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Evaluation of proactive and reactive strategies for polio eradication activities in Pakistan and Afghanistan

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Abstract

Only Pakistan and Afghanistan reported any polio cases caused by serotype 1 wild polioviruses (WPV1s) in 2017. With the dwindling cases in both countries and pressure to finish eradication with the least possible resources, a danger exists of inappropriate prioritization of efforts between the two countries and insufficient investment in the two countries to finish the job. We used an existing differential equation-based poliovirus transmission and oral poliovirus (OPV) evolution model to simulate a proactive strategy to stop transmission, and different hypothetical reactive strategies that adapt the quality of supplemental immunization activities (SIAs) in response to observed polio cases in Pakistan and Afghanistan. To account for the delay in perception and adaptation, we related the coverage of the SIAs in high-risk, under-vaccinated subpopulations to the perceived (i.e., smoothed) polio incidence. Continuation of the current frequency and quality of SIAs remains insufficient to eradicate WPV1 in Pakistan and Afghanistan. Proactive strategies that significantly improve and sustain SIA quality lead to WPV1 eradication and the prevention of circulating vaccine-derived poliovirus (cVDPV) outbreaks. Reactive vaccination efforts that adapt moderately quickly and independently to changes in polio incidence in each country may succeed in WPV1 interruption after several cycles of outbreaks, or may interrupt WPV1 transmission in one country but subsequently import WPV1 from the other country or enable the emergence of cVDPV outbreaks. Reactive vaccination efforts that adapt independently and either more rapidly or more slowly to changes in polio incidence in each country may similarly fail to interrupt WPV1 transmission and result in oscillations of the incidence. Reactive strategies that divert resources to the country of highest priority may lead to alternating large outbreaks. Achieving WPV1 eradication and subsequent successful OPV cessation in Pakistan and Afghanistan requires proactive and sustained efforts to improve vaccination intensity in under-vaccinated subpopulations while maintaining high population immunity elsewhere.

Introduction

Now 30 years into its efforts to globally eradicate all wild polioviruses (WPVs),(World Health Assembly, 1988) the Global Polio Eradication Initiative (GPEI), an international partnership that provides financial and technical support to polio eradication activities, reduced the global burden of paralytic poliomyelitis (polio) due to WPVs by over 99% and enabled the certification of 4 of the 6 World Health Organization regions as WPV-free

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(World Health Organization, 2018). Of the three WPV serotypes, the world declared serotype 2 WPV globally eradicated in 2015 (with the last reported case in 1999) (Global Polio Eradication Initiative, 2015) and did not report any serotype 3 WPV since 2012 (Kew et al., 2014). Outside of Pakistan and Afghanistan, which reported a combined 22 polio cases due to serotype 1 WPV (WPV1) in 2017, no WPV1 detections occurred since four polio reported cases in Borno state in Nigeria in 2016.(World Health Organization, 2018) However, uncertainty still exists about whether WPV1 continues to circulate in Nigeria due to surveillance and vaccination access challenges in the Lake Chad area that includes Borno (Nnadi et al., 2017).

Given the current situation, appropriately the GPEI top priority represents the interruption of WPV1 transmission in Pakistan and Afghanistan, with ambitious goals to do so by end of 2018. While both countries made considerable progress since they experienced a surge of cases during 2013–2015, security challenges, limited access to some areas, and insufficient overall program performance remain serious impediments to the interruption of WPV1 transmission. Environmental surveillance (Alam et al., 2016) continues to frequently find signals of WPV1 transmission in both countries, and WPV1 continues to periodically cross the Pakistan-Afghanistan border to cause local transmission, which suggests that population immunity to WPV1 transmission remains insufficient. Eradication requires complete interruption of transmission, which manifests in zero observed cases and absence of any WPV1 detected in the environment for a prolonged period of time (Eichner & Dietz, 1996; Kalkowska, Duintjer Tebbens, Pallansch, et al., 2015).

