

## ORIGINAL ARTICLE

# Coordinated global cessation of oral poliovirus vaccine use: Options and potential consequences

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## Abstract

Due to the very low, but nonzero, paralysis risks associated with the use of oral poliovirus vaccine (OPV), eradicating poliomyelitis requires ending all OPV use globally. The Global Polio Eradication Initiative (GPEI) coordinated cessation of Sabin type 2 OPV (OPV2 cessation) in 2016, except for emergency outbreak response. However, as of early 2023, plans for cessation of bivalent OPV (bOPV, containing types 1 and 3 OPV) remain undefined, and OPV2 use for outbreak response continues due to ongoing transmission of type 2 polioviruses and reported type 2 cases. Recent development and use of a genetically stabilized novel type 2 OPV (nOPV2) leads to additional potential vaccine options and increasing complexity in strategies for the polio endgame. Prior applications of integrated global risk, economic, and poliovirus transmission modeling consistent with GPEI strategic plans that preceded OPV2 cessation explored OPV cessation dynamics and the evaluation of options to support globally coordinated risk management efforts. The 2022–2026 GPEI strategic plan highlighted the need for early bOPV cessation planning. We review the published modeling and explore bOPV cessation immunization options as of 2022, assuming that the GPEI partners will not support restart of the use of any OPV type in routine immunization after a globally coordinated cessation of such use. We model the potential consequences of globally coordinating bOPV cessation in 2027, as anticipated in the 2022–2026 GPEI strategic plan. We do not find any options for bOPV cessation likely to succeed without a strategy of bOPV intensification to increase population immunity prior to cessation.

## KEYWORDS

dynamic modeling, eradication, oral poliovirus vaccine, polio

## 1 | INTRODUCTION

As the initial target year of 2000 for polio eradication approached, key partners of the Global Polio Eradication Initiative (GPEI) discussed ending the use of oral poliovirus vaccine (OPV) as part of the polio endgame after wild poliovirus (WPV) eradication (World Health Organization, 1997). OPV use comes with rare, but nonzero risks of vaccine-associated paralytic polio (VAPP) and vaccine-derived polioviruses (VDPVs; Duintjer Tebbens et al., 2006). Some early proponents of OPV cessation continue to suggest urgency (John, 2004; John & Dharmapalan, 2022), while oth-

ers argue that OPV use should continue indefinitely and GPEI should abandon the objective of eradication of all poliovirus transmission (Chumakov et al., 2021, 2007). Recently, some studies supported continued use of OPV due to potential benefits of secondary vaccine effects (Aaby et al., 2004; Chumakov et al., 2020; Joffe et al., 2021), although other studies highlighted the uncertainty about these effects and any associated health–economic implications (Thompson & Badizadegan, 2022; Thompson et al., 2021a, 2021c).

Over the last two decades, our integrated global risk, economic, and poliovirus transmission modeling explored numerous aspects of the polio endgame, with vaccine choices

representing a primary focus (Thompson & Kalkowska, 2020). These studies included the identification and quantification of OPV-related risks (Duintjer Tebbens et al., 2006), support for the case for globally coordinated OPV cessation (Thompson & Duintjer Tebbens, 2008; Thompson et al., 2008), development of outbreak response protocols (Thompson et al., 2006), and stockpile creation to manage polio endgame risks prior to OPV cessation (Thompson & Duintjer Tebbens, 2008). Following a 2008 resolution by the World Health Assembly related to OPV cessation (World Health Assembly, 2008), studies in the early 2010s included discussion of polio vaccine options for the endgame and development of prerequisites for successful OPV cessation (Thompson & Tebbens, 2012). Further modeling studies identified risk management strategies to increase the probability of successful OPV cessation (Duintjer Tebbens et al., 2015; Duintjer Tebbens, Pallansch, et al., 2016; Duintjer Tebbens & Thompson, 2014; Thompson & Duintjer Tebbens, 2014a). These studies used available information about routine immunization (RI) and supplemental immunization activities (SIAs) and focused on identifying opportunities to prevent the need for outbreak response after cessation, with emphasis on OPV intensification prior to cessation (Thompson & Duintjer Tebbens, 2014a). One analysis also explored the role of inactivated poliovirus vaccine (IPV) in RI and highlighted its expected inability to stop outbreaks, particularly in the places most likely to experience outbreaks (Duintjer Tebbens & Thompson, 2014).

OPV cessation as a polio endgame strategy comes with costs and risks. If countries and the GPEI partners used the model-recommended risk management strategies for the polio endgame, 2015 model estimates (prior to OPV2 cessation) suggested an approximately 6% chance of needing to restart the production of OPV2 vaccine and its use in RI to respond to significant levels of type 2 poliovirus transmission after OPV2 cessation (Duintjer Tebbens et al., 2015). A 2016 study emphasized the importance of aggressive outbreak response after OPV2 cessation to rapidly shut down any outbreaks and manage risks (Duintjer Tebbens, Pallansch, et al., 2016). Recognition of these risks led the GPEI to develop standard operating procedures for outbreak response SIAs (oSIAs) (World Health Organization Global Polio Eradication Initiative, 2016) and a stockpile of Sabin type 2 monovalent OPV (mOPV2) for oSIAs. Prior to OPV2 cessation, integrated modeling studies demonstrated the importance of shutting down all identified type 2 transmission completely before and as soon as possible after (if any occurred) homotypic OPV cessation (Duintjer Tebbens, Hampton, et al., 2016a, 2016b). These studies used updated information about RI and SIAs to demonstrate the expected decreases in population immunity following OPV2 cessation as a function of time after OPV2 cessation and the anticipated increases in the vulnerability of populations to restarting transmission of type 2 polioviruses following importations of circulating vaccine-derived poliovirus type 2 (cVDPV2) and/or mOPV2 used in oSIAs (Duintjer Tebbens, Hampton, et al., 2016a, 2016b).

