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Insights from modeling preventive supplemental immunization activities as a strategy to eliminate wild poliovirus transmission in Pakistan and Afghanistan

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Abstract

Many countries use supplemental immunization activities (SIAs) with oral poliovirus vaccine (OPV) to keep their population immunity to transmission high using preventive, planned SIAs (pSIAs) and outbreaks response SIAs (oSIAs). Prior studies suggested that investment in pSIAs saved greater health and financial costs associated due to avoided outbreaks. However, questions remain about the benefits of SIAs, particularly with the recent introduction of inactivated poliovirus vaccine (IPV) into routine immunization in all OPV-using countries. The mounting costs of polio eradication activities and the need to respond to oSIAs threatens the use of limited financial resources for pSIAs, including in the remaining countries with endemic transmission of serotype 1 wild poliovirus (WPV1) (i.e., Pakistan and Afghanistan). A recent updated global poliovirus transmission model suggested that the Global Polio Eradication Initiative (GPEI) is not on track to stop transmission of WPV1 in Pakistan and Afghanistan. We use the updated global model to explore the role of pSIAs to achieve WPV1 eradication. We find that, unless Pakistan and Afghanistan manage to increase the quality of bOPV pSIAs, which we model as intensity (i.e., sufficiently high-coverage bOPV pSIAs that reach missed children), the model does not lead to successful eradication of WPV1. Achieving WPV1 eradication, the global objectives of the GPEI, and a successful polio endgame depend on effective and sufficient use of OPV. IPV use plays a negligible role in stopping transmission in Pakistan and Afghanistan and most other countries supported by the GPEI, and more IPV use will not help to stop transmission.

Keywords

polio; eradication; dynamic modeling; oral poliovirus vaccine

Introduction

High coverage with oral poliovirus vaccine (OPV) prevents the circulation of wild polioviruses (WPVs) and the development of circulating vaccine-derived polioviruses (cVDPVs) (Thompson, Kalkowska, & Duintjer Tebbens, 2015; Thompson, Pallansch, Duintjer Tebbens, Wassilak, & Cochi, 2013). Supplemental immunization activities (SIAs) with OPV played a significant role in achieving high population immunity to transmission to

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stop WPVs in many OPV-using countries, and OPV planned, preventive SIAs (pSIAs) continue to contribute to the maintenance of polio-free status in many countries (Duintjer Tebbens et al., 2016; Duintjer Tebbens & Thompson, 2017b; Thompson & Duintjer Tebbens, 2014). However, conducting SIAs requires the investment of resources, and with the Global Polio Eradication Initiative (GPEI) long past its target completion date, resources for the polio endgame remain an issue.

The new 2019–2023 GPEI strategic plan includes continued OPV pSIAs in many GPEI-supported countries, but at a decreasing rate between now and the planned timing of globally-coordinated cessation of bivalent OPV (bOPV) (Global Polio Eradication Initiative, 2019). The GPEI led the effort to globally-coordinate cessation of serotype 2 OPV (OPV2) in 2016, and also supported global introduction of one dose of inactivated poliovirus vaccine (IPV) into all national immunization programs (not already using IPV as of 2016) (Hampton et al., 2017). The GPEI motivated IPV introduction by noting that it would offer protection from paralysis due to serotype 2 poliovirus infection for otherwise unprotected IPV recipients. However, IPV does not induce mucosal immunity or significantly increase population immunity to transmission, and in this regard, it does not represent an effective substitute for OPV (Duintjer Tebbens & Thompson, 2017b). In addition, in most areas at risk for outbreaks, IPV cannot stop outbreaks as well as OPV, if it helps at all, and IPV is not cost-effective compared to OPV (Duintjer Tebbens & Thompson, 2017a). The GPEI expected that OPV-using countries would add an IPV dose to their immunization schedules and still maintain all of their OPV immunization doses until cessation of the last OPV serotype. Unfortunately, however, some national immunization leaders may incorrectly perceive that with the introduction of IPV and limited budgets, they no longer need OPV pSIAs. As a result of decreased OPV use, even with increased IPV use, the population immunity to transmission in many OPV-using countries is declining (Thompson et al., 2015).