Various mathematical and statistical models studied the poliovirus situation in Pakistan and Afghanistan to inform strategies to finish eradication in the two countries (Duintjer Tebbens et al., 2018; Mercer et al., 2017; Molodecky et al., 2017; Shirreff, Wadood, Vaz, Sutter, & Grassly, 2017). Immunization plans available as of late 2017 suggest no increase in the frequency of supplemental immunization activities (SIAs) in 2018 and 2019 compared to prior years, which implies insufficient intensity of efforts to interrupt WPV1 transmission unless the quality of activities substantially improves (Duintjer Tebbens et al., 2018; Kalkowska, Duintjer Tebbens, Pallansch, & Thompson). Quality effectively comes down to the ability of vaccination efforts (i.e., SIAs or routine immunization (RI)) to reach historically under-vaccinated subpopulations, which can support WPV transmission even in the context of high population immunity to transmission in the surrounding general populations (Blake et al., 2014; Duintjer Tebbens et al., 2018; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013; Kalkowska, Duintjer Tebbens, & Thompson, 2014a, 2014b; Thompson & Duintjer Tebbens, 2017; Wagner et al., 2014). These studies and the experience in other countries suggest that reaching the under-vaccinated subpopulations with OPV will lead to success. However, these subpopulations remain imperfectly identified and probably geographically dispersed, as suggested by continued WPV1 detections from different parts of both countries (Alam et al., 2016). In the absence of perfect information about the under-vaccinated subpopulation(s), a risk exists of relying on WPV1 detections to guide the immunization efforts, which amounts to a reactive approach to achieving eradication (i.e., chasing the virus, but not getting in front of it by preventing it from finding susceptible children). Moreover, with Pakistan reporting only 8 polio cases due to WPV1 in 2017, compared to 14 in Afghanistan (World Health Organization, 2018), a risk exists of a

premature sense of success in Pakistan and/or prioritization of efforts in Afghanistan (Kahn & Taylor-Robinson, 2017; Mushtaq, Mehmood, & Hyder, 2017). Prior modeling of polio transmission in India demonstrated the danger of setting priorities based on reactive considerations in the context of eradication efforts (Duintjer Tebbens & Thompson, 2009; Thompson & Duintjer Tebbens, 2007). Building on this work and our existing model of poliovirus transmission in Pakistan and Afghanistan (Duintjer Tebbens et al., 2018), this analysis explores the impact of various hypothetical reactive and proactive strategies to pursue WPV1 eradication in Pakistan and Afghanistan.

Methods

We use a previously-developed deterministic differential equation-based model of poliovirus transmission and OPV evolution (Duintjer Tebbens et al., 2014; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013) tailored to Pakistan and Afghanistan.(Duintjer Tebbens et al., 2018) Briefly, the model uses the generic structure and associated input assumptions (Duintjer Tebbens, Pallansch, et al., 2013a; Duintjer Tebbens, Pallansch, et al., 2013b) that reproduced the evidence about poliovirus behavior in a diverse set of conditions (Duintjer Tebbens et al., 2014; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013; Kalkowska, Duintjer Tebbens, Grotto, et al., 2015). The generic structure includes appropriate immunity states, infection processes, waning stages, transmission routes, OPV transmission and evolution (i.e., reversion from attenuated OPV strains to vaccine-derived poliovirus (VDPV) strains with assumed neurovirulence and transmissibility comparable to homotypic WPV strains), age-heterogeneous mixing, deterministic approximation of die-out, and methods to characterize immunization, including mixed inactivated poliovirus vaccine (IPV) and OPV use in RI or SIAs and the probability of children repeatedly missing successive SIAs (Duintjer Tebbens et al., 2014; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013; Duintjer Tebbens, Pallansch, Kim, et al., 2013; Duintjer Tebbens & Thompson, 2017b; Kalkowska et al., 2014a, 2014b). Table 1 summarizes key model inputs for the Pakistan and Afghanistan model from prior work (Duintjer Tebbens et al., 2018).

