transmission through circulating vaccine-derived poliovirus (cVDPV), in addition to an increasingly unacceptable burden of vaccine-associated paralytic poliomyelitis (VAPP).

In 2015, the global health community (World Health Assembly [WHA], the governing body of the World Health Organization [WHO]) determined that the conditions were appropriate to withdraw Sabin poliovirus type 2 (OPV2). In April 2016, across a 2-week window, OPV2 was withdrawn globally. The magnitude of the effort was staggering. It represented the largest coordinated public health effort in history, with 155 countries and territories recalling trivalent OPV (tOPV) and replacing it with bivalent (types 1 + 3) OPV (bOPV) (i.e., the “switch”), and 126 countries required to introduce at least 1 dose of inactivated poliovirus vaccine (IPV), as a risk mitigation measure, with some starting as early as 2012.

Although extensive evaluations in the aftermath of the switch generally presented a picture of successful implementation, in the nearly 8 years since the switch we have observed continued and uncontrolled cVDPV2 transmission and a 10-fold increase in the cVDPV2 case burden compared to pre-switch era. The Global Polio Eradication Initiative (GPEI) is currently in a better position to look back and evaluate where we are, why cVDPV2 is still circulating, what lessons we can learn, and how this effort may influence future OPV withdrawal efforts and secure a world free of all polio.



In August 2023, a formal evaluation of the switch was commissioned by the Strategy Committee (SC), the managing body of GPEI.

Objective and Methods: Following approval of specific terms of reference, the evaluation team, consisting of Drs R Sutter and N Molodecky, was established. The evaluation commenced in August 2023 and was completed in April 2024.

The objective of the evaluation was to help better understand what factors led to the continued and uncontrolled cVDPV2 outbreaks following OPV2 withdrawal, to provide recommendations for GPEI strategy and future OPV withdrawal efforts.

The foundation for the evaluation was based on Objective 2: Immunization systems strengthening & OPV withdrawal of the Polio Eradication & Endgame Strategic Plan 2013-2018.

The plan specified the main objectives of OPV2 withdrawal, triggers for executing the switch, along with prerequisites and readiness criteria that needed to be fulfilled to meet the conditions to implement the OPV2 withdrawal.

The evaluation focused on these triggers, prerequisites and readiness criteria and included both qualitative and quantitative methods. Moreover, the evaluation relied on an extensive peer-review process to ensure that the findings were accurate, and the conclusions were supported by the available data and analyses.

Findings: The findings are unambiguous: the switch was an unqualified failure. After nearly 8 years of unsuccessful efforts, 53 countries have been infected or re-infected with circulating vaccine-derived polioviruses type 2 (cVDPV2), resulting in >3,300 children paralyzed by cVDPV2 (across 43 countries), and >\$1.8 billion spent by GPEI on outbreak response.

The single overriding cause of the failure was (and continues to be) the inability of the program to close out outbreaks and stop cVDPV2 transmission. Outbreak response scope, timing and quality have been consistently insufficient, resulting in increased scope and magnitude of cVDPV2 transmission over time (with few improvements over the past few years). This, coupled with the inability or unwillingness of program leadership to recognize the seriousness of the evolving problem and take corrective action after 2016, sealed the fate of the switch.

In addition, 10 factors contributed to or exacerbated the switch failure, including:

- 1) IPV supply constraints, affecting IPV introduction/use in routine immunization (RI) and outbreak control, contributing to high case burden (including in lower-risk countries).
- 2) gaps in pre-switch poliovirus type 2 immunity in critical geographies, resulting in early seeding events and undetected transmission at the time of the switch.
- 3) continued and undetected cVDPV2 transmission at the time of the switch.
- 4) limited progress in RI coverage and lack of alternative strategies to increase coverage, leaving a weak foundation of type-2 immunity and contributing to high case burden.
- 5) limited stockpile of monovalent type 2 OPV (mOPV2), resulting in focused and insufficient outbreak response scope.
- 6) revision of outbreak control Standard Operating Protocols (SOPs), reducing the number of rounds and target population, and elimination of IPV from outbreak response.
- 7) delays in nOPV2 introduction and perceived / communicated risk of mOPV2, resulting in substantial delays in outbreak response.
- 8) left over tOPV vials in storage sites, potentially seeding (at least one) cVDPV2 outbreaks.
- 9) inadequate or late detection of cVDPV2 (both new emergences and ongoing transmission), delaying implementation of outbreak control measures.
- 10) delays in processing and notifying cVDPV2 acute flaccid paralysis (AFP) and environmental surveillance (ES) samples, exacerbating delayed responses.

Recommendations from Lessons Learned: For the anticipated bOPV withdrawal we strongly suggest adopting the following triggers for programmatic execution of cessation:

- no “persistent cVDPV” of any serotype (including cVDPV2). This requires outbreak control and elimination of all current outbreaks and endemic transmission. Persistent cVDPV defined as circulation  $\geq 6$  months after designation of circulating.

Prior to bOPV withdrawal, the program needs to demonstrate that it can control and close out outbreaks within 6 months after designation of “persistent” cVDPVs (i.e., meeting the definition of persistent cVDPV); and

- confirmation of eradication of wild poliovirus (WPV) by the Global Certification Commission (GCC).

In addition, the following 10 prerequisites should be considered:

- 1-3) Vaccine Availability: ensure sufficient stockpile quantities of all required vaccines, especially nOPV1 and ntOPV, continue manufacturing these vaccines, and modify containment specifications to enable production, storage, and laboratory processing.
- 4-6) Population Immunity: conduct preventive supplemental immunization activities (SIAs) that reach and maintain high population immunity (with clearly defined benchmarks and methods of evaluation), design realistic outbreak response SOPs using a back-to-basics approach (with appropriate funding), and institute special strategies in consequential geographies (i.e., Yemen, Eastern Democratic Republic of the Congo, Northern Nigeria, Somalia).
- 7-9) Routine Immunization: design new strategies to reach and maintain threshold levels for herd immunity, use novel OPV2 (nOPV2) in RI in consequential geographies and/or highest risk areas, and accelerate introduction and promote high coverage with hexavalent vaccine, especially in consequential geography countries; and
- 10) Surveillance: further increase surveillance sensitivity and speed of detection/processing for timely notification and action.

The planning for bOPV cessation must also be strengthened: a) commission a plan B (of critical voices); b) compile a detailed risk matrix, risk reduction & risk mitigation, and contingencies for unexpected eventualities; c) define a priori success and failure; d) evaluate progress every 3 months; and e) review status at end of year 2 post-cessation for final determination.

Moreover, to minimize risk and gain experience, consider a phased withdrawal by region, rather than a synchronized global cessation (e.g. low-risk regions go first [European Region, Region of the Americas, Western Pacific Region], then South-East Asian Region, followed by Eastern Mediterranean and African Regions)). Furthermore, developing new ways of rapidly determining population immunity to support real-time decision-making, streamlining the decision-making structure to facilitate programmatic action in the field, and further research into a non-infectious vaccine that induces mucosal immunity, would ensure a path to success.

Conclusions: The lessons for the GPEI are unambiguous. At present, the emperor [i.e., outbreak control] has NO clothes, and achieving the triggers may be virtually impossible without drastic strategy changes. For the anticipated bOPV cessation, it would be better to take the time, get it right, then to rush, and fail spectacularly. A repeated failure cannot be an option. The consequence of failure for bOPV cessation is even greater than for OPV2 (given the 10-fold

higher case to infection ratio for poliovirus type 1). Closer collaboration with RI and a focus on system building (including the design of new strategies to reach the unreached and minimize impact of security-compromised areas), will greatly increase likelihood of success! Furthermore, prioritizing programmatic approaches for outbreak response that incorporate innovative ideas with a consistently implemented back-to-basics strategy (that was used to eradicate WPV from African Continent), will heighten the likelihood of success.

Way Forward: At this juncture in 2024, the program is neither ready for a next cessation attempt or in a position to rapidly control the massive outbreaks of cVDPV2 on the African continent. Until GPEI has eliminated the chains of cVDPVs transmission (and eradicated WPV1), it should diligently improve the enabling conditions for the anticipated bOPV cessation.

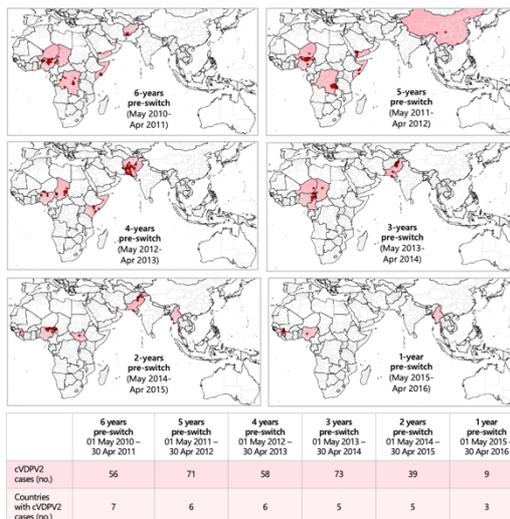
Despite the severe setback, achieving polio eradication is only realizable with removing poliovirus from populations everywhere. Currently, we have an opportunity to capitalize on control efforts recently implemented or in development that may facilitate cVDPV2 elimination, including increased population immunity due to large amounts of mOPV2/nOPV2 used, adoption of a two-dose IPV RI schedule in most countries, and new vaccine products (including novel OPVs, ideally as combination products, and hexavalent vaccine) on the horizon. Together, these policies and products provide a sound foundation for immunity, and together with a strong re-commitment to eradication, coupled with improved conditions for programmatic action, will accelerate cVDPV2 elimination and lead us to global polio eradication, once and for all.

## 1. BACKGROUND AND RATIONALE

In 2023, the Strategy Committee (SC), the managing body of the Global Polio Eradication Initiative (GPEI), commissioned a formal evaluation of the 2016 global withdrawal of OPV2 and switch from tOPV to bOPV (the “switch”). While the switch was initially perceived to be an overwhelming success, the global cVDPV2 case burden has increased 10-fold compared to pre-switch era. The evaluation was intended to generate critical lessons learned, in order to guide the direction of the GPEI, including future OPV withdrawal efforts (i.e., bOPV).

In order to achieve global eradication of polio, poliovirus needs to be removed from populations everywhere, including the Sabin viruses in oral poliovirus vaccine (OPV). While OPV has played a key role in polio eradication and reduced the global polio case burden by >99.9%, its continued use is not compatible with eradication. OPV is a live-attenuated vaccine. It is genetically unstable and can revert rapidly back to neurovirulence and transmissibility after weeks of replication in a single vaccinee or after prolonged replication in a community, causing vaccine-associated paralytic poliomyelitis (VAPP) and circulating vaccine-derived polioviruses (cVDPV), respectively. The continuing VAPP burden due to tOPV (~200-400 cases each year) was becoming more and more unacceptable to parents and health care providers. Moreover, cVDPVs, typically emerging and spreading in populations of low immunity were becoming increasingly concerning (and would continue to increase due to decline in preventive SIAs). With declining WPV cases and relatively larger cVDPV case burden, withdrawal of OPV became increasingly urgent since continued use of Sabin type 2 in OPV2 appeared to do more harm than good. Since the last detection of indigenous wild poliovirus type 2 (WPV2) was in 1999 and cVDPV2 outbreaks were reported each year (Figure), OPV2 was selected as the first Sabin vaccine serotype to be withdrawn globally.