To date (i.e., as of the end of 2019), the epidemiology of poliovirus demonstrates sustained transmission of WPV serotype 1 (WPV1) in a large number of geographic areas in Afghanistan and Pakistan, with an increasing trend in WPV1 cases reported in recent years (i.e., 22, 33, and 173 in 2017, 2018, and 2019, respectively (World Health Organization, 2020). Recent updated modeling of the polio endgame suggested that WPV1 transmission would continue through 2024 (i.e., the GPEI would not succeed with WPV1 eradication under its new strategic plan without additional efforts) (Kalkowska, Wassilak, Cochi, Pallansch, & Thompson, 2020). We previously demonstrated the importance of OPV pSIA intensity in the context of stopping WPV1 transmission in northern India to achieve eradication (Thompson & Duintjer Tebbens, 2007). In Pakistan and Afghanistan, at this critical time, remarkably OPV pSIAs stopped completely in some areas in 2019, which contributed to widespread WPV1 transmission with over 5 times more reported cases in 2019 than in 2018. For the GPEI to succeed in its goal of eradicating all WPVs, it must stop transmission of WPV1 in Pakistan and Afghanistan and proactively raise population immunity to transmission (Duintjer Tebbens & Thompson, 2019).

Methods

We used an updated global model (Kalkowska et al., 2020) to evaluate different preventive SIA (pSIA) scenarios to explore options that could lead to the eradication of WPV1. We applied the model to compare alternative options that use different SIA schedules, vaccine types, and vaccination intensity. Briefly, the updated global model (Kalkowska et al., 2020) divides the word into 72 blocks that each consist of 10 subpopulations of approximately 10.7 million people in 2019 (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2017). The subpopulations within a block mix homogenously in space and heterogeneously by age. The model also groups blocks into 9 preferential mixing areas (PMAs, of variable number of blocks per PMA), representing large geographical regions (e.g., Africa, Australasia, Europe) (Kalkowska et al., 2020). The model further characterizes the blocks by income level (low-income, LI; lower middle-income, LMI; upper middle-income, UMI; high-income, HI (World Bank, 2019)) and current vaccine use (OPV+IPV, IPV/OPV, IPV-only (World Health Organization, 2018)), with the epidemiological, demographic, and transmission assumptions representing conditions existing in the world as of the end of 2018. For the blocks that represent conditions like Pakistan and Afghanistan in the global model, the reference case (RC) (or *status quo*) used for this analysis assumes an OPV+IPV routine immunization (RI) schedule (Kalkowska et al., 2020). This refers to 3 doses of OPV delivered at different scheduled ages, and one dose of IPV given at the same time as the third OPV dose. The RC also assumes the assumes the same expected OPV pSIAs as the prior analysis (i.e., 4, 6, 6, 6, 6, and 6 bOPV pSIAs in 2019, 2020, 2021, 2022, 2023, and 2024, respectively) (Kalkowska et al., 2020).

Since the RC does not include successful eradication of WPV1 (Kalkowska et al., 2020), we focused this analysis on pSIA strategies to eliminate WPV1. As discussed in prior publications, the GPEI currently maintains a strategy of high control for WPV1 due to insufficient pSIAs with bOPV in the remaining endemic areas of Pakistan and Afghanistan (Kalkowska et al., 2020), and as evidenced by experience over the past several years (Duintjer Tebbens et al., 2019; Duintjer Tebbens & Thompson, 2019). For this analysis, we sought to identify alternative scenarios that may achieve WPV1 eradication. We considered the alternative scenarios listed in Table 1 compared to the RC of continued planned bOPV use through 2023. The alternative scenarios include: (1) an alternative RC (RC*) that uses the same assumptions as the RC except for using an increased pSIA impact level from 2020 on, (2) the use of 8 bOPV SIA rounds in 2020 followed by 6 bOPV pSIA rounds per year from 2021 with current pSIA impact level from 2020, (3) the use of 8 bOPV SIA rounds in 2020 followed by 6 bOPV pSIA rounds per year from 2021 with an increased pSIA impact level from 2020, (4) the use of 4 bOPV and 2 mOPV1 SIA rounds per year with the current pSIA impact level from 2020, and (5) the use of 4 bOPV and 2 mOPV1 SIA rounds per year with an increased pSIA impact level from 2020. We also considered the impact of introducing a second IPV dose in RI added to the scenario that uses 6 bOPV SIA rounds per year with the current pSIA impact level from 2020. For this scenario we used two approaches of adding a second IPV dose to the RI schedule, which provide two bounding estimates of impacts: (i) a lower bound, in which only children that received the first IPV dose will also receive second IPV dose and thus benefit from the efficacy of 2 doses, and (ii)

an upper bound, in which the second IPV dose goes to different children, effectively covering double the number of children with one IPV dose in a schedule that includes two IPV doses. In reality, the situation will fall somewhere between these two bounds, with some fraction of kids getting 2 doses, some getting 1 dose, and many not receiving any due to the low RI coverage in these blocks.