The model divides both countries into two subpopulations (i.e., a relatively small historically under-vaccinated subpopulation and a larger general population better reached by vaccination efforts). For all analyses in this study, we use the “more isolated” mixing assumptions from the prior model, which assumes a low degree of mixing between all four subpopulations (Duintjer Tebbens et al., 2018). The model uses national data to characterize demographic model inputs (size, birth rates, age-specific mortality rates), national RI coverage by dose with OPV and IPV, and the timing, vaccines, and target populations of SIAs. The model iteratively fits the impact of individual SIAs in the general populations using the overall average coverage (i.e., true coverage) and the coverage among children targeted but missed in the previous SIA (i.e., repeated missed probability) to the dose histories of non-polio acute flaccid paralysis (AFP) cases reported by the surveillance system. The model implicitly assumes accuracy of reported doses, and assumes that the reported non-polio AFP cases provide a representative sample of the general population.

To calibrate the model to the reported incidence of polio cases in each country, the model manually fits the annual relative RI coverage in the under-vaccinated subpopulations

compared to the corresponding national estimates and the relative SIA coverage (RSC) of individual SIAs in the under-vaccinated subpopulations compared the corresponding general populations. The model results show a close match between reported and modeled incidence since the establishment of comprehensive AFP surveillance in each country (Duintjer Tebbens et al., 2018). Consistent with the actual experience, the model includes the 2014 introduction of IPV in immunization activities and the 2016 switch from trivalent OPV (tOPV), which contained attenuated strains of all three serotypes, to bivalent OPV (bOPV), which does not contain serotype 2. Thus, all SIAs conducted after April 2016 include only bOPV or IPV, with the exception of 3 SIAs in 2017 that used serotype 2 monovalent OPV to respond to a serotype 2 circulating VDPV (cVDPV) outbreak.

The model uses information about planned SIAs as of late 2017, which included 9 SIAs each in Pakistan and Afghanistan in 2018, all with bOPV only (i.e.., 5 in Pakistan and 4 in Afghanistan). SIAs include national immunization days (NIDs) that target all children under five years of age in the entire country, or sub-national immunization days (SNIDs) that target only a fraction of the children under five years of age (i.e., children in some areas). In the absence of detailed information about targeted populations of the SNIDs, we assumed that they target the same fraction of the under-vaccinated and general subpopulations as the reported national fraction of the children under five years targeted during these SNIDs, which varies between 0.4 and 0.6. The fitted values in the model used to estimate the true coverage for SIAs in the general population in Pakistan and Afghanistan at the end of 2017 equal 0.8 and 0.7, respectively. The fitted repeated missed probabilities for SIAs in the general population in Pakistan and Afghanistan at the end of 2017 equal 0.5 and 0.55, respectively. The RSCs for SIAs in the under-vaccinated subpopulations needed to reproduce the reported incidence patterns in Pakistan and Afghanistan at the end of 2017 equal 0.25 and 0.2, respectively. Assuming that the relative coverage reduces the true coverage proportionally and the coverage among previously missed children by the same proportion as the coverage among previously reached children,(Duintjer Tebbens et al., 2014) the RSCs imply true coverage values of 0.20 and 0.14 for the Pakistan and Afghanistan under-vaccinated subpopulations, respectively, and repeated missed probabilities of 0.83 and 0.87, respectively.

For the base case, we assume that the SIA schedule for 2018 continues in each year in perpetuity with the coverage assumptions from late 2017. We also assume continuing RI coverage at the same level as 2017. Figure 1 shows the timing of the SIAs from 2018 onwards (symbols at the top of the chart) and the polio incidence (solid lines) due to serotype 1 polioviruses for continuation of the *status quo* (i.e., the base case) in both countries, which reflects polio cases occurring predominantly in the under-vaccinated subpopulations. As previously reported (Duintjer Tebbens et al., 2018), in the absence of an improvement in SIA frequency or quality, the base case scenario does not result in interruption of WPV1 transmission. Consequently, we assume that the cessation of bOPV does not occur for any of the prospective analyses, which also allows us to explore the longer term equilibrium behavior that occurs for the various strategies.