After OPV2 cessation occurred, integrated modeling studies that reported on the status of OPV2 cessation as of end-2016 (Thompson & Duintjer Tebbens, 2017a), early 2018 (Duintjer Tebbens & Thompson, 2018), end of 2019 (Kalkowska, Pallansch, Wassilak, et al., 2021), early 2020 (Kalkowska, Pallansch, Cochi, Kovacs, et al., 2021), and late 2021 (Thompson, 2022) focused on the need for improvements in implementing oSIAs and highlighted that the polio endgame was off-track. Continued deficiencies in the promptness, scope, and/or quality of mOPV2 oSIAs continue to exacerbate the situation in many settings (Macklin et al., 2020). After updating the characterization of OPV2 cessation risks based on immunization and epidemiological experience through early 2020, updated model estimates of the probability of OPV2 restart increased to over 80% (Kalkowska, Pallansch, Cochi, Kovacs, et al., 2021). A 2021 reflection (Thompson & Kalkowska, 2021b) on the OPV2 experience compared the (i) then-prospective assumptions about GPEI strategies and performance used in modeling to support the 2013–2018 GPEI strategic plan (World Health Organization Global Polio Eradication Initiative, 2013) prior to OPV2 cessation, with the (ii) polio endgame path actually observed through 2020. That reflection identified model assumptions that required updating (Thompson & Kalkowska, 2021b) prior to conducting further prospective polio endgame modeling, including the observation of worse oSIA performance than required for success in pre-cessation modeling (Kalkowska, Pallansch, Cochi, Kovacs, et al., 2021; Kalkowska, Pallansch, Wassilak, et al., 2021; Kalkowska, Pallansch, Wilkinson, et al., 2021; Kalkowska & Thompson, 2021b; Thompson, 2021). A recent look back analysis quantified the probability of successful OPV2 cessation if the modelers knew then what we know now about OPV2 cessation risks and post-OPV2 cessation oSIA characteristics (Thompson et al., 2023). As of early-2023, type 2 transmission continues (World Health Organization Global Polio Eradication Initiative, 2023).

The development and deployment of a genetically modified novel type 2 OPV (nOPV2), which designers engineered for increased genetic stability and lower risk of gaining neurovirulence while retaining immunogenic properties when used in populations (Konopka-Anstadt et al., 2020; Yeh et al., 2020), leads to some additional potential vaccine options, with further complexity and trade-offs (Kalkowska, Pallansch, et al., 2023; Kalkowska, Pallansch, Wilkinson, et al., 2021; Kalkowska, Voorman, et al., 2023; Kalkowska, Wassilak, Pallansch, et al., 2023; Thompson et al., 2021b). Recent studies suggest that failures to contain and respond aggressively to type 2 outbreaks are the root cause for OPV2 cessation failure to date (Kalkowska, Pallansch, Cochi, Kovacs, et al., 2021; Macklin et al., 2020; Thompson et al., 2023). In response to setbacks, in 2018 the GPEI commissioned additional filled doses of Sabin OPV2 (World Health Organization and UNICEF, 2018) and accelerated efforts to develop and produce large supplies of nOPV2 (Macklin et al., 2023). Some of the mOPV2 bulk procured also went into filled doses of trivalent OPV (tOPV, containing types 1, 2,

and 3) for use in Pakistan and Afghanistan (Global Polio Eradication Initiative, 2020), which 2018 modeling suggested would likely be needed (Duintjer Tebbens, Pallansch, et al., 2018). Both Pakistan and Afghanistan used tOPV to respond to outbreaks in late 2020 and 2021 (Kalkowska, Badizadegan, et al., 2023), and Yemen (Relief Web, 2022) and Somalia (Global Polio Eradication Initiative, 2022) used it in 2022.

The 2022–2026 GPEI strategic plan does not include restarting OPV2 use in RI (World Health Organization Global Polio Eradication Initiative, 2021). The plan assumes successful interruption of global transmission by the end of 2023 of both wild poliovirus type 1 (WPV1) and cVDPV2s, and briefly discusses ending all use of bivalent OPV (bOPV, containing types 1 and 3) in all RI. The plan states that: “Planning for OPV withdrawal will start at least two years in advance of cessation...[and] address three main issues: strategies for pre-cessation SIAs; the availability of new, more genetically stable vaccine options; and the time-interval between certification of eradication and OPV cessation” (World Health Organization Global Polio Eradication Initiative, 2021, p. 42). Modeling that explored the health-economics of the 2022–2026 GPEI plan without bOPV cessation or OPV2 restart as the baseline scenario compared to shifting to control in OPV-using countries using exclusively either IPV or tOPV reported essentially no chance of type 2 transmission dying out (Thompson et al., 2022).

Specific to bOPV cessation, several pre-OPV2 cessation integrated modeling studies discussed differences between the poliovirus types and implications of vaccine choices and OPV cessation timing for supply forecasting (Duintjer Tebbens & Thompson, 2015; Thompson & Duintjer Tebbens, 2015a, 2015b). An additional study that focused specifically on bOPV cessation highlighted the risks associated with implementation of bOPV cessation and discussed similarities and differences of the three poliovirus types (Typo et al., 2016). This study also emphasized the need to globally synchronize homotypic OPV cessation, and the importance of ensuring the absence of types 1 and 3 circulating VDPV (cVDPV1 and cVDPV3) transmission prior to cessation, as well as monitoring to confirm complete withdrawal of all doses of the stopped OPV in the supply chain (Duintjer Tebbens et al., 2016). Most importantly, this study demonstrated that maintaining bOPV preventive (or planned) SIAs (pSIAs) prior to bOPV cessation would substantially lower the risks associated with implementation of bOPV cessation, whereas the use of IPV in RI would only prevent some cases of paralysis (Duintjer Tebbens et al., 2016). A study published after OPV2 cessation focused on bOPV cessation and characterized the expected increases in vulnerability of populations to importations of types 1 and 3 outbreak viruses and Sabin type 1 or 3 monovalent OPV (mOPV1 or mOPV3) use for oSIAs as a function of time since bOPV cessation (Duintjer Tebbens, Hampton, et al., 2018), similar to prior studies for OPV2 cessation (Duintjer Tebbens, Hampton, et al., 2016a, 2016b).