Global cVDPV2 cases pre switch (May 2010-Apr 2016)



The globally synchronised withdrawal of OPV2 (i.e., ‘switch’ from tOPV to bOPV) occurred in April 2016, across a 2-week period, in all 155 OPV-using countries and territories (Figure). It represented the largest coordinated public health effort in history, as well as the largest recall of a medicinal product and the fastest introduction of a vaccine (i.e., inactivated poliovirus vaccine, IPV). Routine immunization (RI) switched from tOPV to bOPV and subsequent campaigns could only use bOPV. All remaining OPV2-containing vaccines were to be destroyed as they posed a risk of seeding new cVDPV2 outbreaks. As a risk mitigation measure (primarily to reduce the paralytic burden caused by poliovirus type 2 in a world where OPV2 contribution to type 2 humoral and mucosal immunity was no longer available), all OPV-using countries introduced  $\geq 1$  dose of IPV into RI.

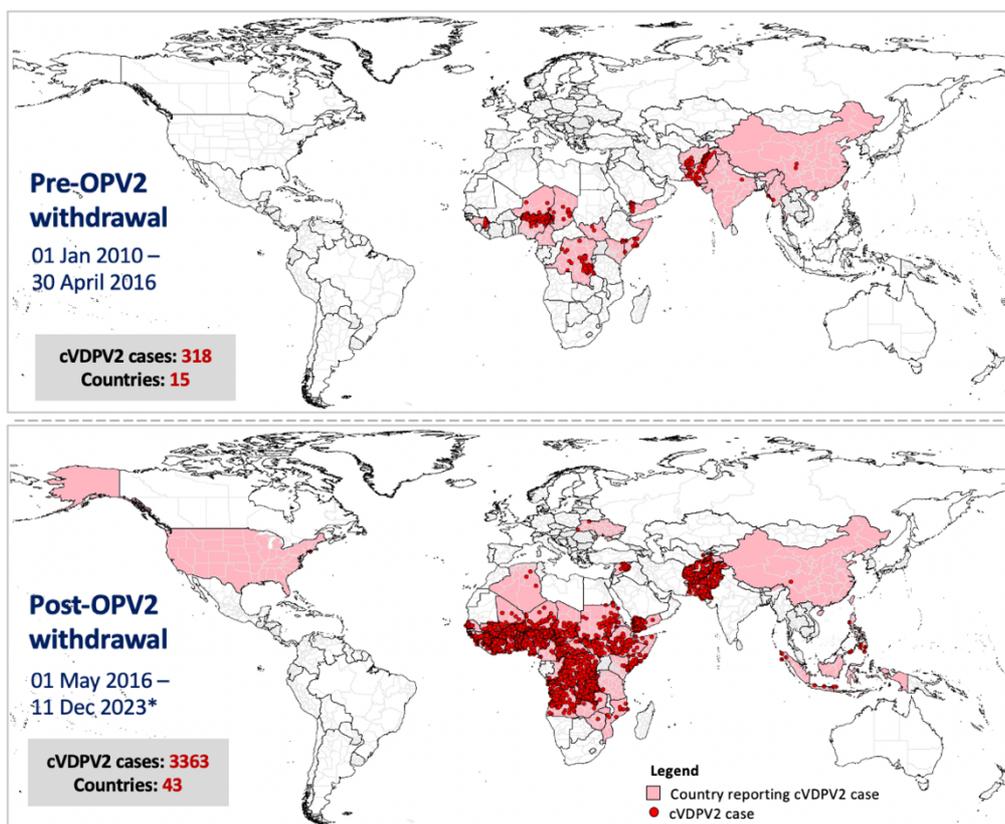
Countries where OPV2 was withdrawn in April 2016



The GPEI was aware that the first two years following OPV2 withdrawal were critical, as susceptible birth cohorts accumulated and type-2 mucosal immunity waned rapidly, especially in countries with suboptimal hygiene and sanitation. The GPEI was also cognizant that it needed to rapidly control any cVDPV2 outbreak before the outbreak virus could spread and infect other geographies, preventing a downward spiral of vaccine use leading to new cVDPV2 seeding, requiring more vaccine.

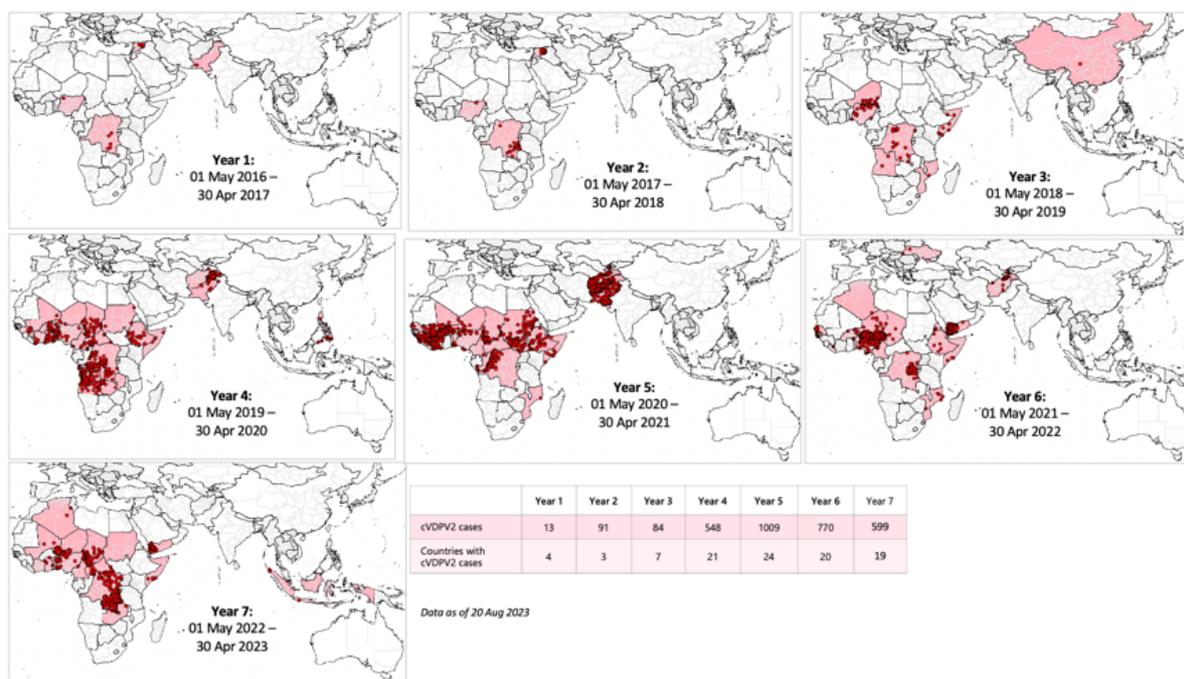
OPV2 withdrawal marked a turning point in global polio eradication. With OPV2 cessation, the GPEI entered the polio end game, trying to eliminate the vaccines that brought the initiative to the brink of success. Many evaluations were conducted immediately following OPV2 withdrawal (REF JID), highlighting the success of the effort. The early evaluations reported that the many prerequisites and readiness criteria for a successful switch had largely been met (Annex A). However, eradication is unforgiving and an all-or-nothing goal, as demonstrated by wild poliovirus (WPV), whereby the >99.9% reduction in cases still qualifies as a failure. Therefore, despite excellent planning and implementation, the switch must be judged on outcome and not on effort.

Since OPV2 withdrawal, there have been >3,300 cVDPV2 cases across 43 countries globally (Figure). This contrasts ~300 historic cases across 15 countries leading up to the switch across a similar duration of time. A 10-fold increase in cVDPV2 cases has been observed since the world withdrew OPV2, the intention of which was to wipe out the cVDPV2 case burden. Historically, the programme would observe <80 cVDPV2 cases annually across fewer than 10 countries, and since 2019, we have been observing >500 cVDPV2 cases annually across >20 countries. The worst-case scenario materialized and GPEI struggled to respond.



\*Data as of 21 Feb 2024. ~2 month delay in AFP reporting.

### Global cVDPV2 cases post switch (May 2016-Apr 2023)



In the first two years following OPV2 withdrawal, the global cVDPV2 situation was promising with only 3-4 infected countries (Pakistan, Syria, DRC and Nigeria) and cVDPV2 cases being focused to select geographies within these countries (Figure). While outbreaks in Pakistan and Syria were interrupted, ongoing transmission (and seeding) in Nigeria and DRC posed immense challenges, with local and cross-national spread into neighboring countries. This, coupled with detection of “silent” transmission in 7 countries, led to larger scope of transmission, surpassing pre switch era. The point of no return for the programme occurred between years 3 and 4, with an increase in cVDPV2 case burden from 84 (from 7 countries) to 548 (from 21 countries). With >80% of the entire cohort susceptible, we were in uncharted territory. In year 5, a peak case burden of >1,000 was observed, and transmission was beginning to appear endemic-like. These patterns have continued, but with detections becoming increasingly more divergent, indicating ongoing and long-term cVDPV2 transmission. While there has been modest progress over the past year, much work remains to be done.

In order to move forward, the GPEI must better understand what has led to the continued and uncontrolled cVDPV2 outbreaks post OPV2 withdrawal. This is critically important not only to address current programmatic issues to interrupt cVDPV2 transmission but inform strategy and planning for bOPV withdrawal. Emerging challenges with cVDPV1 parallel those we observed with cVDPV2 in the years leading up to the switch. We must ask ourselves, “Are we better prepared as to not repeat history?”. With the 10-fold higher case to infection ratio for poliovirus type 1 (i.e., 1/200 versus 1/2000), there is a greater consequence of failure.

While many evaluations were conducted immediately following OPV2 withdrawal (REF JID), currently at nearly 8 years since the switch from tOPV to bOPV, the evaluation team is in a unique position to look back and evaluate what worked, what didn’t work, and which factors contributed most to epidemiology we have observed. With findings from the evaluation, the GPEI is in a better position to chart a path forward to success and a world free of poliovirus.

## 2. OBJECTIVE AND METHODS

The objective of the evaluation was to help better understand what factors led to the continued and uncontrolled cVDPV2 outbreaks following OPV2 withdrawal, in order to provide recommendations for GPEI strategy and future OPV withdrawal efforts. The timing of this evaluation coincided with the initial planning phase of bOPV cessation.

The evaluation was based on approved terms of reference (TORs) and conducted by an external team of two polio experts. The evaluation team was composed of Drs R Sutter & N Molodecky and funded by the US Centers for Disease Control and Prevention (CDC), a GPEI core partner organization. The evaluation started in August 2023 and was completed at the end of April 2024. The evaluation team was external to GPEI and asked to conduct a “tough but fair” review.

The foundation for the evaluation was based on Objective 2: Immunization systems strengthening & OPV withdrawal of the Polio Eradication & Endgame Strategic Plan 2013-2018. The plan specified the main objectives of OPV2 withdrawal, which were to strengthen immunization services in “focus countries”, introduce IPV, and withdraw OPV2 globally. The plan also specified a trigger for executing the switch, along with prerequisites and readiness criteria that needed to be fulfilled to meet the conditions to implement the OPV2 withdrawal. Subsequently, some of the prerequisites were clarified as readiness criteria (WER 2014;89:561-567).