We consider proactive and reactive alternative strategies to stop transmission. For the proactive strategy, we model a sustained increase in the RSC to 0.35 in both under-

vaccinated subpopulations, regardless of observations of polio incidence, which suffices to interrupt all WPV transmission. This strategy represents a sustained intensification in all under-vaccinated subpopulations. In contrast, for the analysis of reactive strategies, we first define the triggers for reacting based on prior work that used the concept of "perceived incidence" to model the reality that strategies do not instantaneously change as the paralytic infections occur (Duintjer Tebbens & Thompson, 2009; Thompson & Duintjer Tebbens, 2007). We then characterize how the SIA quality may change depending on the perceived incidence, considering two types of reactive strategies: strategies that independently adapt to the perceived incidence in each under-vaccinated subpopulation, and strategies that prioritize SIA quality based on the perceived urgency of each under-vaccinated subpopulation.

The perceived incidence provides a stylized approach to average over incidence information with more weight given to more recent incidence (i.e., it serves to delay and smooth) (Duintjer Tebbens & Thompson, 2009; Thompson & Duintjer Tebbens, 2007). We use the concept of the perception time to represent the average time to perceive the situation on the ground and adapt reactive vaccination efforts to it, which accounts for the delays between onset of infection and paralysis (i.e., approximately 10 days (Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013)), paralysis onset and confirmation (several weeks), observation of confirmed cases and planning of programmatic efforts to respond, and on any assumed effect on SIA quality. For a given perception time, we calculate the perceived annual incidence assuming standard first-order exponential smoothing (Duintjer Tebbens & Thompson, 2009) using Equation 1:

$$\frac{dPI(t)}{dt} = \frac{Inc(t) - PI(t)}{T} \quad (1)$$

where PI denotes the perceived annual incidence of polio cases, Inc denotes the instantaneous annual incidence of polio cases, uppercase T denotes the perception time, and lowercase t denotes time. Figure 1 (dotted lines) shows the perceived incidence for different values of T. Figure 1 illustrates how shorter values of T result in more rapid changes in the recognition of the need to act in response to changes in the instantaneous incidence, while longer values of T imply slower recognition of the need to act to changes in the instantaneous incidence. For example, the surge in cases that occurred in Pakistan in 2014 still manifests in elevated perceived incidence during 2018 for T of 12 months, while the surge in 2014 does not impact the perceived incidence for T of 3 months.

We assume that the reactive strategies adapt the SIA quality in response to the perceived incidence, such that higher perceived incidence leads to more investments in high SIA quality. Specifically, we hold the vaccination coverage in the general population fixed at the 2018 levels described above, and define SIA quality as the RSC in the under-vaccinated compared to the general population. We use the function in Equation 2 to describe how the RSC exponentially depends on the perceived incidence for the independently reactive strategies:

$$RSC(PI) = 1 - e^{-\ln(0.5) \times PI/H} \quad (2)$$

where H describes how fast the RSC increases with increases in perceived incidence. Analogous to concepts of half-life and doubling time (Sterman, 2000), we define H as the perceived incidence for which the RSC becomes 0.5 (although any other point on the curve could similarly uniquely define its shape). Figure 2 shows the relationship between RSC and the perceived incidence for three different values of H.

For the priority-based reactive strategies, we use a different relationship for the RSC. We assume that the RSC for the reactive strategies in each under-vaccinated subpopulation depends on the relative contribution of the perceived incidence in all subpopulations(Duintjer Tebbens & Thompson, 2009) according to Equation 3:

$$RSC(s) = TRCS \times \frac{PI(s)}{TPI} \quad (3)$$

where RSC(s) denotes the RSC for under-vaccinated subpopulation s (s=1, 2 for Pakistan and Afghanistan, respectively), $TRSC$ denotes the total RSC achieved in both under-vaccinated subpopulations combined, $PI(s)$ denotes the perceived incidence in under-vaccinated subpopulation s, and TPI denotes the total perceived incidence from all four subpopulations in the model. We note that the TPI equals approximately the incidence in the two under-vaccinated subpopulations as long as we keep the frequency and quality of SIAs in the general populations fixed at the current high levels. For the $TRSC$, we consider strategies that use the sum of the RSCs in both under-vaccinated subpopulations for the base case, which equals 0.45. We also consider a higher $TRSC$ value of 0.70, corresponding to the sum of the RSCs of 0.35 required in each under-vaccinated subpopulation to interrupt WPV1 transmission with the proactive strategy.