Studies of lessons learned from the experience with OPV2 cessation for bOPV cessation highlighted the differences in

transmissibility and neurovirulence among poliovirus types (Thompson & Duintjer Tebbens, 2017a) and the important role of un- and undervaccinated subpopulations (Thompson & Duintjer Tebbens, 2017b). Following the global certification of the eradication of indigenous transmission of type 3 WPVs in 2019 (World Health Organization, 2019), which several modeling studies supported by showing high confidence about no circulation given the available surveillance and immunization data (Duintjer Tebbens et al., 2019; Kalkowska, Duintjer Tebbens, Pallansch, et al., 2015; Kalkowska, Duintjer Tebbens, Pallansch, et al., 2019; Kalkowska, Duintjer Tebbens, & Thompson, 2019), integrated modeling explored the option of globally coordinating cessation of type 3 OPV (OPV3) prior to type 1 OPV (OPV1) cessation (Kalkowska & Thompson, 2021a). This study highlighted the importance of coordination with vaccine manufacturers to procure sufficient vaccine supplies while also ensuring the use of vaccines produced, highlighted key differences between types 1 and 3, and suggested potential benefits of coordinating OPV3 cessation prior to OPV1 cessation (Kalkowska & Thompson, 2021a). However, the 2022–2026 GPEI strategic plan (World Health Organization Global Polio Eradication Initiative, 2021) did not consider OPV3 cessation followed by OPV1 cessation as a viable option.

With evidence for ongoing transmission of WPV1 in Pakistan and Afghanistan as of early-2023 and exportations leading to WPV1 cases in Malawi (2021) and Mozambique (2022) (World Health Organization, 2023), the targeted cessation of indigenous WPV1 transmission may not occur by the end of 2023. In addition, even with the potential for faster certification following no detected surveillance evidence of WPV1 transmission as early as 1.5 years after the last reported detection (Kalkowska, Badizadegan, et al., 2023a, 2023b; Kalkowska, Pallansch, Cochi, & Thompson, 2021), uncertainty remains about when bOPV cessation might occur. However, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) recently called for creation of an OPV cessation team (World Health Organization, 2022a). To support the efforts of this team, we applied an integrated model to explore the potential polio endgame trajectory assuming that it includes bOPV cessation in 2027 and it does not include OPV restart. We then discuss bOPV cessation immunization options as of 2022 and explore potential prerequisites (or readiness criteria) that the GPEI may want to consider for bOPV cessation.

## 2 | METHODS

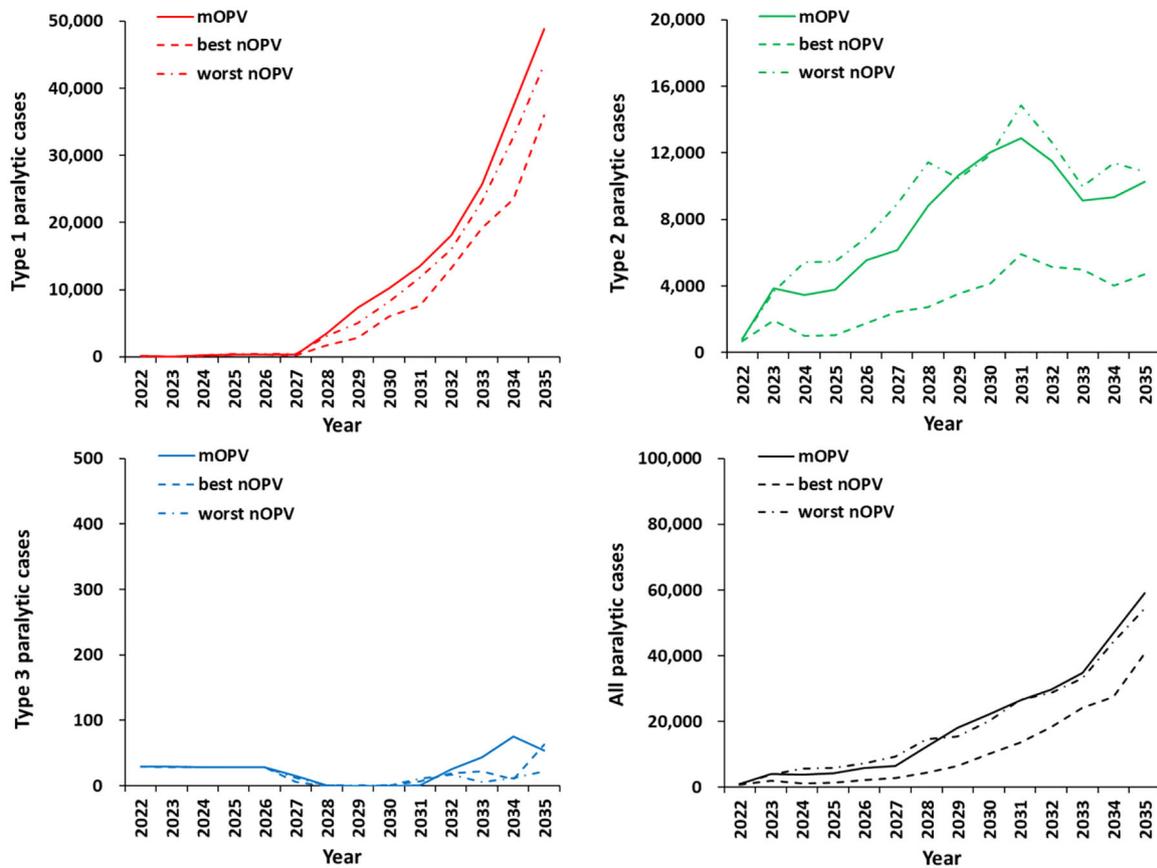
We use our updated global poliovirus transmission model to explore the implications of implementing bOPV cessation without coordinated improvements in population immunity, which represents the current global path that we model in this analysis (Kalkowska, Pallansch, Cochi, Kovacs, et al., 2021; Kalkowska, Pallansch, Wassilak, et al., 2021; Kalkowska, Pallansch, et al., 2023; Kalkowska, Pallansch, Wilkinson, et al., 2021; Kalkowska, Voorman, et al., 2023; Kalkowska,