The trigger, prerequisites and readiness criteria devised in advance of the switch included:

1) confirmation of WPV2 eradication; 2) validation of elimination of “persistent” cVDPV2; 3) bOPV licensed for RI; 4) sufficient bOPV product for all OPV-using countries; 5) globally-coordinated cessation of all tOPV use; 6) all remaining stocks of tOPV collected and destroyed; 7) phase II biocontainment for all type-2 cVDPV and WPVs; 8) sufficient supply and affordable IPV options for all OPV only-using countries; 9) introduction of at least one dose of IPV in OPV only-using countries; 10) strengthened RI coverage (10% annual increase in high risk areas); 11) high type-2 immunity in all geographies; 12) type 2 poliovirus surveillance and response protocols; 13) surveillance capacity to detect cVDPV; and 14) mOPV2 stockpile and response capacity.

These trigger, prerequisite and readiness criteria were evaluated (both quantitatively and qualitatively) by following a model that is organized into the following seven evaluation steps:

1. Identify elements for evaluation (trigger, prerequisites and readiness criteria).
2. Determine a standard against which to evaluate each element (directly obtained from the Strategic Plan 2013-2018). In instances where a standard was not specified in the Plan, the evaluation team proposed standards to a “sounding board” of global polio experts (details below) for review, modification and endorsement.
3. Evaluating the standard versus what was achieved.
4. Estimating the implication of a “failing” standard.
5. Determining the relevance of the “failing” standard (to the planned bOPV cessation).
6. Compiling the lessons learned (for bOPV cessation).
7. Drawing policy implications and recommendations.



The peer review process and the gathering of public comment was a high priority of the evaluation process: It included input from key stakeholders, across GPEI core partner organizations, and addressed all levels of policy, strategy and implementation. A “sounding board” of senior polio experts from around the world was established to provide ongoing detailed comment and guidance on the respective evaluation and the implications for the bOPV cessation. Specifically, the board reviewed the newly proposed trigger and prerequisites for the bOPV cessation.

In addition, calls for public comment were issued at the beginning and near the end of the evaluation process. Preliminary findings were discussed individually with each of the GPEI core partner organizations (WHO, UNICEF, CDC, BMGF, Rotary International & GAVI), WHO AFRO and EMRO for regional country-level perspectives and WHO’s technical oversight committees (SAGE Polio Working Group on 7-8 February 2024, and SAGE in March 10-14 March 2024).

After concluding the quantitative and qualitative evaluation, a summary of preliminary findings and recommendations was presented to several audiences for comment and suggestions, including the BOCet (bOPV Cessation Evaluation Team) on 18 January 2024, GPEI’s Strategy Committee (SC) on 1 February 2024, the SAGE (Strategic Advisory Group on Immunization) Polio Working Group on 7 February 2024, the full SAGE on 12 March 2024. In addition, the draft report was made available for public comment. After careful consideration of all inputs, the evaluation team finalized this report of their findings.

Although many contributed to making the findings more succinct and actionable, the final conclusions and suggestions contained in the report are owned entirely by the evaluation team.

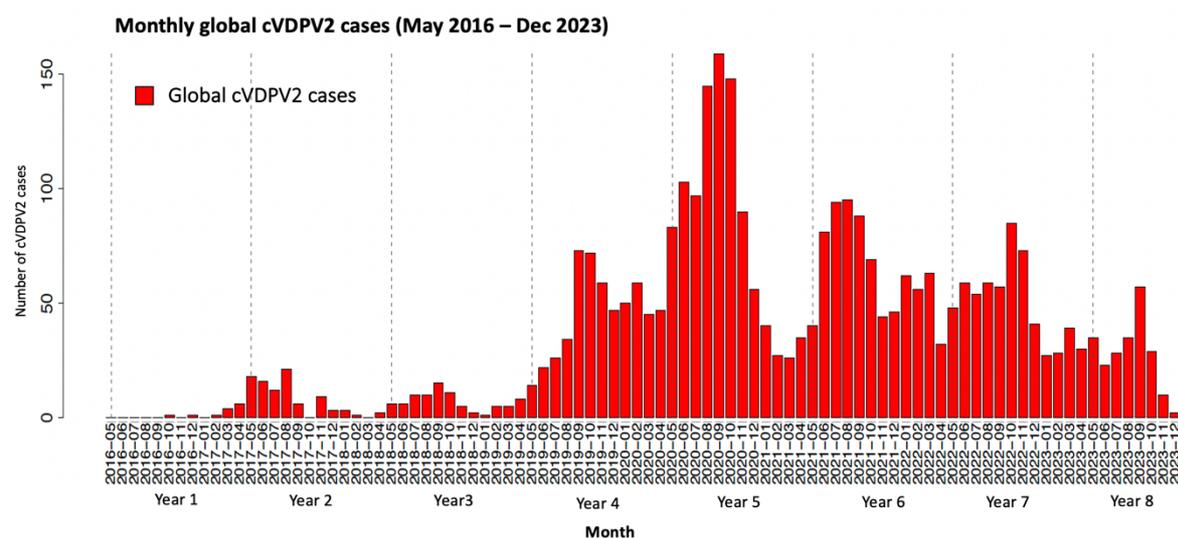
### 3. FINDINGS FROM THE EVALUATION OF OPV2 WITHDRAWAL

The outcome following our evaluation is unambiguous: the switch was an unqualified failure. After 8 years of unsuccessful programmatic efforts, 53 countries were infected or re-infected with cVDPV2, >3,300 children paralyzed by cVDPV2 (across 43 countries), and the GPEI expended >\$1.8 billion just on outbreak response. To contrast, between January 2010 and 30 April 2016 a total of 318 cases were detected globally in 15 countries. Therefore, the worst-case scenario developed, and continues to paralyze children in many countries globally.

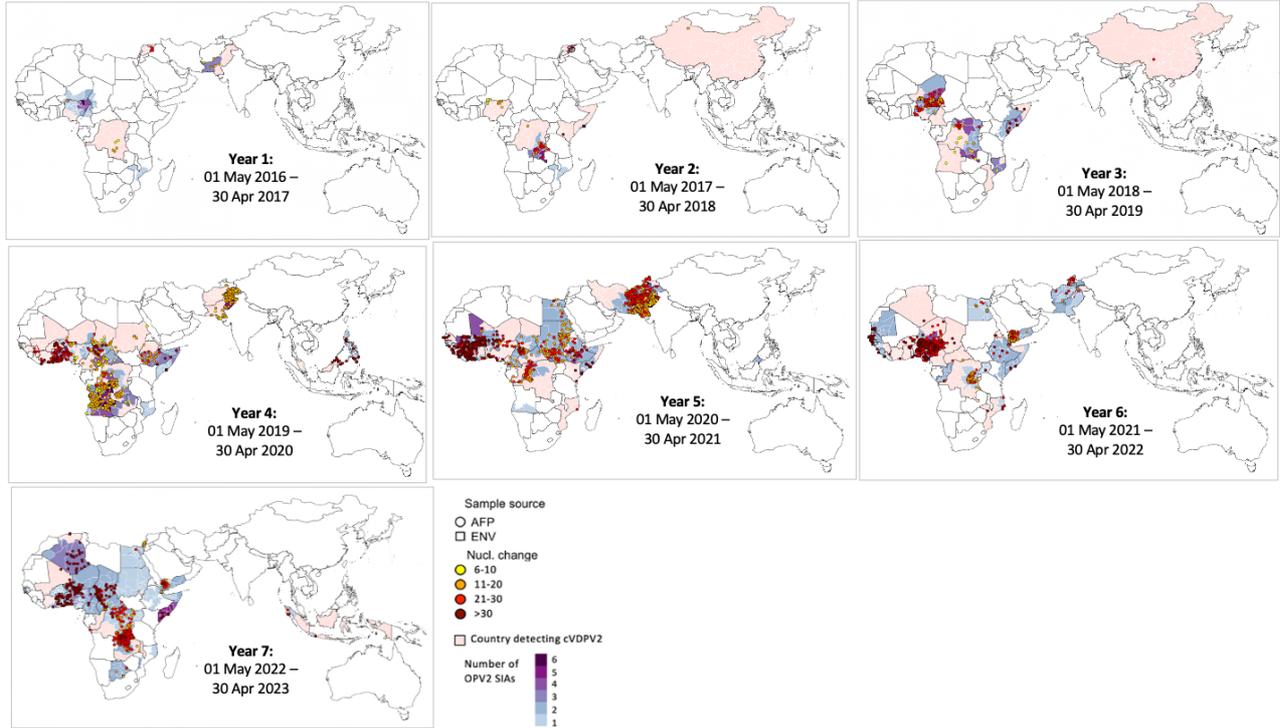
Although extensive evaluations in the aftermath of the switch generally presented a picture of successful implementation, it has been nearly 8 years and we have been unable to stop cVDPV2 transmission. The scope and magnitude of cVDPV2 transmission has increased over time, with limited improvements over the past few years (Figure). Moreover, we continue detecting highly divergent virus, indicating ongoing and long-term cVDPV2 transmission (Figure). While continued seeding of new cVDPV2 emergences (despite extensive nOPV2 use) is concerning, ongoing transmission remains the greatest challenge (Figure).

While OPV2 cessation was a monumental undertaking of unprecedented scale, however, it must be judged on the outcome and not the tremendous effort. As with the eradication of wild poliovirus (WPV), which is an all or nothing event (and despite >99.9% reduction in poliomyelitis cases, WPV continues to circulate in Afghanistan and Pakistan), the same principle must apply to cVDPV2 elimination.

Below we provide a summary of our findings, including: i) key factor(s) in the switch failure; and ii) factors that contributed to or exacerbated the switch failure. Details are presented in Annex A and B.