Finally, we consider one additional variation on a priority-based reactive strategy that shifts all efforts for SIAs in under-vaccinated subpopulations to the under-vaccinated subpopulation with the highest perceived incidence (Duintjer Tebbens & Thompson, 2009). This strategy effectively conducts a high-quality SIA only in the under-vaccinated subpopulation of highest priority at the expense of not conducting any SIAs at all in the other under-vaccinated subpopulation (while still maintaining SIAs in both general populations).

Results

Table 2 summarizes the strategies we evaluated and the main results, while Figures 3–6 show the dynamics for the different types of strategies. Figure 3 (dashed lines) shows that proactively and simultaneously increasing the quality of SIAs in both under-vaccinated subpopulations results in a rapid and sustained decrease in the incidence. Interruption of WPV1 transmission occurs in April, 2020, with 13 cumulative polio cases in 2018, less than 3 in 2019, and less than one during the first months of 2020 (i.e., several months before transmission dies out). Further increasing the RSC shortens the time until interruption (not shown).

Figure 4a shows the results for reactive strategies that adapt independently to the perceived incidence in each under-vaccinated subpopulation, with H equal to 100 polio cases per year.

Regardless of the perception time T, each reactive strategy involves deteriorating SIA quality during 2018 due to the low current actual and perceived incidence level, which enables the occurrence of a large outbreak at the end of the year in both countries (i.e., larger than for the base case in Figure 1). For the moderate perception time T of 6 months (solid lines), this outbreak results in a moderately quick and moderately sustained improvement of SIA quality. Coupled with the natural immunity induced by the 2018 outbreak, this suffices for WPV1 elimination in Pakistan in early 2020. However, it does not suffice in Afghanistan owing to its lower number of NIDs per year (Figure 1). As the perceived incidence decreases and results in complacency in sustaining SIA quality, Afghanistan experiences another large outbreak in 2021, which reintroduces WPV1 in Pakistan. After this second cycle of outbreaks, WPV1 elimination from both countries finally occurs in early 2023. With a shorter perception time (T=3 months, short dashes), the cycles follow each other up more rapidly and remain somewhat less dramatic. WPV1 circulation continues into 2025 and the number of cases remains larger than for T=6 months. With a longer perception time (T=12 months, long dashes), WPV1 circulation also continues into 2025, with a longer time between outbreaks and even more cases overall (Table 1).

Figure 4b shows that an overall increase in RSC implied by a lower H of 50 polio cases per year (see Figure 2) results in much lower incidence throughout, but still fails to avoid continuing outbreaks. Notably, for T equal to 3 months, WPV1 elimination occurs during 2022 in Pakistan but not in Afghanistan. For this strategy, the subsequent deterioration in SIA quality in Pakistan does not result in a WPV1 importation outbreak because the WPV1 incidence in Afghanistan remains sufficiently small to prevent a WPV1 importation from occurring (i.e., for the assumed intensity of mixing between the subpopulations). However, the failure to sustain high SIA quality in Pakistan results in an indigenous serotype 1 circulating VDPV (cVDPV1) outbreak that emerges in 2024 (Figure 3b, short dashes). For longer T of 6 or 12 months and H equal to 50, no interruption of WPV1 or indigenous cVDPV1 occurs in either country. Increasing H to 200 implies overall lower RSCs, which leads to even larger outbreaks than for the moderate or low H, despite temporary local die-out in one of the under-vaccinated subpopulations followed by reintroduction of WPV1 from the other under-vaccinated subpopulation (Figure 4c, Table 1).