Pallansch, Wassilak, et al., 2023; Kalkowska, Wassilak, et al., 2023; Thompson et al., 2022). Since the GPEI plan (World Health Organization Global Polio Eradication Initiative, 2021) assumes globally coordinated bOPV cessation by 2027, we assume WPV1 eradication in 2023, followed by global certification of WPV1 eradication, implementation of the planning required for coordinated bOPV cessation, no bOPV intensification, and coordinated bOPV cessation on May 1, 2027. The model divides the world into 72 blocks of 10 subpopulations of approximately 10.7 million total population, stratified by World Bank Income Level (low-income, LI; lower middle-income, LMI; upper middle-income, UMI; high-income, HI) and current vaccine use in RI (i.e., OPV+IPV, IPV/OPV, IPV-only; Kalkowska, Pallansch, Cochi, Kovacs, et al., 2021; Kalkowska, Pallansch, Wassilak, et al., 2021; Kalkowska, Pallansch, et al., 2023; Kalkowska, Pallansch, Wilkinson, et al., 2021; Kalkowska, Voorman, et al., 2023; Kalkowska, Wassilak, et al., 2023; Thompson et al., 2022). We further stratify each subpopulation using multiple age groups. Mixing within blocks occurs heterogeneously by age and homogeneously in space. Mixing between blocks occurs according to nine varying preferential mixing areas of different size representing larger geographical regions. We consider a prospective analytical time horizon of January 1, 2022, to December 31, 2035, for which we assume current SIA performance characteristics and three vaccine options for post type-specific OPV cessation outbreak responses. Specifically, we assume that oSIAs target children <5 years of age, start 45 days after detection in the model, and include two rounds separated by 30 days with two additional rounds after breakthrough transmission, with a scope that spans only the outbreak subpopulation when WPV1  $R_0 < 10$  or the outbreak subpopulation and its four worst-performing neighbor subpopulations within the same block when WPV1  $R_0 \geq 10$ . In the model, detection occurs at the time of onset of paralysis and without considering additional delays that may exist in practice (e.g., collection of the specimen for laboratory testing, specimen transport and laboratory processing, and/or notification of the case, in the event that total time required for these takes longer than 45 days; Kalkowska, Duintjer Tebbens, Pallansch, et al., 2015). The oSIA intensity varies for different subpopulations, ranging from 15% true coverage and 95% repeatedly missed probability to 80% true coverage and 50% repeatedly missed probability. We include a scenario: (i) *mOPV*, which assumes that only type-specific mOPV would be used for outbreak response post type-specific OPV cessation. Considering the current shift toward nOPV2 use for outbreak response and efforts to develop nOPV for types 1 and 3 (i.e., nOPV1 and nOPV3), we consider additional scenarios that assume that nOPV1 and nOPV3 will become available for outbreak response at the time of bOPV cessation. For this analysis, we consider the implications of using nOPV2 starting at the beginning of the time horizon in 2022 for the nOPV scenarios, and nOPV1 and that nOPV3 become available at the time of bOPV cessation in 2027, with bOPV used for type 1 and/or 3 oSIAs prior to 2027. However, given uncertainty about nOPV performance in field use, we

explore the bounds of the potential trajectories for the novel vaccine. Specifically, we consider the scenarios of (ii) *best nOPV*, which uses type-specific nOPV for outbreak response assuming the same effectiveness as type-specific mOPV, no reversion despite transmissibility, and no VAPP (Kalkowska, Pallansch, Wilkinson, et al., 2021; Thompson et al., 2021b), and (iii) *worst nOPV*, which uses type-specific nOPV for outbreak response post type-specific OPV cessation, assuming the 90% of the effectiveness of mOPV, prior assumptions for reduced reversion (Kalkowska, Pallansch, Wilkinson, et al., 2021), which we further reduced here by 10%, and VAPP occurring at a rate 10% lower than the VAPP rate of mOPV in vaccine recipients. We present the results of the model simulations using the expected value of 100 stochastic iterations, performed using JAVA™ programming language in the integrated development environment Eclipse™, starting with the same random number seeds and initial conditions to control the stochasticity for each scenario to focus on direct comparisons of the different scenarios (i.e., in this analysis, different assumptions about vaccine use of oSIAs).

### 3 | RESULTS

Figure 1A shows that following modeled WPV1 eradication in 2023, the total number of expected type 1 paralytic polio cases remains low as long as bOPV use continues. However, with bOPV cessation anticipated in 2027, the model results show a rapid and significant rise in expected type 1 paralytic polio cases. This increase occurs due to: (i) substantially less-than-ideal immunization coverage before modeled globally coordinated bOPV cessation anticipated in some countries, which provides fertile ground for the highly transmissible and neurovirulent type 1 polioviruses and leads to creation and circulation of cVDPV1, and (ii) expected inadequate outbreak response and no restart of OPV1 use in RI, even in the context of increasing numbers of cases. Thus, this analysis does not include any feedback that might occur if decision makers observe an increase in transmission and they implement different strategies and practices than we assumed here. The use of type 1 mOPV (mOPV1) for oSIAs after bOPV cessation leads to more expected cases than using nOPV1. The introduction of nOPV1 for outbreak response at the time of bOPV cessation comes with a lower risk of seeding new type 1 cVDPVs relative to the risk of seeding using mOPV1, which leads to lower expected cases for both best and worst nOPV1 than with mOPV1. As shown in Figure 1A, the expected cases after bOPV cessation reflect the insufficient use of bOPV to intensify population immunity prior to bOPV cessation, and the reduction in seeding when even the best nOPV1 does not compensate for the failure to close type 1 immunity gaps prior to bOPV cessation. Overall, these model results suggest that current GPEI plans for OPV1 cessation would likely repeat the experience that occurred with OPV2 cessation. Given the discussion of bOPV cessation readiness criteria, if the GPEI insisted on a requirement of ending all cVDPV1 transmission before bOPV cessation, then the model results shown in Figure 1A would not apply



**FIGURE 1** Expected global number of polio cases by year for 100 stochastic iterations of bivalent oral poliovirus vaccine (bOPV) cessation under the 2022–2026 strategy (on May 1, 2027) with monovalent OPV (mOPV; solid line), a best nOPV (dashed line), or a worst novel type 2 OPV (nOPV; dotted-dashed line) as the vaccine used for outbreak response.

because they include expected cVDPV1 transmission at the start of the time horizon.