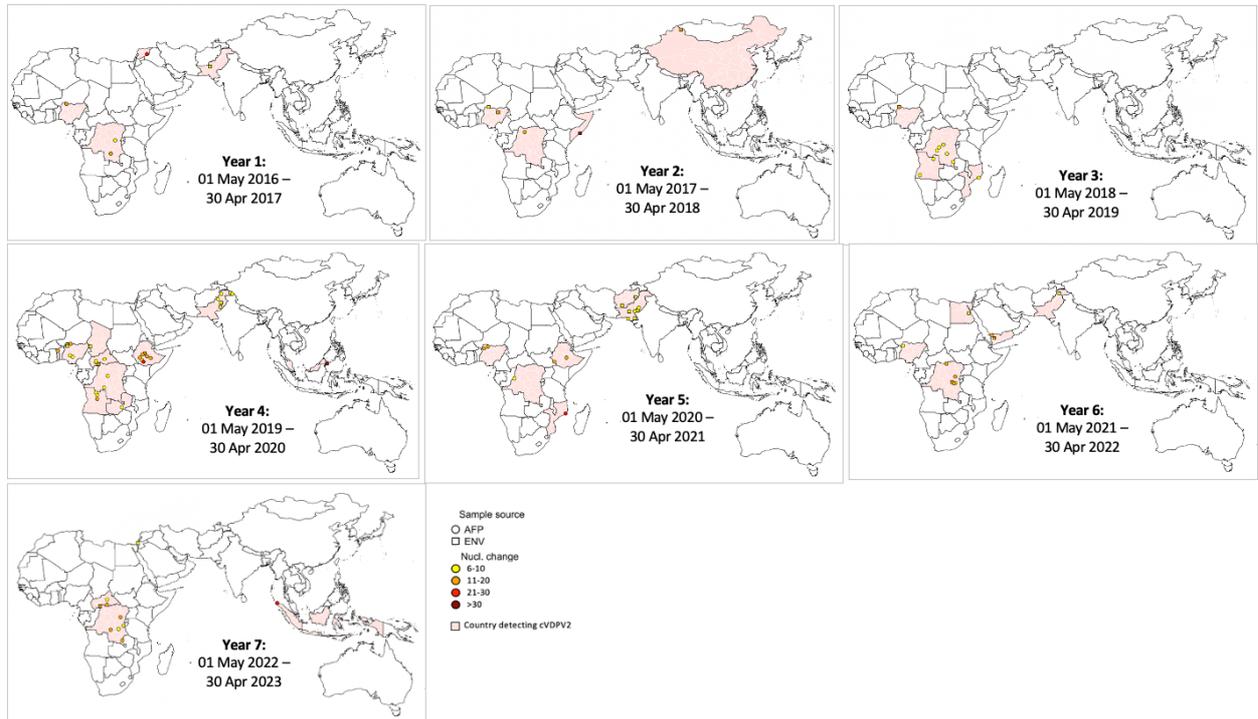


### cVDPV2 epidemiology and outbreak response post switch



Data as of 20 Aug 2023

### New cVDPV2 emergences post switch



Data as of 20 Aug 2023

Nucleotide (nt) change is a measure to quantify duration of transmission, under the assumption of a molecular clock of ~1% (or  $\geq 10$ nt emanating from sequence window of 906 nt in viral protein 1 [VP1]) mutations per year. Nt change per se is unrelated to paralytic rate (i.e., reversion to neurovirulence), and is tracked in a different region of the viral genome (i.e., VP1 region). Loss of the attenuating mutations (in the 5' untranslated region, UTR) are typically assumed to occur quickly, resulting in viral transmission and paralytic rate indistinguishable from WPV.

## Key factor(s) in the switch failure:

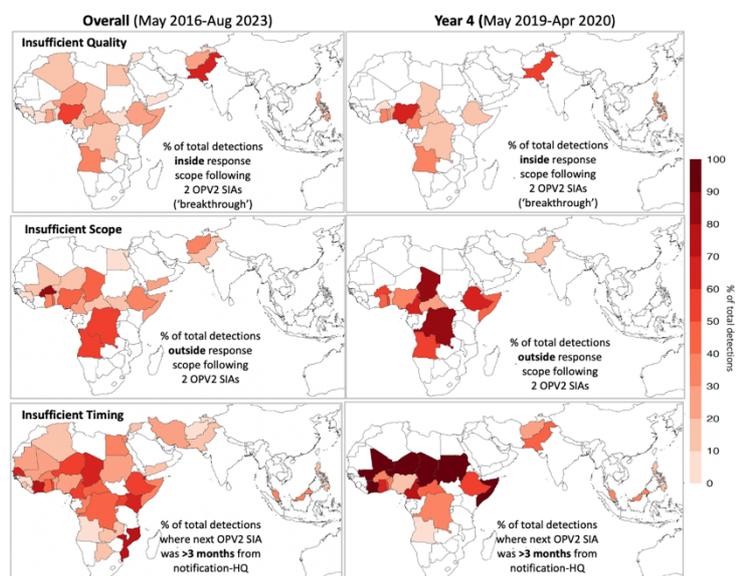
The single overriding cause of the OPV2 cessation failure was (and continues to be) the inability of the program to close out outbreaks. While seeding of new cVDPV2 outbreaks has played an important role, it has been the program's lack of ability to stop transmission that has been the greatest contributor to the switch failure. Equally important, the inability or unwillingness of the GPEI leadership to recognize the seriousness of the evolving problem and take corrective action sealed the fate of the switch.

**Key factor 1:** Consistently insufficient outbreak response scope, timing and quality, resulting in increased scope and magnitude of cVDPV2 transmission, impacting vaccine supply and surveillance.

**Requirement:** Sufficient capacity to stop cVDPV2 outbreaks post switch, ensuring timely, high quality responses of sufficient scope.

**Evaluation and implications:** The program's lack of capacity to stop cVDPV2 outbreaks (especially in the first three years, when we had a foundation of type-2 immunity), was the greatest contributor of continued and uncontrolled cVDPV2 outbreaks, straining vaccine supply and surveillance capacity.

While quality of OPV2 responses remained sub-optimal in many of the highest-risk countries (especially those in which response scope is typically large, i.e., Pakistan and Nigeria), inadequate scope and timing were greater issues (especially in DRC, Chad, Angola and Burkina Faso), contributing most to the increased scale of transmission (Figure). This is particularly true in year 4 (which was the turning point for the program), when 42% and 43% of cVDPV2 detections were outside of the response scope following 2 OPV2 SIAs and the next OPV2 SIA was >3 months from notification to HQ, respectively. In comparison, 26% of cVDPV2 detections were inside the response scope following 2 OPV2 SIAs (i.e., breakthrough), indicating insufficient quality (definitions and brief methods described below). The program's focus has typically been placed on addressing issues with quality; however, ensuring adequate scope and timing of responses, which are inextricably linked (i.e., substantial delays in response lead to outdated, and therefore insufficient, scope), are critically important and often overlooked, despite being more directly in the programs' control. There are many factors that led to insufficient scope and timing of response (including vaccine supply constraints, waiting for nOPV2 due to communicated/perceived risk of mOPV2), which will be highlighted in the subsequent sections.



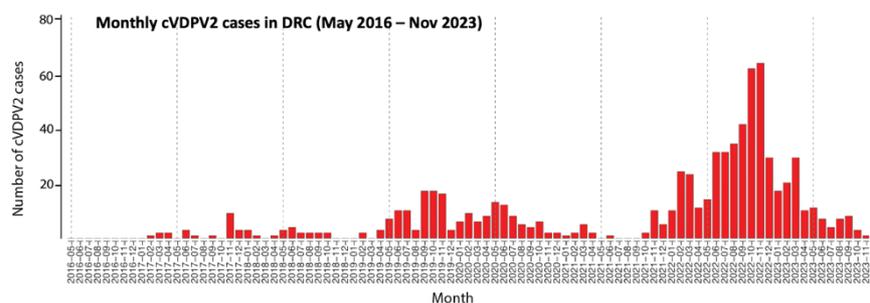
**Lessons for bOPV withdrawal:** Outbreak response capacity must be improved before future withdrawal efforts. It will likely be the critical factor determining success or failure of the GPEI. We must remember that these countries interrupted WPV, indicating that stopping transmission in these populations is possible.

Definitions and methods of determining insufficient quality, scope and timing of responses: For each cVDPV2 detection through AFP or ES, it may be classified as resulting from insufficient quality or scope based on the OPV2 SIAs implemented or absent in the previous 6-months (from date of onset or collection, factoring in a 21-day buffer) in the particular admin1. If  $\geq 2$  OPV2 SIAs were implemented in the admin1 of the detection in the previous 6-months, it would be classified as resulting from insufficient quality. If  $\geq 2$  OPV2 SIAs were implemented within the country's National boundaries, but not in the admin1 of the detection, in the previous 6-months, it would be classified as resulting from insufficient scope. Different emergences were not separated, as outbreak response does not differentiate between emergence groups but bases responses simply on presence or absence of detections. Moreover, whether subsequent detections within the OPV2 response zone are due to ongoing transmission or new emergence, both indicate insufficient quality. Similarly, whether subsequent detections outside of the OPV2 response zone (but within National boundaries) are due to ongoing transmission or new emergence, both indicate insufficient scope of response. Detections of insufficient quality and scope are mutually exclusive. Insufficient timing was defined as  $>3$  months between when the detection was notified to HQ and the subsequent OPV2 SIAs in the admin1.

**Key factor 2:** Inability or unwillingness of GPEI leadership to recognize the seriousness of the evolving problem and take corrective action.

**Requirement:** Not considered

**Evaluation and implications:** In the nearly 8 years since the switch, we have been unable to stop cVDPV2 outbreaks. The overall magnitude and scope of transmission has increased, and we continue detecting highly divergent virus. In high-risk areas, such as DRC, we have seen an increase in transmission and case burden over the past few years, not a decline (Figure), indicating we still have not learned how to close out cVDPV2 outbreaks in these critical geographies. One wonders where we would be if the early detections in Nigeria and DRC had been successfully interrupted, as was done in Pakistan and Syria. The narrative would be very different. Recognizing the likelihood that some detection of virus post switch is inevitable (despite best efforts at consistently sensitive surveillance and high levels of immunity across all geographies), being able to interrupt early transmission while base levels of immunity is high is essential.



**Lessons for bOPV withdrawal:** This evaluation is coming at nearly 8 years following the switch. A formal review at year 2 or 3 would have ensured corrective measures were implemented before transmission of cVDPV2 became endemic-like in many high-risk countries. Ensuring continuous evaluation of progress and course correction, as needed, is essential for a successful bOPV withdrawal.

## Factors that contributed to or exacerbated the switch failure:

There were 10 factors that contributed to or exacerbated the switch failure.

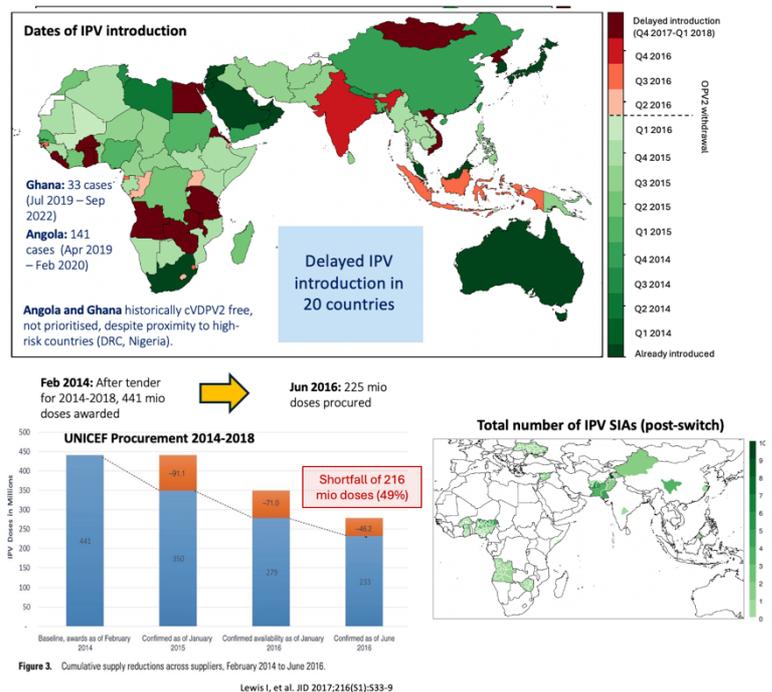
### 1. IPV supply constraints, affecting IPV introduction/use in routine immunization (RI) and outbreak control, contributing to high case burden (including in lower-risk countries)

**Requirement:** As a risk mitigation measure,  $\geq 1$  dose of IPV was expected to be introduced into RI of all OPV using countries prior to the switch. IPV was also initially recommended for outbreak response, to be used in the second SIA targeting a large scope. The rationale was to quickly close humoral immunity gaps and boost mucosal immunity, with no risk of seeding.