Table 1 summarizes the pSIA assumptions for the RC and alternative scenarios and provides some of the key associated inputs for the model. For this analysis, we focused on a time horizon of modeling the scenarios between the beginning of 2019 through the end of 2024 to correspond with the pSIAs planned under the current 2019–2023 GPEI strategic plan (Global Polio Eradication Initiative, 2019). The model characterizes the quality of pSIAs as a function of the impact level shown in Table 1, which depends on the model inputs for true coverage (TC) and the probability of repeatedly missed children (P_{RM}) (i.e., the chance that children missed in the prior SIA are missed again in the current SIA). The pSIA impact level determines the number of children who receive OPV directly, and thus the number who remain unexposed to direct OPV immunization and can either become first infected by circulating OPV-related viruses or WPV1. While the actual impact level of pSIAs varies, the model assumes the same level from round to round for each subpopulation, although it uses different values for the 10 subpopulations in the blocks that represent conditions like Pakistan and Afghanistan (Kalkowska et al., 2020). The third column of Table 1 shows the assumed impact level for the worst-performing subpopulation and alternative minimum impact levels assumed as a function of time for that subpopulation, with all other subpopulations maintained at the impact levels assumed in the RC.

We coded the model in general-purpose programming language JAVA™ using the integrated development environment Eclipse™. For this analysis we present the same deterministic run as in the previously published RC (i.e., without stochastic realizations of the long-term reintroduction risks and using Euler's numerical integration method with a time step of 0.5 day (Kalkowska et al., 2020).

Results

Table 2 provides the simulation results for the RC and the alternative scenarios for the expected numbers of WPV1 cases and the expected elimination timing of WPV1 transmission (if die out occurs) or the result of no elimination (as occurs in the RC). The results suggest that none of the scenarios that assume the continuous current OPV pSIA impact level through the end of 2024 lead to elimination of WPV1. In contrast, increasing the quality of pSIAs could lead to elimination as early as the first quarter of 2021 (i.e., for the assumption of 8 pSIAs in 2020 followed by 6 pSIAs per year from 2021 with a higher impact level), which represents an increase in both the intensity (or quality) and the number of pSIA rounds in 2020. In addition, increasing only the intensity but not the number of pSIA rounds in 2020 leads to later elimination in the beginning of 2022 (i.e., for the assumption of 6 SIAs per year from 2020 in RC*).

The increase in OPV coverage remains essential to ending WPV1 transmission, independent of mOPV1 or IPV use. Specifically, using 6 bOPV SIA rounds compared to 4 bOPV and 2

mOPV1 rounds does not significantly change the elimination time, although it somewhat reduces the expected number of WPV1 cases. However, we emphasize that this analysis does not explore the impact of using mOPV1 instead of bOPV on serotype 3 population immunity and the risks of creating serotype 3 circulating vaccine-derived polioviruses. As expected, adding a second dose of IPV to the existing RI schedule in the scenario with 6 bOPV SIAs per year from 2020 and the continuous current pSIA impact level (from the RC) reduces the expected number of WPV1 cases, but it does not lead to elimination of WPV1. Although IPV introduction led to significant enthusiasm about the introduction of a new vaccine, which many individuals and national health leaders may have misperceived as "better" than OPV, the use of IPV in endemic countries has not accelerated WPV1 eradication to date, and our results suggest than more IPV will also not accelerate eradication.

Discussion

While this analysis highlights the importance of achieving quality (i.e., higher coverage and reaching more previously unreached children with OPV), the results depend on maintaining the population immunity and modeled pSIA impact levels in other subpopulations in the block. Thus, although it might seem tempting to shift all resources to the current low-performing areas, this would create new other low-performing areas (as modeled for Nigeria (Duintjer Tebbens, Pallansch, Wassilak, Cochi, & Thompson, 2015)). Eliminating WPV1 transmission in Pakistan and Afghanistan requires raising population immunity to transmission high enough with bOPV in all areas at the same time. Chasing the WPV1 by moving resources to areas with cases will not lead to elimination (Duintjer Tebbens & Thompson, 2019). Achieving elimination requires creating conditions in which the WPV1 cannot find enough infectible individuals to survive.