Given no assumed improvements in outbreak response compared to the current oSIA characteristics, as shown in Figure 1B, type 2 trajectories remain off track. Replacing mOPV with *best nOPV* lowers the overall expected burden of paralytic disease, but the model still does not predict poliovirus elimination (i.e., none of the 100 stochastic iterations lead to die out of type 2 transmission at the end of the model time horizon).

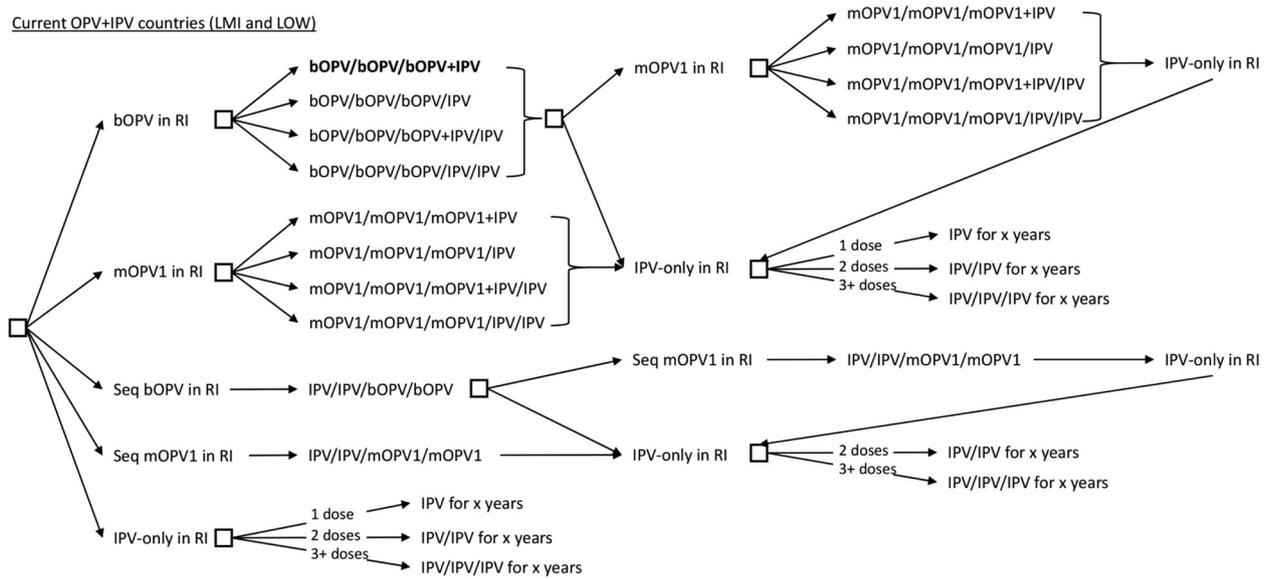
Compared to types 1 and 2, early cessation of OPV3 could be considered as a better option as shown in Figure 1C, although this would depend on addressing logistical, political, economic, and other challenges. Figure 1D shows the expected total cases for all three poliovirus types. Type 1 poliovirus cases account for most of the global burden, which reflects its relatively greater transmissibility and paralysis-to-infection ratio.

#### 4 | OPV CESSATION IMMUNIZATION OPTIONS AND PREREQUISITES

Prior studies that systematically explored OPV cessation used decision trees to discuss vaccine options (Sangruej

et al., 2003; Thompson & Duintjer Tebbens, 2014b; Thompson & Kalkowska, 2019; Thompson et al., 2013; Thompson & Tebbens, 2012), and characterized the real differences between the choices of national immunization programs for countries of different World Bank income levels. For these discussions and related modeling, the most recent studies classified RI schedules briefly as IPV-only, IPV/OPV sequential, or OPV+IPV, the last of which indicates primary use of OPV but adds a coadministered dose of IPV as indicated by the “+IPV” (Kalkowska, Pallansch, Wassilak, et al., 2021; Thompson & Kalkowska, 2019). For HI and UMI using IPV-only, we assume that they will continue to do so for the foreseeable future (Kalkowska, Pallansch, Wassilak, et al., 2021; Thompson & Kalkowska, 2019). Similarly, for countries currently using an IPV/OPV sequential schedule, we assume that current polio vaccine policies would not change their immunization schedules for the foreseeable future, except that cessation of any of the remaining OPV type(s) would change the formulation of the OPV they use for the OPV doses, until all OPV cessation occurs and they shift to an IPV-only schedule.

However, for countries that historically relied on OPV only for RI, the current options include increased complexity compared to those in 2019 (Kalkowska, Pallansch, Wassilak, et al., 2021; Thompson & Kalkowska, 2019). Prior to



**FIGURE 2** Vaccine options for oral poliovirus vaccine (OPV) + inactivated poliovirus vaccine (IPV) in their national immunization programs in 2022: Continued OPV cessation (current status quo shown in bold).

and as a readiness criteria for OPV2 cessation, the SAGE recommended that all countries include at least one dose of IPV in their RI schedules (World Health Organization, 2014), which led to the category of OPV+IPV RI schedules (Kalkowska, Pallansch, Wassilak, et al., 2021; Thompson & Kalkowska, 2019). Building on this prior work, we provide an updated structure of the RI options for the countries using OPV+IPV. We note that some differences would arise in the sets of options if global health leaders decided to either (i) continue (World Health Organization Global Polio Eradication Initiative, 2021) or (ii) abandon (Chumakov et al., 2021; Chumakov et al., 2007) OPV cessation as the global polio endgame strategy. In both cases, we assume that restarting the use of OPV2 in RI would not occur, and we leave the discussion of that topic to other studies (Kalkowska, Wassilak, Wiesen, et al., 2023).