**Evaluation and implications:** By 2015, it had become clear that we would not have sufficient IPV supply to ensure full introduction into all OPV using countries, as a risk mitigation measure. At the time of the switch in 2016, the program had secured only half of the required supply of IPV (i.e., 233 million doses, a shortfall of 208 million doses). Given the limited supply of IPV, countries were prioritized for introduction into RI based on historic cVDPV2 outbreaks and ongoing WPV1 transmission.

Supply constraints resulted in delayed RI IPV introduction into 20 countries, deemed to be lower risk (Figure). In addition, 16 additional countries faced stock-outs impacting their IPV delivery. Some of these de-prioritised countries (historically free of cVDPV2) reported large cVDPV2 outbreaks. For example, Ghana and Angola, historically free of cVDPV2, were not prioritized for IPV, despite their close proximity to our highest-risk countries (DRC, Nigeria). Both countries reported large cVDPV2 outbreaks (Angola: 141 cVDPV2 cases between Apr 2019-Feb 2020) and Ghana: 33 cVDPV2 cases between Jul 2019-Sep 2022).

Moreover, due to supply shortage, IPV was quickly removed as a recommended tool for cVDPV2 outbreak response. Despite high cVDPV2 case burden globally, there has been limited IPV use in cVDPV2 outbreak response. Since OPV2 withdrawal, IPV has been used as an adjunct in outbreak response in only 14 countries globally (Figure). In the African Region, which has contributed to  $\sim 71\%$  of global cVDPV2 cases since the switch, only 6 countries have conducted IPV SIAs, 4 of them as catch-up due to delayed IPV introduction (Angola, Ghana, Burkina Faso and Zimbabwe), Nigeria (recently WPV1 endemic) and Burundi. Similarly, in the Eastern Mediterranean Region ( $\sim 27\%$  of global cases), apart from Pakistan and Afghanistan, which remain WPV1 endemic, only Syria and Somalia have conducted IPV SIAs.



While the use of fractional IPV (fIPV), as a dose sparing strategy, was recommended by SAGE in 2017 and could have potentially addressed the early supply constraints of IPV, it was only adopted into RI in select countries (i.e., India, Nepal, Sri Lanka, Bangladesh, Ecuador, and Cuba) and its use in cVDPV2 outbreak response was limited to India, Pakistan and Nigeria. The greatest barrier to widespread use of fIPV in both RI and SIAs was operational feasibility of vaccine administration through the intradermal (ID) route. While ID adapters facilitating the ease of administering fIPV are available and have demonstrated safety and injection quality, costs of devices have largely limited its widespread use. Furthermore, as ID fIPV is considered off-label, it requires additional approvals for use in country, increasing the complexity of use.

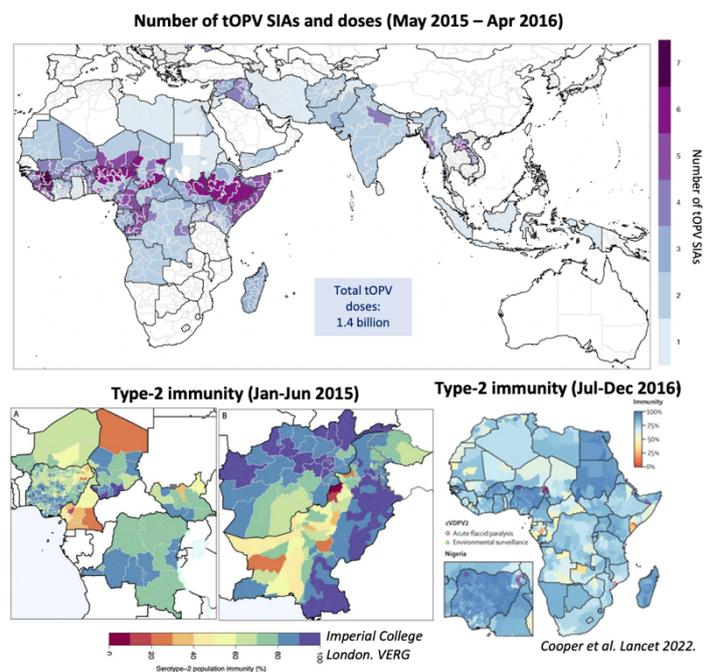
**Lessons for bOPV withdrawal:** Ensuring sufficient IPV supply for RI (and outbreak response) across all countries (even those deemed lower risk) is critical in advance of global OPV cessation. This may include adoption of new strategies (e.g., fIPV), especially for outbreak control, that ensure continued sufficient supply of IPV.

2. Gaps in pre-switch poliovirus type 2 immunity in critical geographies, resulting in early seeding events and undetected transmission at the time of the switch

**Requirement:** Type-2 immunity at the time of the switch was expected to be high to reduce risk of cVDPV2 emergence/spread. To ensure high immunity, countries were required to implement tOPV SIAs prior to OPV2 withdrawal. Type-2 immunity was estimated in early 2015 to guide number of tOPV SIAs required.

**Evaluation and implications:** In 2015, known poliovirus type 2 immunity gaps were identified in many high-risk geographies (Figure). While most countries conducted  $\geq 2$  tOPV NIDs in the year leading up to the switch (with additional rounds in the highest-risk areas), pockets of low immunity remained. This is supported by early cVDPV2 detections in Nigeria, Pakistan and DRC (all of which were seeded from pre-switch tOPV use), and later detections in Somalia, Syria and the Philippines that remained “silent” at the time of the switch.

The rush to fulfil requirements in advance of the switch, led to inadequate immunity and critical seeding events that set us up for failure. For example, in DRC, 2 NIDs were conducted back to back in March and April 2016 following nearly 1-year without OPV2 SIAs. Seeding events were detected ~1 year later, which resulted in cascading cycles of transmission and seeding. DRC has reported >700 cVDPV2 cases since the switch with cases reported in 70/82 total months.

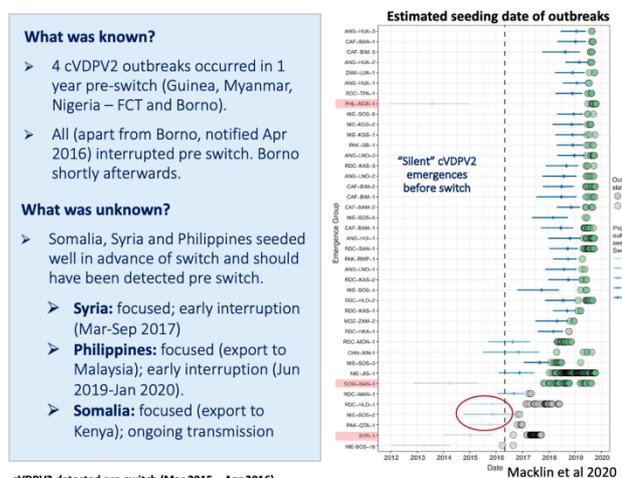


**Lessons for bOPV withdrawal:** Leading up to OPV withdrawal, additional focus to increase and maintain immunity in priority countries is required (especially known pockets of low immunity), with numerous OPV SIAs spread throughout the year prior to withdrawal.

### 3. Continued and undetected cVDPV2 transmission at the time of the switch

**Requirement:** In advance of the switch, all countries needed to be free of ‘persistent’ cVDPV2 (i.e., cVDPV2s of the same genetic lineages in circulation for  $\geq 6$  months). The criteria specified that the period of absence of persistent cVDPV2 was between March-September 2015, to allow for decision-making. If detected, the switch was to be delayed until at least April 2017. Note that there was no information provided on action for detections between October 2015 to April 2016.

**Evaluation and implications:** Four cVDPV2 outbreaks were detected between Mar 2015 and Apr 2016 (Guinea, Myanmar, Nigeria – FCT and Borno). All were interrupted pre switch, using tOPV SIAs, apart from Borno, notified April 2016, which was interrupted shortly afterwards.



**cVDPV2 detected pre-switch (Mar 2015 – Apr 2016)**

Country	Admin1	Source	Date of onset/coll.	Date of notif. to HQ	Nt change	Comments
Guinea	Kankan	6 cases	20.07.2015 - 14.12.2015	04.09.2015 - 18.02.2016	22-27	7 tOPV SIAs (Sep 2015 – Apr 2016). Interrupted transmission before switch.
Myanmar	Rakhine	2 cases	16.04.2015, 05.10.2015	11.11.2015	13-15	5 tOPV SIAs (Dec 2015 – Apr 2016). Interrupted transmission before switch.
Nigeria	FCT	1 case	16.05.2015	?	13	3 tOPV SIAs (Jul 2015 – Apr 2016). Interrupted transmission before switch.
	Borno	1 ES	23.03.2016	29.04.2016	32	

However, there were at least 3 outbreaks that went undetected, including Somalia, Syria and the Philippines, with cVDPV2 seeded in these geographies well in advance of the switch. These undetected outbreaks remained fairly focused in scope and/or interrupted shortly after detection (the exception for the latter is Somalia, with continued transmission for nearly 10 years, despite being relatively focused in scope). Syria interrupted early (March-September 2017) and remained focused; Philippines interrupted early (June 2019-January 2020) and remained focused (apart from exportation to Malaysia); and Somalia remained focused (apart from exportation to Kenya).

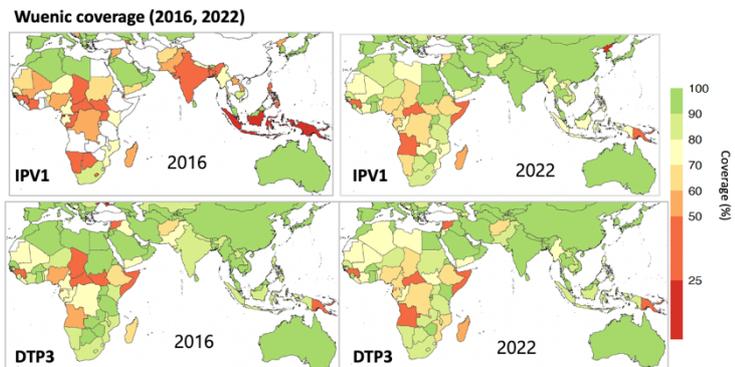
Other undetected outbreaks (DRC, Nigeria, Pakistan) were seeded from tOPV use in the 1-year leading up to switch. If these had been detected pre-switch, they may not have been classified as ‘persistent’. These seeding events in DRC and Nigeria resulted in cascading effects of transmission and seeding, setting off many of the ongoing cVDPV2 outbreaks.

**Lessons for bOPV withdrawal:** Maintaining and further enhancing surveillance is critical in advance of OPV withdrawal. Clear definition, time window and action following detections is required.

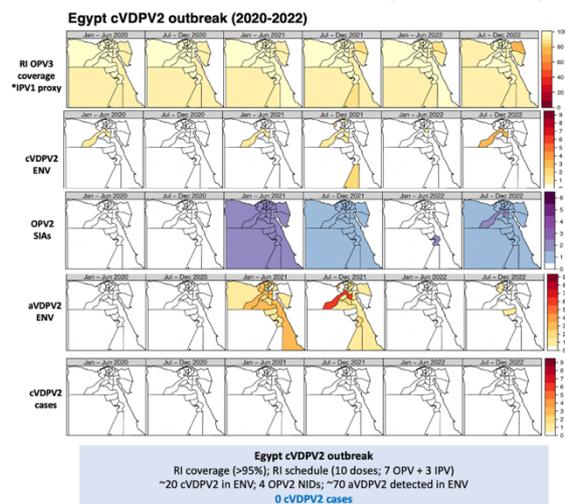
### 4. Limited progress in RI and lack of alternative strategies to increase coverage, leaving a weak foundation of type-2 immunity and contributing to high case burden

**Requirement:** To ensure impact of IPV in RI, ‘sufficient’ coverage was required, with emphasis on system strengthening (i.e., 10% increase in RI coverage annually, in highest risk geographies).