Figure 5 shows the results for reactive strategies based on priority, as determined by the perceived incidence in each under-vaccinated subpopulation, without increasing the combined RSC of the under-vaccinated subpopulations compared to the base case (Figure 1). Figure 5 suggests that regardless of how fast we adapt to the changing priorities on the ground, reallocating efforts to the subpopulation of highest priority does not lead to WPV1 interruption in either country. Rather, it leads to alternating outbreaks in the two countries, with ultimately somewhat more cases compared to the base case that maintains the same combined RSC coverage in the two under-vaccinated subpopulations (Table 1). Shorter perception times imply that priorities shift more quickly, which leads to outbreak cycles with increasing amplitude and ultimately results in more polio cases compared to the longer perception times.

Following a priority-based reactive strategy with the same combined RSC in both under-vaccinated subpopulations similarly results in few remaining polio cases and slightly later

interruption of transmission in May 2020 (Figure 6, short dashes). However, prioritizing the same level of SIA efforts exclusively to the under-vaccinated with the highest perceived incidence for each SIA amounts to highly-reactionary behavior that only results in WPV1 interruption in August, 2021, after experiencing another outbreak cycle in each country (Figure 6, long dashes). Moreover, with the last WPV1 outbreak occurring in Pakistan, this strategy would subsequently ignore the under-vaccinated subpopulation of Afghanistan, which leads to the occurrence of cases due to partially reverted viruses related to serotype 1 OPV. This triggers a return to prioritizing all SIAs in Afghanistan, which prevents this event from becoming a full-blown cVDPV1 outbreak. Nevertheless, such a scenario would seriously jeopardize the prospects for successful bOPV cessation.

Discussion

Vaccination by its nature represents a preventive health intervention. At the individual level, we administer pediatric vaccines to children before they become infected to protect them from infection and any associated disease. No cure exists for polio (with the exception of possible future limited use of polio antiviral drugs (McKinlay et al., 2014)), and it remains well-recognized that vaccination represents the only tool to avoid the devastating paralytic disease in individuals (Sutter, Kew, Cochi, & Aylward, 2013). This study strongly suggests that the need for proactive use of vaccination extends to populations. Our analyses demonstrate that neither reacting to cases after they occur, nor diverting efforts to the highest priority of the moment lead to the interruption of WPV1 transmission in Pakistan and Afghanistan. In contrast, strategies that improve the coverage among all under-vaccinated subpopulations contemporaneously in both countries can lead to WPV1 elimination, with better results for strategies that do so proactively rather than reactively. The time until success decreases with better quality (Thompson & Duintjer Tebbens, 2007), and thus the optimal strategy involves raising performance well above the minimum performance needed to eradicate as quickly as possible. The context of a global eradication effort that depends on interrupting WPV1 interruption in all countries makes success in Pakistan and Afghanistan essential, with delays in global eradication imposing aggregate global costs on countries on the order of $1 billion per year (Duintjer Tebbens et al., 2011). While smallpox eradication ultimately succeeded with reactive vaccination (Fenner, Henderson, Arita, Jezek, & Ladnyi, 1988), due to the high proportion of asymptomatic poliovirus infections (Nathanson & Kew, 2010) and the ability of WPV1 to spread rapidly across geographies (Mach, Tangermann, Wassilak, Singh, & Sutter, 2014), global polio eradication requires a proactive approach and a focus on prevention.

Achieving and maintaining polio eradication requires getting immunization coverage well over the threshold required to stop transmission in all places at the same time and keeping it at that level long enough such that the virus dies out. Strategies that use signals of transmission from surveillance (i.e., cases or positive environmental samples) may end up chasing the virus around, while failing to get in front of it to prevent transmission. The GPEI and the world cannot afford to tolerate a reactive strategy that focuses on limiting short-term resource use in Pakistan and Afghanistan at the expense of much higher long-term global resource demands. This is the time to proactively focus on using as much OPV as possible to raise population immunity to transmission in Pakistan and Afghanistan at the same time

such that transmission dies out. The global introduction of IPV into routine immunization programs to provide individual children born since the tOPV-bOPV switch with protection from paralysis in the event that they become exposed to a live serotype 2 poliovirus provides limited impact on WPV1 transmission (Duintjer Tebbens et al., 2018) and should not distract from OPV immunization efforts in Pakistan and Afghanistan.