#### 4.1 | Continued commitment to globally coordinated OPV cessation

While prior studies included the theoretical option of OPV1 cessation prior to OPV3 cessation, we exclude it as not under consideration by the GPEI. We implicitly assume that if the world continues to pursue OPV cessation as a strategy, then the efforts will be coordinated (Thompson & Duintjer Tebbens, 2008) and would follow current WHO recommendations. Notably, in October 2020, SAGE recommended a minimum of two doses of IPV in all RI schedules (World Health Organization, 2015b), and OPV+IPV countries vary with respect to their adoption of this recommendation.

Figure 2 shows the decision tree of the options for countries currently using OPV+IPV RI schedules. We highlight the *status quo* in bold, and depict the additional permutations

of schedules that may arise with the addition of a second dose of IPV by also allowing for the splitting of coadministered doses (i.e., bOPV+IPV) into separate contacts (i.e., bOPV/IPV). Moreover, Figure 2 includes the option that at any point on the path to all OPV cessation, an LMI OPV+IPV country may prefer to switch to sequential (seq) IPV/OPV schedule instead of including the second IPV dose in its OPV schedule.

Commitment to OPV cessation includes the decision about when to implement cessation and may depend on prerequisites (i.e., firm requirements) or readiness criteria (i.e., desired conditions). Table 1(a) summarizes some potential options in the left column. In the middle column, we indicate whether the GPEI applied the option in the first column prior to 2016 and the rightmost column indicates whether the readiness criterion was effectively implemented or met prior to 2016 OPV2 cessation (Thompson & Tebbens, 2012). Global certification of the eradication of indigenous transmission of WPV1 represents a prerequisite, as already occurred in 2015 for type 2 (World Health Organization, 2015a) and 2019 for type 3 (World Health Organization, 2019). Requiring the end of transmission of cVDPV transmission for types 1 and/or 3 prior to homotypic OPV cessation would help to reduce the risks of the coordinated OPV cessation failing, although questions remain about whether, when, and how to verify or validate the end of cVDPV transmission (World Health Organization, 2022b). Prerequisites or readiness criteria for bOPV cessation may include increasing population immunity to transmission prior to OPV cessation by performing homotypic OPV pSIAs intensively between now and/or in the months running up to OPV cessation, and/or achieving immunization coverage targets for OPV and/or IPV in RI. The development of a vaccine stockpile of homotypic mOPV and/or nOPV for outbreak response prior to OPV cessation

**TABLE 1** Options for prerequisites or readiness criteria for oral poliovirus vaccine (OPV) cessation.

<b>(a) Prerequisite or readiness criteria prior to 2016 OPV2 cessation and completion status prior to OPV2 cessation</b>		
<b>Option</b>	<b>Prior</b>	<b>Done</b>
Global certification of the eradication of indigenous homotypic wild poliovirus (WPV)	Y	Y
Stockpile(s) homotypic OPV (Sabin) vaccine for outbreak response	Y	Y
End transmission of homotypic cVDPV prior to homotypic cessation	Y	N
Increase homotypic population immunity to transmission prior to cessation	Y	N
Develop protocols and needed financial resources for outbreak response	Y	N
Achieve specific minimum immunization dose or coverage targets using inactivated poliovirus vaccine (IPV)	Y	N
Achieve specific minimum immunization dose or coverage targets using OPV	N	
Stockpile(s) homotypic nOPV for outbreak response	N	
Institute requirements for surveillance	N	
Implement containment for homotypic WPV	N	
<b>(b) Risk management strategies that could represent post-OPV cessation prerequisites or readiness criteria</b>		
Develop plans for OPV restart that should include specific trigger(s)		
Ensure accountable management of outbreak response resources		
Ensure sufficient quantities of polio vaccines needed for national routine immunization (RI) programs		
Implement plans to manage risks of immunodeficiency-associated VDPV		
Develop communication strategies to facilitate risk management		
Stockpile(s) homotypic novel OPV for outbreak response		

could represent another anticipated prerequisite, as well as instituting specific requirements for surveillance.

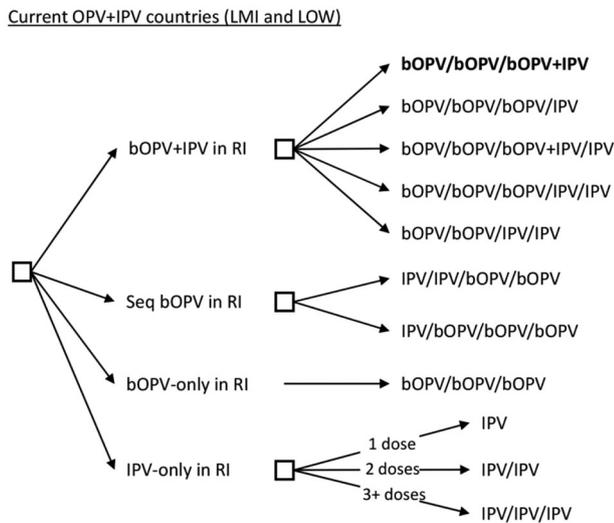
Table 1(b) includes potential postcessation risk management strategies. The experience with OPV2 cessation should motivate revisions and/or the development of explicit and detailed plans for risk management to address the previously encountered problems that now represent known risks. These strategies should recognize the potential for cessation and outbreak response failure and identify the potential triggers for OPV restart, if needed. Additional lessons from OPV2 cessation to date may also include efforts to ensure accountable management of outbreak response resources (e.g., vaccine doses in stockpiles and logistical, technical, and/or financial support) and/or the need to ensure access to sufficient quantities of polio vaccines needed for national RI programs as vaccine schedules evolve after cessation. The development of communication strategies related to risk management, including the possibility of OPV restart, should also become part of the postcessation strategy. Long-term risk management also will require the development and implementation of plans to manage risks posed by immunodeficiency-associated VDPV excretors and sustaining surveillance to rapidly detect any future poliovirus events.

The adoption of prerequisites could possibly delay the implementation of OPV cessation if adequate time for preparation is not provided, which would substantially increase the costs for polio immunization and surveillance in the run-up to OPV cessation.