**Evaluation and implications:** The GPEI (in partnership with IVB) continues to set targets for improvements in RI (i.e., 10% annual increase in Strategic Plan) without making substantial improvements that result in meaningful impact. The lack of progress in RI system strengthening in high-risk countries limited the benefit of IPV and contributed to the high cVDPV2 case burden. IPV1 coverage has remained <80% at the National-level across high-risk geographies, with many countries reporting coverage <60% and <50% (WUENIC), along with substantial sub-national heterogeneity.



Strong RI systems are critical to mitigate impact of cVDPV outbreaks. Egypt provides an excellent example as to what can be achieved with a solid foundation of RI (Figure). Egypt has consistently high (>95%) and homogeneous RI coverage. They reported a cVDPV2 outbreak between 2020-2022. Despite many cVDPV2 detections in ES across the country, and many seeding events due to sub-optimal quality of 4 OPV2 NIDs (plus additional rounds in select areas), no cVDPV2 cases were reported. Egypt was treated as a success story, despite transmission for ~2 years. The foundation of IPV provided Egypt time to interrupt transmission and “get things right”, without facing the immediate consequence of cases. In the absence of strong RI, cVDPV2 case burden in Egypt would have been high. In contrast, DRC with RI as low as 38% (and no IPV SIAs), reported >700 cVDPV2 cases. Strong RI will be of even greater importance for type-1 (due to higher-case to infection ratio).

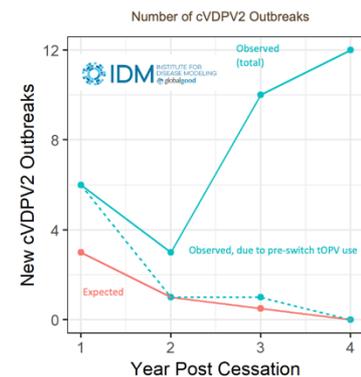


**Lessons for bOPV withdrawal:** Strong RI systems are critical to prevent case burden from cVDPV outbreaks. Greater improvements in high-risk geographies are essential in advance of bOPV withdrawal.

## 5. Limited stockpile of mOPV2 vaccine, resulting in focused and insufficient outbreak response scope

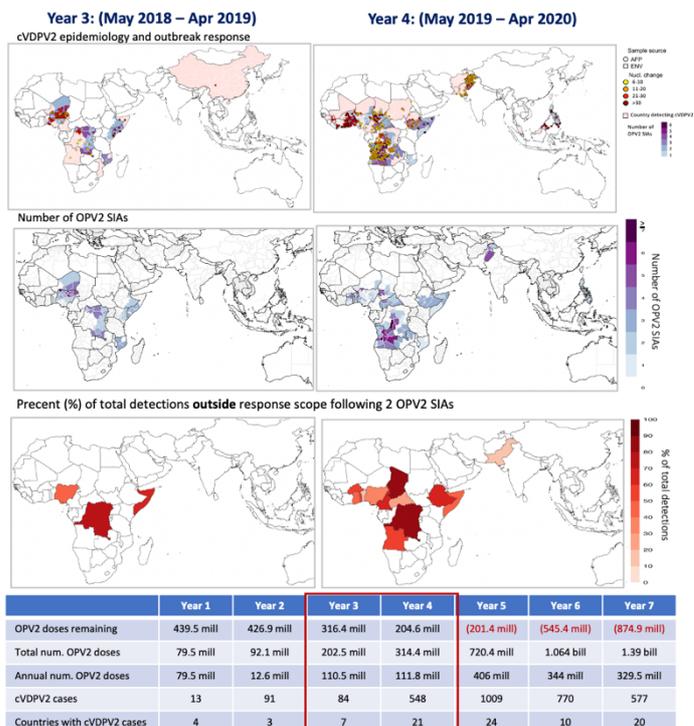
**Requirement:** A global stockpile of mOPV2 was required to respond to cVDPV2 outbreaks. Due to the strict containment protocols formulated in advance of the switch and the resulting discontinuation of OPV2 bulk production, the stockpile needed to be sufficient to adequately respond to any and all cVDPV2 outbreaks in the post switch era.

**Evaluation and implications:** The initial plan (devised in 2009) was to secure 750 million mOPV2 doses; however, this was modified in the years leading up to the switch, with 519 million mOPV2 doses ultimately determined to be a sufficient stockpile. The mOPV2 stockpile requirements were based on the expected number of cVDPV2 outbreaks post switch (i.e., three outbreaks in the first year, with declining risk in each subsequent year) (Figure). Observed outbreaks from pre-switch tOPV use were in close alignment with expectations. What the plans didn't account for was the lack of capacity to stop outbreaks (and continued seeding of new cVDPV2), resulting in not a decline but ever-increasing outbreak magnitude, case burden and number of infected countries.



The 'worst-case' scenario materialized and the program quickly began running out of outbreak control vaccine (i.e., mOPV2), without the ability to rapidly procure more. Because of the containment priorities, the production of type 2 bulk had already been discontinued by the manufacturers. By the end of year 3, >200 million mOPV2 doses had been used and transmission was expanding (Figure). The strain on the mOPV2 stockpile drove focused outbreak responses, and in year 4 nearly half of all detections were outside of the response scope following 2 OPV2 SIAs (with scope particularly inadequate in DRC).

Despite a substantial increase in cases and infected countries between years 3 and 4 after the switch (i.e., from 84 cVDPV2 cases in 7 countries, to 548 cases in 21 countries), the number of mOPV2 doses used in these two years was nearly the same (i.e., ~110 million). Focused scope of responses in year 4 led to a peak of cVDPV2 transmission and cases in year 5, with >1,000 cVDPV2 cases reported across 24 countries. Supply constraints were addressed by year 5 (and novel OPV2 became available and was used extensively), resulting in larger responses (>400 million doses used in year 5); however, transmission was already widespread and endemicity established in many countries.



**Lessons for bOPV withdrawal:** Ensuring sufficient supply of essential OPV vaccines (and IPV) is critical for a successful switch, allowing for responses to be driven by epidemiology and not supply constraints. Continuing to manufacture these OPV vaccines at pre-switch levels will be essential and will ensure a continuing increasing stockpile after bOPV withdrawal and the option to reverse the OPV cessation, if required.

6. Revision of outbreak control SOPs, reducing the number of rounds and target population, and eliminating IPV from outbreak response

**Requirement:** Appropriate cVDPV2 outbreak response protocol was required, ensuring clear guidance to countries on scope, timing and frequency of SIAs.

**Evaluation and implications:** Supply constraints resulted in a substantial reduction in the recommended number and scope of mOPV2 SIAs and removal of IPV from outbreak response guidelines (Table). The initial cVDPV2 outbreak response guidelines developed in advance of the switch included 5+ SIAs of a minimum 2 million population target and IPV included in the second SIA. By mid 2017, the

guidelines cut both the number of SIAs and scope in half, with IPV no longer recommended. While the reduced number of SIAs was informed by research (Bangladesh study), the reduced scope was largely driven by supply constraints, as it was well understood that scope would need to increase with time from switch due to the increasingly susceptible populations. The greatest impact on reduced scope was in DRC, which conducted highly focused responses failing to capture extent of transmission.

**OPV2 response guidelines**

Date	Number of SIAs	Timing	Scope/target	Vaccine
V2.0 (01 May 2016 – 30 Apr 2017) <i>*developed pre-switch</i>	SIA1 SIA2 (mOPV2+IPV) SIA3 SIA4 (SIA5+ in high-risk areas)	<14 days 2-3 week intervals (if SIA2 includes mOPV2+IPV may require up to 4 weeks)	500,000 Min. 2 million (SIA1-SIA5+) For SIA2 (mOPV2+IPV), IPV in expanded high risk subpopulation (Min 2 million)	mOPV2 (+IPV for confirmed transmission in high-risk areas).
V2.3 (01 May 2017 – 31 Oct 2017)	SIA1 SIA2 (SIA3+ if necessary)	<14 days 2-3 week intervals	1-2 million children	mOPV2. fIPV no longer recommended.
V2.4 (01 Nov 2017 – 30 Apr 2018)	SIA1 SIA2 (SIA3+ if necessary)	<14 days 2-3 week intervals	1-2 million children	mOPV2. fIPV no longer recommended.
V3.0 (Dec 2018/Jan 2019)	SIA1 (R0) SIA2 (R1) SIA3 (R2)	<14 days 2-3 week intervals	200,000 – 500,000 1-2 million children	
V3.1 (Jan 2020)	SIA1 (R0) SIA2 (R1) SIA3 (R2)	<14 days 2-3 week intervals	100,000 – 400,000 1-4 million children	
V4.0 (Mar 2022)	RR SIA1 SIA2 Mop-up	<14 days <28 days <45 days (latest <56 days) <21 days after SIA2	100,000 – 400,000 Min. 2-4 million Min. 2-4 million Based on SIA1/2 quality	mOPV2 or nOPV2 or TOPV to be used. IPV not recommended.

Messaging to countries for reduced scope of mOPV2 response centered on the risk of seeding from mOPV2 use (which had serious implications discussed in the next section), while messaging for removal of IPV from guidelines focused on its use as only a tool for RI. This messaging was reinforced by the strict measures for releasing vaccine through the mOPV2 Advisory Group. This created confusion at the country level and impacted their ability to propose and implement appropriate and effective outbreak control plans.

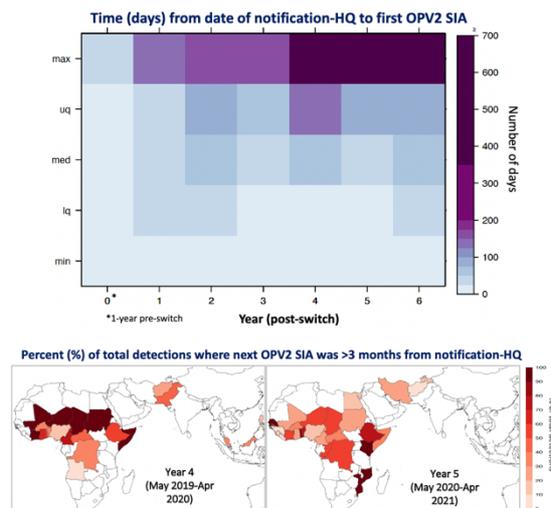
**Lessons for bOPV withdrawal:** Guidelines should be driven by epidemiology, and not continuously change unless there is critical new information or vaccine products (e.g. nOPV2).

7. Delays in nOPV2 introduction and perceived/communicated risk of mOPV2, resulting in substantial delays in outbreak response.

**Requirement:** No requirement.

**Evaluation and implications:** At the time of the switch, nOPV2 was not available, but as development progressed it was perceived as a ‘magic bullet’. Once nOPV2 became available in 2021, countries were willing to wait to receive the vaccine, given the perceived and communicated risk of mOPV2 (coupled with the promise of nOPV2). Many countries substantially delayed outbreak responses as they waited for nOPV2 to be available, and once it was ready for use, supply constraints resulted in additional delays.