The polio endgame remains complex, but this analysis suggests that achieving the goals of polio eradication remain possible if we can use the existing tools well. Unfortunately, the remaining endemic countries and thus the GPEI do not appear on track to achieve this success. As indicated by these results, major re-alignment of GPEI resources would need to occur for success. Notably, the GPEI and Pakistan and Afghanistan continue to emphasize the delivery of IPV, which has not accelerated the disruption of WPV1 transmission. In addition, the introduction of IPV may have affected OPV acceptance, because some people may perceive that IPV is a "better vaccine" since it is newer, and/or they may object to even more polio vaccine doses since the IPV doses were added to the existing schedule of OPV doses. However, pSIAs with OPV appear essential to the cessation of WPV transmission in Pakistan and Afghanistan, just as maintaining OPV pSIAs remains essential to maintaining high population immunity to transmission to prevent cVDPVs in all OPV-using countries that conduct pSIAs to compensate for low RI coverage.

Although this analysis focused on WPV1 and the transmission of serotype 1, the events that occur with serotypes 2 and 3 may impact pSIA planning for WPV1. Notably, the detection of serotype 2 cVDPVs (cVDPV2s) in Pakistan combined with a limited budget for SIAs, may lead to the need to perform outbreak response SIAs (oSIAs) with serotype 2 monovalent OPV (mOPV2) that may compete for total SIA resources with bOPV pSIAs.

This may further exacerbate the situation for WPV1, or alternatively, make responding to the cVDPV2s more challenging, and increase the global chances of an OPV2 restart (Duintjer Tebbens & Thompson, 2018; Thompson & Kalkowska, 2019).

Although misperceptions about the role of IPV appear to drive some decisions, we emphasize that the cost of IPV significantly exceeds the cost of OPV, and in the context of resource limitations, OPV use should represent a priority for polio national elimination and global eradication efforts in OPV-using countries. The epidemiological experience in Pakistan and Afghanistan since the introduction of IPV demonstrates that IPV has not accelerated WPV1 eradication, and multiple studies warn that IPV use in national immunization programs can mask live poliovirus transmission (Duintjer Tebbens & Thompson, 2014; Mangal, Aylward, & Grassly, 2013; Thompson & Duintjer Tebbens, 2012). Consequently, the GPEI and the governments of Pakistan and Afghanistan should consider stopping all donor- and government-supported IPV use until WPV1 elimination occurs and instead focus all of their financial and human resources on achieving high coverage with OPV. While performance remains an ongoing challenge (Thompson, 2014), delivering high-quality SIAs remains a prerequisite to achieving the GPEI mission. Modeling demonstrates that achieving and maintaining high SIA quality (or not) remains a choice, not a forgone conclusion (Thompson & Duintjer Tebbens, 2007). We recognize that modeling high performance is not the same as achieving it in practice, particularly in the current geo-political climate, but experience with polio elimination in India and other challenging areas suggest the elimination is possible with the right strategy, commitments, and sufficient resources. Alternatively, if the GPEI and Pakistan and Afghanistan cannot achieve high quality pSIAs with OPV and stop WPV1 transmission, then the GPEI will fail to achieve WPV1 elimination by 2023.

As with any model, our model comes with some limitations (Kalkowska et al., 2020). In this comparison of the results of different scenarios to the RC, we use the same assumptions for inputs that do not change across scenarios. Our findings depend completely on the selected scenarios and pSIA assumptions. We recognize that pSIA quality and intensity in our model do not translate directly to interventions in the field, and that they represent somewhat abstract concepts. We used varying scenarios to highlight different generic strategies that we believe represent the range of ongoing discussions about what to do in Pakistan and Afghanistan. We recognize that different assumptions would lead to different results, and all of the scenarios considered may differ from the actual path ultimately taken.

Conclusions

OPV pSIAs continue to play an essential role in the success of the polio endgame, and more intensive OPV pSIAs will be needed to stop WPV1 transmission in Pakistan and Afghanistan. IPV does not effectively replace OPV pSIAs, and national and global health policy leaders should carefully consider whether the strategies they use are likely to lead to the desired outcomes.