## 4.2 | Abandoned globally coordinated OPV cessation

As an alternative, even if unlikely, in the event that the currently unsuccessful experience with OPV2 cessation leads to the decision not to pursue globally coordinated OPV cessation as a polio endgame strategy, then country leaders could choose the path of coordinated or uncoordinated control. Figure 3 shows the decision tree for these options, while still assuming no OPV2 restart in RI. The tree includes the possibility of using bOPV-only in RI, which would imply type 2-containing poliovirus vaccine use would only occur in the event of an outbreak. Coordinated control would assume that the GPEI, or some successor group, would continue to manage the globally interdependent risks associated with poliovirus transmission, and that this group would maintain some capacity related to outbreak response and polio vaccine stockpile management for type 2 outbreak response, since we have not assumed that OPV2 use would restart in RI. Notably, in the absence of a continued global commitment to eradication, coordinated control and continuance of current GPEI activities and sufficient resources to support them appears unlikely, which would imply uncoordinated control.

National leaders could maintain continued use of both OPV and IPV, either with the current OPV-first approach (i.e., OPV+IPV) or by shifting to a sequential approach (i.e., IPV/bOPV) to mitigate the risks of VAPP. Similar to the options shown in Figure 2, we assume that countries could



**FIGURE 3** Vaccine options for oral poliovirus vaccine (OPV) + inactivated poliovirus vaccine (IPV) in their national immunization programs in 2022: Abandoned OPV cessation without OPV2 restart in RI (current status quo shown in bold).

decide to add a second IPV dose, as SAGE has recommended, and that bOPV and IPV coadministration may or may not occur. Alternatively, they could opt just to use bOPV only and stop their use of IPV. Finally, national leaders could decide to shift to using only IPV, for which they would need to achieve very high coverage to keep population immunity high to avert the risks of large outbreaks after poliovirus importation or VDPV emergence. Achieving and maintaining high population immunity would imply high costs of control. Even with a global decision to abandon OPV cessation as a polio endgame strategy, individual countries or regions may still choose to coordinate OPV cessation within their borders. However, the risks of importation of OPV-related viruses from areas that do not stop OPV use would pose an ongoing threat (Thompson & Duintjer Tebbens, 2008).

Even in countries with very high IPV-only coverage, imported live polioviruses may sustain some transmission in populations and potentially cause paralytic cases in under-vaccinated subpopulations (Duintjer Tebbens et al., 2005; Kalkowska, Duintjer Tebbens, Grotto, et al., 2015; Thompson et al., 2012, 2015). Recent detections of polio transmission in the United Kingdom (United Kingdom Department of Health & Social Care, 2022), Israel Zuckerman et al., 2022), and the United States (Link-Gelles et al., 2022; Ryerson et al., 2022) in un- or underimmunized populations provide proof of concept. Thus, in the event that OPV use continues, countries will need to consider their national immunization policies and decide which vaccines and how many doses to deliver as part of RI. For middle-income countries using multiple doses of bOPV plus one or two doses of IPV in RI, the decision to revert to only using three doses of a bOPV formulation may prove more attractive from a financial perspective than continuing to deliver multiple OPV and IPV doses (Kalkowska & Thompson, 2021b). Alternatively, with the development of

hexavalent vaccines that contain IPV, countries may prefer to rely on only IPV in this type of combined vaccine for RI, and to use OPV only if and when needed for outbreak response, if OPV supplies remain available in the absence of any regular demand for RI.

### 4.3 | Implications for forecasting polio vaccine needs

The substantial differences in the current options with respect to potential RI vaccine needs, even without OPV2 restart in RI, make efforts to forecast vaccine demand very challenging. This may create issues related to over- or undersupply of specific polio vaccines due to small numbers of manufacturers who face unclear market incentives. National policies developed by large self-producing countries, like China, India, and the Russian Federation, will likely affect the large populations in these countries as well as influence vaccine options available to other populations that might import their poliovirus vaccines.

## 5 | DISCUSSION

The current status of type 2 poliovirus transmission, with nearly 3000 reported cVDPV2 cases since 2016 (as of April 3, 2023; World Health Organization Global Polio Eradication Initiative, 2023) continues to lead to questions about OPV cessation as a global polio endgame strategy as well as the role of nOPV. The accelerated development of nOPV2 for outbreak response, now in use under an Emergency Use Listing (EUL; Macklin et al., 2023), is being followed by a similarly accelerated development of genetically modified nOPV strains for types 1 and 3 (i.e., nOPV1 and nOPV3), and consideration of a potential trivalent nOPV product. Given the absence of performance data for these products in development, we leave the discussion of those options to future studies.

Our assumption in this analysis of no restart of OPV2 (i.e., either Sabin OPV2 or nOPV2) in RI represents the current GPEI strategy. We note that in the event of OPV2 restart in RI, the possibility of multivalent OPV formulations could quickly become even more challenging for national immunization program managers and vaccine manufacturers to navigate due to the large number of possible OPV-containing vaccines. The combinatoric multivalent combinations after OPV2 restart could include simply returning to Sabin-strain tOPV with its predictable properties, using only nOPVs (e.g., nOPV1, nOPV2, and/or nOPV3 independently or in various possible combinations), or using both Sabin OPVs and nOPVs (e.g., a trivalent OPV containing novel strains of all types of OPVs or Sabin bOPV and nOPV2). We do not provide the exhaustive list of combinations of potential OPV options here, but highlight the anticipated complexity discussed elsewhere (Kalkowska, Wassilak, Wiesen, et al., 2023). If OPV2 restart occurs, then countries might change their willingness to pay for multiple doses of IPV, particularly if

a trivalent OPV formulation again becomes available. Prior to the development of combination OPV products containing any nOPV, clinical trials could be required to demonstrate the noninferiority of the combination schedule compared to the schedule with individual OPV components to support licensure. This could theoretically become very complicated given the number of possible combinations. In practice, the possible set narrows considerably due to unlikely licensure of mOPV1 for RI in the foreseeable future (required for OPV3 cessation if it occurred), and unlikely development of novel bivalent products. In addition, the current lack of full licensure of nOPV2 (with licensure anticipated for use in outbreak response as early as the first quarter of 2023 (Macklin et al., 2023), but not yet obtained) and restrictions on its use by the GPEI under the EUL that preclude coadministration with other OPVs (World Health Organization Global Polio Eradication Initiative, 2020), may make studies related to coadministration more challenging. Thus, any RI schedules that include OPV2 (mOPV2 or nOPV2) would need to occur after a global decision to restart OPV2 use in RI.