Delays in responding resulted in continued and expanding transmission in many countries in year 4 and 5, particularly in the African Region (Figure). In the context of increasing susceptibility and expanding transmission, this created ‘the perfect storm’ of factors accelerating the extent of cVDPV2 transmission.



**Lessons for bOPV withdrawal:** At the time of the switch nOPV2 was not anticipated. For bOPV withdrawal, at a minimum nOPV1 and nOPV3 must be ready, including manufacturing capacity, robust supply security (>2 manufacturers) and regulatory approvals.

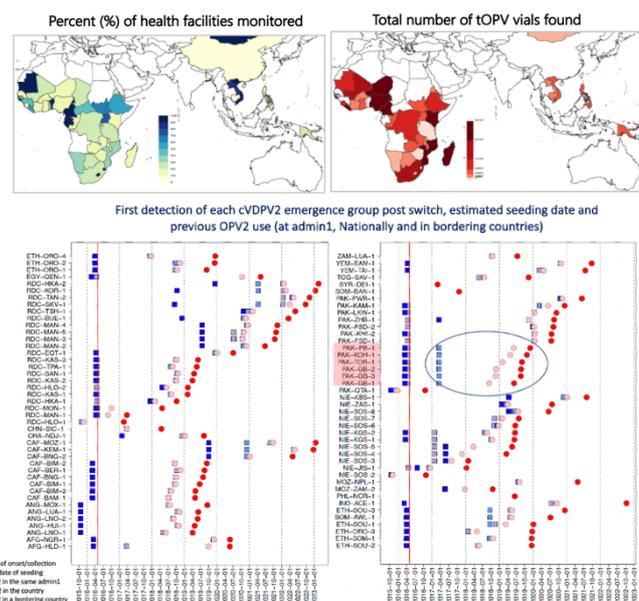
### 8. Left over tOPV vials in storage sites, potentially seeding (at least one) cVDPV2 outbreaks

**Requirement:** Following OPV2 cessation, all remaining stocks of tOPV were to be collected, destroyed and independently validated at the country level.

**Evaluation and implications:** While countries checked all National and Provincial/State storage facilities, the majority of countries only monitored <30% of health facilities (at District level or below) for tOPV (Figure). Substantial amounts of tOPV was found at monitored facilities. Collecting tOPV from private sector was particularly difficult.

While tOPV vials were likely present in many countries, inadvertent use resulting in cVDPV2 outbreaks appears limited (Figure). Nearly all seeding events coincide with OPV2 use (either at the same admin1 level, in the same country or bordering country). Pakistan is the exception and may have seeded its cVDPV2 outbreak in 2019 from inadvertent tOPV use.

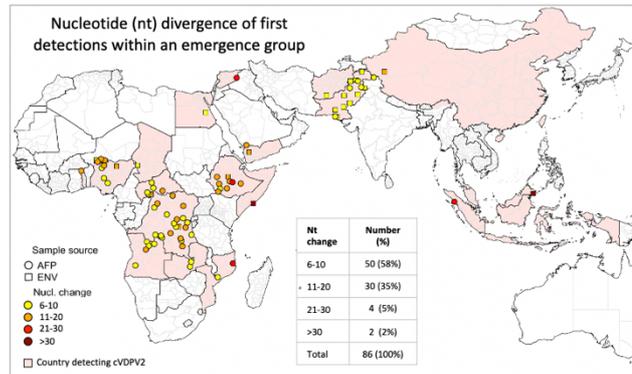
**Lessons for bOPV withdrawal:** Moving forward, ensuring all OPV is collected and contained post switch, that there is better engagement with private sector, and the validation process includes a majority (if not all) health facilities will be essential.



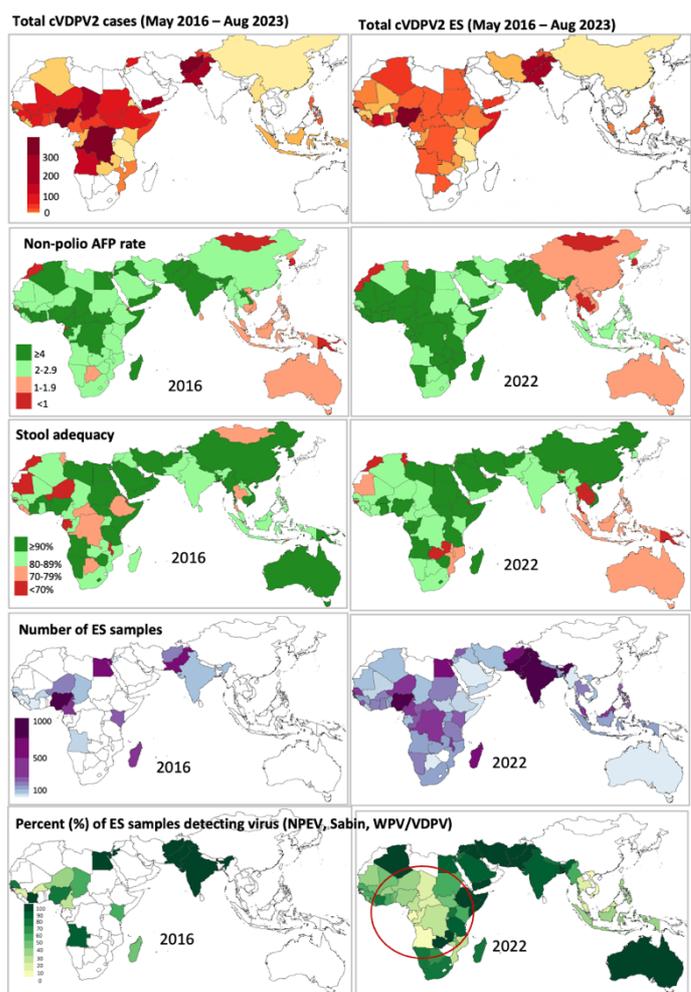
9. Inadequate or late detection of cVDPV2 (both new emergences and ongoing transmission), delaying implementation of outbreak control measures

**Requirement:** Surveillance capacity must be ‘sufficient’ to detect all cVDPV2 post switch.

**Evaluation and implications:** In the post switch era, new cVDPV2 emergences have typically been detected early, especially in consequential geographies. The majority (58%) of first detections within a new emergence were 6-10 nucleotide divergent, indicating early detection; however, there were substantial gaps (>20 nucleotides divergence from parental Sabin virus) in select geographies (Somalia, Ethiopia, Syria, Mozambique, Indonesia, Malaysia) indicating surveillance gaps, particularly in areas or countries with limited environmental surveillance (Figure).



The global surveillance system has detected >3,300 cVDPV2 cases and >1,600 cVDPV2 ES samples between May 2016-Aug 2023, across 52 countries (Figure). Overall surveillance quality is strong, especially the acute flaccid surveillance (AFP) arm, that covers almost every single country. Most countries report a non-polio AFP rate  $\geq 2$  cases per 100,000 population <15 years of age (however, there are sub-national gaps). Stool adequacy remains a greater concern, and despite improvements over the past few years in high-risk geographies (DRC, Chad), many geographies continue to fall <80% achievement.



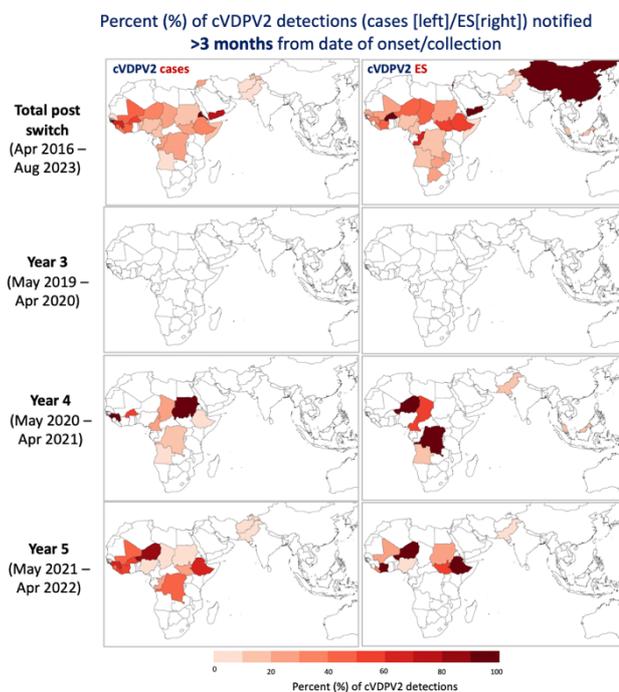
Environmental surveillance (ES) has been strengthened to support AFP, and there has been an increased frequency/scope of sampling, enabling faster detection of cVDPV2 in select geographies (Figure), with 33% of new emergences and 22% of new geographies (admin1) first detected through ES. However, sensitivity of ES remains sub-optimal in many high-risk countries, particularly in the African Region. In many high-risk countries, <30% of ES samples detect virus, i.e., NPEV, Sabin, WPV/VDPV.

**Lessons for bOPV withdrawal:** While the program’s issue was not necessarily determining which areas have virus, ensuring consistent detection and capacity to capture extent of transmission will be critical. Strengthening ES sensitivity in high-risk areas (in parallel to efforts in strengthening RI, which may impact AFP surveillance sensitivity) and ensuring expansion of ES includes appropriate sites (i.e., optimization and not simply expansion) will be essential. In the context of transition planning, surveillance (and outbreak response) capacity must be maintained.

10. Delays in processing and notifying cVDPV2 AFP and ES samples, exacerbating delayed responses

**Requirement:** Surveillance capacity must be ‘sufficient’ to timely process all cVDPV2 post switch.

**Evaluation and implications:** While overall surveillance quality is relatively strong, select geographies had substantial delays in shipping and/or processing samples (a greater issue than detection for both new emergences and cVDPV2 overall). With the increased strain from high cVDPV2 burden (in year 4 onwards), surveillance processing time greatly increased (Figure). Time to notification was >3 months in a large number of countries. Delays in notification have downstream effects in delayed response (as by the time it is notified, transmission has already spread, outdating the assessed risk and response strategy.)



**Lessons for bOPV withdrawal:** Ensure surveillance processing time is consistently <3 months across countries and shorten both field collection, shipment and laboratory processing time as much as possible. The surveillance system must be able to withstand increased burden of high case numbers and ES detections. Remaining vigilant with surveillance is critical in advance of OPV withdrawal.

#### 4. RECOMMENDATIONS FOR THE ANTICIPATED bOPV CESSATION

While, in 2016, the GPEI had a can-do approach, a perception of being able to overcome any challenge, and perhaps relied on some wishful thinking, any new vaccine withdrawal attempt must pass greatly increased hurdles and scrutiny. This is to avoid another failure, which would have even greater consequences in the form of paralyzed cases due to the 10-fold higher case to infection ratio (1:2000 for type 2 against 1:200 for type 1) and could also cause irreparable reputational damage to the organizations involved in GPEI, influence funding and confidence of the public.

Therefore, we propose the following guiding principles for a bOPV cessation: a) plan for “worst-case” scenario (i.e., concentrate on source versus sink, reservoir versus indicator community); b) assume no difference in transmissibility (or force-of-infection) among the three Sabin strains; and c) be aware and communicate: Surveillance will be more sensitive for Sabin type 1, but plan for higher case burden for type 1. The situation of Sabin type 3 is less well understood but may be more likely to be similar to type 2.