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Table 1:

Modeled scenarios and input assumptions based on planned supplemental immunization activities (pSIAs) for endemic blocks

Scenario	pSIA schedule: vaccine (day(s) of year)	Minimum pSIA impact level (TC, P_{RM})	RI schedule
Reference case (RC) (Comparator or *status quo* of continued planned bOPV use through 2024)			
≥2019	bOPV (15, 45, 75, 290, 320, 350)	2 (0.35, 0.95)	OPV+IPV
Alternative reference case (RC*) with increased pSIA impact level from 2020			
2019	bOPV (15, 45, 75, 290, 320, 350)	2 (0.35, 0.95)	OPV+IPV
≥2020	bOPV (15, 45, 75, 290, 320, 350)	3 (0.50, 0.80)	OPV+IPV
8 bOPV SIAs in 2020 followed by 6 bOPV pSIAs per year from 2021 with current pSIA impact level from 2020			
2019	bOPV (15, 45, 75, 290, 320, 350)	2 (0.35, 0.95)	OPV+IPV
2020	bOPV (15, 45, 75, 105, 260, 290, 320, 350)	2 (0.35, 0.95)	OPV+IPV
≥2021	bOPV (15, 45, 75, 290, 320, 350)	2 (0.35, 0.95)	OPV+IPV
8 bOPV SIAs in 2020 followed by 6 bOPV pSIAs per year from 2021 with increased pSIA impact level from 2020			
2019	bOPV (15, 45, 75, 290, 320, 350)	2 (0.35, 0.95)	OPV+IPV
2020	bOPV (15, 45, 75, 105, 260, 290, 320, 350)	3 (0.50, 0.80)	OPV+IPV
≥2021	bOPV (15, 45, 75, 290, 320, 350)	3 (0.50, 0.80)	OPV+IPV
4 bOPV and 2 mOPV1 SIAs with current pSIA impact level from 2020			
≥2019	bOPV (45, 290, 320, 350), mOPV1 (15, 75)	2 (0.35, 0.95)	OPV+IPV
4 bOPV and 2 mOPV1 SIAs with increased pSIA impact level from 2020			
2019	bOPV (45, 290, 320, 350), mOPV1 (15, 75)	2 (0.35, 0.95)	OPV+IPV
≥2020	bOPV (45, 290, 320, 350), mOPV1 (15, 75)	3 (0.50, 0.80)	OPV+IPV
6 bOPV SIAs with current pSIA impact level from 2020 with second IPV dose in RI from 2020 (see text for assumptions used)			
2019	bOPV (15, 45, 75, 290, 320, 350)	2 (0.35, 0.95)	OPV+IPV
≥2020 (lower bound)	bOPV (15, 45, 75, 290, 320, 350)	2 (0.35, 0.95)	OPV+2IPV
≥2020 (upper bound)	bOPV (15, 45, 75, 290, 320, 350)	2 (0.35, 0.95)	OPV+2IPV

Abbreviations: bOPV, bivalent oral poliovirus vaccine (containing serotypes 1 and 3); IPV, inactivated poliovirus vaccine; mOPV1, serotype 1 monovalent oral poliovirus vaccine; OPV, oral poliovirus vaccine; pSIA, planned SIA; P_{RM}, repeatedly missed probability; RC, reference case; RI, routine immunization; SIAs, supplemental immunization activities, TC, true coverage

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Table 2:

Expected number of WPV1 cases and WPV1 elimination for different scenarios

Scenario	Expected number of WPV1 cases in 2019–2024	Expected WPV1 elimination
Reference case (RC) (Comparator or *status quo* of continued planned bOPV use through 2024)	781	No elimination
Reference case (RC) with increased pSIA impact level from 2020	324	January 18, 2022
8 bOPV SIAs in 2020 followed by 6 bOPV pSIAs per year from 2021 with current pSIA impact level from 2020	624	No elimination
8 bOPV SIAs in 2020 followed by 6 bOPV pSIAs per year from 2021 with increased pSIA impact level from 2020	243	March 30, 2021
4 bOPV and 2 mOPV1 SIAs with current pSIA impact level from 2020	754	No elimination
4 bOPV and 2 mOPV1 SIAs with increased pSIA impact level from 2020	308	January 15, 2022
6 bOPV SIAs with current pSIA impact level from 2020 + second IPV dose in RI from 2020		
lower bound	679	No elimination
upper bound	631	No elimination

Abbreviations: bOPV, bivalent oral poliovirus vaccine (containing serotypes 1 and 3 IPV, inactivated poliovirus vaccine; mOPV1, serotype 1 monovalent oral poliovirus vaccine; OPV, oral poliovirus vaccine; RC, reference case; pSIA, planned SIA, RI, routine immunization; SIAs, supplemental immunization activities; WPV1, wild poliovirus serotype 1