Although we mentioned the potential prerequisite of requiring the end of transmission of types 1 and 3 cVDPVs prior to homotypic OPV cessation as one potential postcessation risk reduction strategy, confidence about no circulation of these will only come as the time since cessation increases and with no observed signals of transmission despite ongoing and well-performing surveillance (Kalkowska, Badizadegan et al., 2023b; Kalkowska, Duintjer Tebbens, Pallansch, et al., 2015; World Health Organization, 2022b). Challenges to achieving high confidence about meeting such a requirement and the OPV2 cessation experience may motivate discussions about introducing novel OPV strains for types 1 and 3 prior to bOPV cessation.

The importance of effective containment of all live polioviruses also emerges after OPV cessation. The poor outcomes observed to date with respect to managing type 2 live poliovirus risks after OPV2 cessation (Duintjer Tebbens & Thompson, 2018; Kalkowska, Pallansch, Cochi, Kovacs, et al., 2021; Kalkowska, Pallansch, Wassilak, et al., 2021; Macklin et al., 2020; Thompson, 2022) should lead to questions about effective removal of all OPV from supply chains and the field, containment, and stockpile management. In the context of any potential ongoing nOPV use, such that children in some areas may inadvertently continue to receive oral doses of poliovirus vaccines, containment issues may continue to face challenges related to the delivery of different formulations.

The risks of bOPV cessation based on the current polio endgame trajectory (Figure 1) include substantial type 1 poliovirus transmission, including type 1 cVDPVs, with potentially large consequences given the high transmissibility of these viruses. The introduction of IPV prior to OPV2 cessation did not reduce the consequences of OPV2 cessation substantially, in part due to low IPV coverage achieved and delays in introduction as well as limited IPV effect on intestinal immunity. Efforts to develop combination vaccines that contain IPV for use in RI for low- and middle-income coun-

tries may offer the potential to achieve higher coverage with IPV-containing vaccines, but this will come with added costs (Kalkowska & Thompson, 2021b; Thompson & Kalkowska, 2021a).

As discussed in 2018 (Duintjer Tebbens & Thompson, 2018), the ramp down of the global polio budget led to diminished capacities and performance of both preventive and outbreak immunization activities, since countries did not self-fund continued activities (Fortner, 2021). The reduction in polio eradication-dedicated staff (Fortner, 2021), disruptions in polio immunization and surveillance activities during COVID-19, and the failure of the 2016 switch from tOPV to bOPV to end cVDPV2 outbreaks to date create substantial hurdles. Although the GPEI partners remain committed to OPV cessation as the global strategy, the failure to complete successful OPV2 cessation to date and the results of this analysis may affect perceptions about the potential for successful bOPV cessation and motivate demands for a different bOPV cessation or polio endgame strategy.

Related to OPV2 cessation, in 2017 we expected that within a few years, population immunity to type 2 transmission in OPV using countries would continue to decrease, and that the fraction of the population with no type 2 vaccine protection would accumulate to a level that reestablished endemic transmission of cVDPV2s could occur (Duintjer Tebbens & Thompson, 2017). Our observations of poor performance with respect to the operational management of many outbreak responses following OPV2 cessation as of early 2019 led to discussions about the potential need to plan for restarting the OPV2 vaccine production and use in RI (Thompson & Kalkowska, 2019). In 2019, prior modeling did not anticipate successful OPV2 cessation given GPEI performance and plans at the time (Thompson & Kalkowska, 2019). Notably, in response to the epidemiological situation and programmatic challenges, in 2018, the GPEI partners procured additional bulk of mOPV2 (World Health Organization and UNICEF, 2018), and in 2019 they accelerated efforts to develop and produce nOPV2 (Macklin et al., 2023). However, the GPEI partners did not abandon OPV cessation as a strategy and have not recommended restarting OPV2 use in RI, to date. If nothing changes in the operational management of outbreak responses, the model shows essentially no chance of successful poliomyelitis eradication, which requires cessation of all OPV use (including potential repeated cessation of OPV2, both Sabin and novel). With continued suggestions by some to limit the global polio eradication goal to certification of eradication of polio cases caused by the transmission of all three WPVs (disease) and allowing continued use of OPV (Chumakov et al., 2021; Chumakov et al., 2007), we highlight the inability to achieve the eradication of all polio cases using nOPV given the observations of paralytic cases (both VAPP and cVDPV) associated with nOPV2 use. With the challenges to date and that continue to arise, questions may arise about the feasibility of implementing strategies and tactics that can successfully implement OPV cessation. The increasing use of nOPV2 (and potential future use of nOPV1 and/or nOPV3) may create some new opportunities, but may also lead to

substantial challenges related to managing vaccine supplies and expectations related to cases and costs.

Urgently stopping all cVDPV2 transmission by implementing necessary operational changes represents a priority of the GPEI strategic plan (World Health Organization Global Polio Eradication Initiative, 2021). Regarding prospective OPV withdrawal options, GPEI partners and stakeholders need to review the possibilities and make transparent, carefully considered, and globally coordinated decisions, vaccine policies, and risk management choices. This analysis highlights the importance of risk management activities and contingency planning. The currently decentralized GPEI structure and emphasis on 12-month budgets and planning cycles presents challenges for longer term forecasting by modelers, analysts, national and international policy makers, vaccine manufacturers, and others. Without a clear path and contingent alternatives declared in the near future, and given the continued expansion of the available vaccine options (e.g., nOPVs, IPV combination formulations), the polio eradication endgame will become increasingly uncertain and difficult to manage and model.

## 6 | CONCLUSION

As the polio endgame increases in complexity and continued delays extend the timelines for ending all poliovirus transmission, the potential consequences do not currently support global coordination of bOPV cessation in 2027 due to the need to substantially increase population immunity using bOPV in many countries prior to implementation of the endgame strategy.

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