The program needs to demonstrate that it can control and close out outbreaks within 6 months after designation of “persistent” cVDPVs. After bOPV withdrawal, type 1 and type 3 population immunity will decrease, and a race will start for virus elimination in the face of a growing susceptibility gap. We must remember that most countries currently use a RI schedule that includes 3-4-dose bOPV + 2-dose IPV. In future, IPV will be the only vaccine for polio prevention, a vaccine that has no ability for secondary spread and secondarily “immunize” some susceptible contacts. Therefore, the GPEI faces a “grave” risk. If the population immunity falls below threshold level for herd immunity, the unintentional or intentional reintroduction of poliovirus could cause massive outbreaks of poliomyelitis.

Therefore, for the anticipated bOPV withdrawal we propose that the following triggers must be achieved for programmatic execution of cessation: i) no “persistent cVDPV” of any serotype. This requires outbreak control and elimination of all current outbreaks and endemic transmission; and ii) confirmation of eradication of wild poliovirus (WPV) by the Global Certification Commission (GCC).

In addition, the following 10 prerequisites should be achieved before bOPV cessation can be considered. The first three address vaccine availability, the next three address population immunity, the next three address routine immunization and the last addresses surveillance.

- 1) Ensure sufficient stockpile quantities of all required vaccines for “worst-case” outbreak scenario, including IPV, bOPV, nOPV1, nOPV2, nOPV3 and bnOPV, tnOPV. Stockpile the best vaccine based on sufficient evidence. The opportunity costs of single serotype SIAs assign a further priority to tnOPV.
- 2) Continue to purchase (commitment) the outbreak vaccines during >5 years after bOPV cessation (and re-set clock after each outbreak); this would allow the manufacturers to plan, and maintain bulk production & the fill-finish capacity;

- 3) Modify containment requirements temporarily (until all poliovirus type 2 has been eradicated) to contribute to eradication (not just make the world safer after eradication). These requirements need to be applied in a flexible and realistic way (i.e., cannot interfere with outbreak control, production of required vaccines, or laboratory processing, all serving the overall eradication goal). Laboratory methods should minimize reliance on live Sabin virus, should switch to S19, use pseudovirus and facilitate direct detection);
- 4) Conduct preventive SIAs that reach and maintain high population immunity. Current strategies must be revised to ensure sufficient number and quality of preventive SIAs. Clearly defined benchmarks and methods of evaluation are required. Develop rapid methods to measure population immunity.
- 5) Design realistic outbreak response SOPs (that incorporate innovative ideas with back-to-basics principles) and obtain sufficient outbreak control funding for “worst-case” scenario. Outbreak control scope must guide funding needs – not opposite (draft new SOPs to reflect this pre-requisite). Streamline decision-making of outbreak response plans and approval/release of required vaccine to facilitate timely implementation. Track progress and make refinements, as required;
- 6) Consequential geographies require special pre- and post-switch strategies. For the pre-switch period: Increase population immunity to surpass threshold for herd immunity. Develop context-specific strategies and ring vaccination around inaccessible areas. For the post-switch period: Pre-positioning of stockpile vaccines in consequential geographies. Pre-approval of outbreak activities (including funding);
- 7) Improve RI coverage to reach and surpass threshold for herd immunity. Design new strategies (with innovative approaches to reaching children, e.g., door-to-door fIPV SIAs) and ensure closer collaboration with IVB. Consequential geographies should be assigned the highest priority, with the next highest priority to areas with high proportion of “zero-dose” children (state, districts);
- 8) Include nOPV2 into pre-switch routine immunization schedule in highest-priority countries (or consequential geographies). For example: nOPV2/bOPV at birth, 6, 10, and 14 weeks, and IPV at 14 weeks + >9 month, or, when available, nOPV2/bOPV plus hexavalent vaccine at 6, 10, and 14 weeks (and an additional dose of hexavalent vaccine in the second year of life);
- 9) Accelerate introduction and promote high coverage with hexavalent vaccine. Introduction should prioritize high-risk countries, especially GAVI-eligible countries;
- 10) Further increase surveillance sensitivity and speed of detection/processing for timely notification and action. Focus on optimizing (instead of simply increasing) ES sites. Accelerate implementation of direct detection methods and institute special strategies to reduce shipping delays in complex situations/contexts. Ensure transition plans do not impact surveillance capacity.

Furthermore, GPEI should place careful attention to plans and planning that will also help minimize potential downstream problems, such as: a) commission a plan B (of critical voices); b) compile a detailed risk matrix, risk reduction & risk mitigation, and contingencies for unexpected eventualities; c) define a priori success and failure; d) evaluate progress every 3 months; and f) review status at end of year 2 post cessation for final determination.

Moreover, the GPEI should consider implementation of bOPV cessation in a phased manner to minimize risk and gain experience. Phased options should be explored (e.g., risk status (African Continent + Yemen + Afghanistan/Pakistan), countries with cVDPV1 outbreaks, etc.) versus rest of world. Low-risk WHO Regions could go first (European Region, Region of the Americas, Western Pacific Region), then South East Asian Region, followed by Eastern Mediterranean and African Regions).

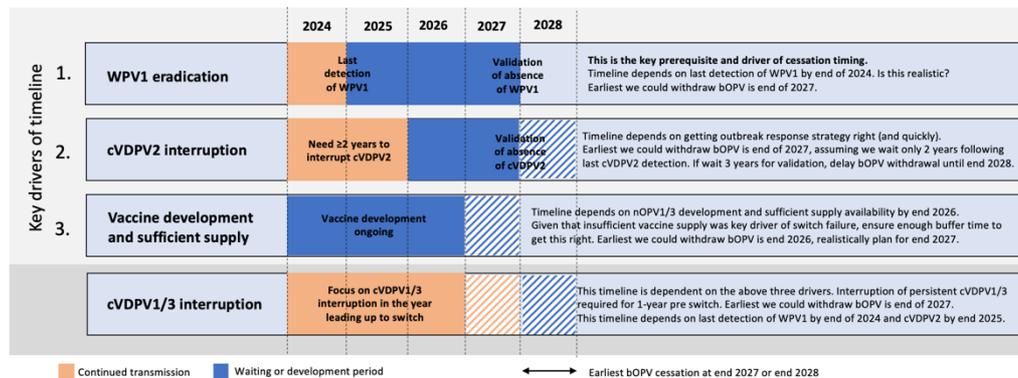
## 5. CONCLUSIONS

The OPV2 cessation, the “switch”, has not been successful, and the world’s children continue to pay the price in terms of morbidity (i.e., paralytic disease) and mortality (death from poliomyelitis). This failure must be weighed against the >20 million children that walk today because of GPEI, supported by routine immunization programs and the associated vitamin A distribution campaigns.

However, the GPEI must strive to do better:

- At present, the emperor [i.e., outbreak control] has NO clothes → achieving the two triggers for bOPV cessation may be most challenging. In our view, the key to controlling cVDPV2 poliovirus endemicity requires a way back to the basics; conduct national immunization days (NIDs) when transmission is widespread, supplemented by subnational NIDs (SNIDs) when transmission becomes localised, supported by high-quality surveillance, and improving routine immunization programs.
- In the current situation it is better to take the time, get it right, then to rush, and fail spectacularly (Failure, this time, cannot be an option). At this point in time, all realistic options for achieving trigger and prerequisite require at least 5 years of maximal effort. The program should use the time wisely to build up population immunity and find ways to maintain this population immunity above the threshold for herd immunity. This is especially important in consequential geographies.
- Institute closer collaboration with RI will greatly increase likelihood of success! This could be very productive at all levels, in the field, and in the organizational parts of the GPEI core organizations, especially WHO, UNICEF, GAVI and BMGF. GPEI and RI could work closely together to extend the reach of all recommended vaccines, and thus greatly increase the benefits of these vaccines. The current resurgence of measles, but also diphtheria, is a stark reminder that complacency invariably comes with a price that requires payment in morbidity and mortality.
- With adherence to proposed trigger and prerequisites, GPEI has a “fighting chance” for success, but will this be sufficient? The additional strategies, some outlined in the proposed

prerequisites, others in development, could help raise the population immunity above the threshold for herd immunity, and maintain it there, until at least 5 years after the last detection of poliovirus type 2 in communities. The introduction of hexavalent vaccine (with an IPV component) could be a game changer, also for polio eradication.



## 6. WAY FORWARD (Proposed Priorities)

At this juncture in 2024, the program is neither ready for a next cessation attempt or in a position to rapidly control the massive outbreaks of cVDPV2 on the African continent or wipe out the stubborn transmission of WPV1 in Afghanistan and Pakistan.

Until GPEI has achieved eradication of WPV1 and eliminated the chains of cVDPVs transmission, it should diligently improve the conditions for the anticipated bOPV cessation. These conditions include developing the critical products (especially vaccines) for a post-bOPV world, ensuring adequate manufacturing capacity, and eventually filling up the required stockpiles.

The world is a very diverse place, and success cannot be forced in places where access is limited, and security cannot be granted. However, this realization has not prevented the >100 health workers that have lost their lives in the line of duty in the past decade. All GPEI decisions have consequences, but it is the view of the authors that health workers, especially volunteers, should not be put in harm's way.

In our review, we also noted the cumbersome leadership structure of GPEI ("too many cooks in the kitchen"), and the apparent inability of the program to make rapid decisions. Streamlining the decision-making structure, reducing the number of committees, task teams, advisory groups, could result in focusing resources, especially human resources, to be employed for directly supporting programmatic action in the field.

Innovative new programmatic approaches should be both encouraged by GPEI and be assigned a high priority. Empowering local innovations, evaluating these, and keeping the ones that worked is the hallmark of pragmatic local solutions. Moreover, focusing on a back-to-basics approach that enabled the program to eradicate WPV from the African continent is required, and must be consistently achieved across all geographies.

Further research is critical. A non-infectious vaccine that would induce mucosal immunity is the “holy grail” of polio eradication product development. New ways to rapidly determine population immunity should be developed and made available to cVDPV-endemic countries, so that the program managers in these countries are empowered in real time to make better programmatic decisions.

Furthermore, a confluence of the “four-legged” strategy, RI, supplemented by SIAs, with two new elements, nOPV2 into RI, and house-to-house fIPV given during extended outreach, could substantially increase population immunity in consequential geographies.

In conclusion, polio eradication is imminently doable. The eradication program has come a long way and is struggling to cross the finish line. However, the last inch, the most difficult part of this journey remains a work in progress. We (collectively) need to recommit to eradication, reinforce our efforts, double down and find the right strategies even for inaccessible areas, to ensure that poliovirus can never find a home again in our communities.

### **Epilogue:**

A moral imperative: The switch resulted in >3,300 children getting paralyzed by cVDPV2 (WHO data, end of 2023). This number will likely increase since many cVDPV2 outbreaks are active and cause additional children with paralysis. To mitigate the consequences of this paralytic burden, GPEI, in close cooperation with the affected countries, should enhance support for rehabilitation and education for the affected “crippled” children. In addition, GPEI policies puts volunteers, polio staff and security personnel in harm’s way, with >100 people having been killed. The delays in eradication will further exacerbate this burden. GPEI should take a hard look how to lower risk exposure and whether the currently provided compensation to affected families is adequate.

**Annex A:** Table summarizing the evaluation of prerequisites and readiness criteria for OPV2 withdrawal.

**Annex B:** Table summarizing analyses underpinning the findings from evaluation of OPV2 withdrawal.