The insights from this analysis remain consistent with earlier theoretical work on the economic and epidemiological sub-optimality of shifting priorities when managing multiple eradicable diseases (Duintjer Tebbens & Thompson, 2009) and polio eradication efforts in India (Thompson & Duintjer Tebbens, 2007). The occurrence of cVDPV1 outbreaks despite ongoing OPV use in RI for the reactive strategies in this study also reaffirms the need to maintain performance even after the apparent interruption of WPV1 to (1) prevent WPV1 importations (if other endemic countries remain), (2) prevent indigenous cVDPV1 emergences while OPV continues through certification, and (3) allow safe OPV cessation without subsequent cVDPV1 outbreaks (Duintjer Tebbens et al., 2016; Thompson & Duintjer Tebbens, 2014). We emphasize that Pakistan failed to maintain high tOPV vaccination prior to the tOPV to bOPV switch, which resulted in a (possibly now controlled) serotype 2 cVDPV outbreak due to the use of serotype 2 monovalent OPV for outbreak response after the switch (Duintjer Tebbens et al., 2018). The GPEI did not use tPOV still available immediately after the tOPV-bOPV switch to respond to the outbreak despite research suggesting the superiority of tOPV instead of mOPV2 in that situation (Duintjer Tebbens, Pallansch, Wassilak, et al., 2018). Serotype 1 VDPV outbreaks may prove more difficult to control after OPV cessation than serotype 2 VDPV outbreaks due to the higher transmissibility and lower secondary OPV benefits for serotype 1 than for serotype 2 (Benyesh-Melnick et al., 1967; Duintjer Tebbens & Thompson, 2017a), particularly if the declaration of global WPV1 eradication and transition of resources leads to a deterioration of SIA quality and/or frequency before bOPV cessation. An additional benefit of exceeding the minimum performance and maintaining high performance comes from the resulting reduction in the time needed to achieve high confidence about no circulation following the last detection (Kalkowska, Duintjer Tebbens, Pallansch, et al., 2015; Kalkowska et al.).

This study relies on a comprehensive model of poliovirus transmission in Pakistan and Afghanistan, calibrated to the available evidence to the best of our ability (Duintjer Tebbens et al., 2018). However, the model comes with limitations related to scientific uncertainty, imperfect data, and simplifications of complex, local, and stochastic processes that determine poliovirus behavior in the real world (e.g., virus die-out), as discussed in more detail elsewhere (Duintjer Tebbens et al., 2018; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013). Furthermore, the characterization of the different strategies remains hypothetical and does not reflect the true process that determines strategies and performance. Specifically, decision makers do not really use the perceived incidence or set their coverage targets based on incidence observations. However, arguably the *de facto* strategies and performance of activities in the field may depend on perceived priorities and some shifting of resources may occur in response to local outbreaks. In the light of the model limitations and hypothetical nature of the modeled strategies, this analysis seeks to emphasize the qualitative insights related to reactive versus proactive strategies. We hope that this study provides a warning against reactive behavior and shifting priorities, and motivates strong

commitments to improve performance and to end WPV1 in Pakistan and Afghanistan and prevent cVDPV1 outbreaks throughout the polio endgame.

Conclusions

Polio eradication in Pakistan and Afghanistan requires a sustained, proactive approach with improved performance in OPV SIAs in all under-vaccinated subpopulations. Reactive strategies to interrupt wild poliovirus transmission in Pakistan and Afghanistan without an overall increase in performance will not work.

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List of abbreviations

AFP	acute flaccid paralysis
bOPV	bivalent OPV
cVDPV(1)	circulating VDPV (of serotype 1)
GPEI	Global Polio Eradication Initiative
H	perceived annual polio incidence for which the RSC becomes 0.5
IPV	inactivated poliovirus vaccine
NID	national immunization day
OPV	oral poliovirus vaccine
RI	routine immunization
RSC	relative SIA coverage in an under-vaccinated subpopulation compared to general population in the same country
SIA	supplemental immunization activity
SNID	sub-national immunization day
T	perception time
tOPV	trivalent OPV
VDPV	vaccine-derived poliovirus
WPV(1)	wild poliovirus (of serotype 1)

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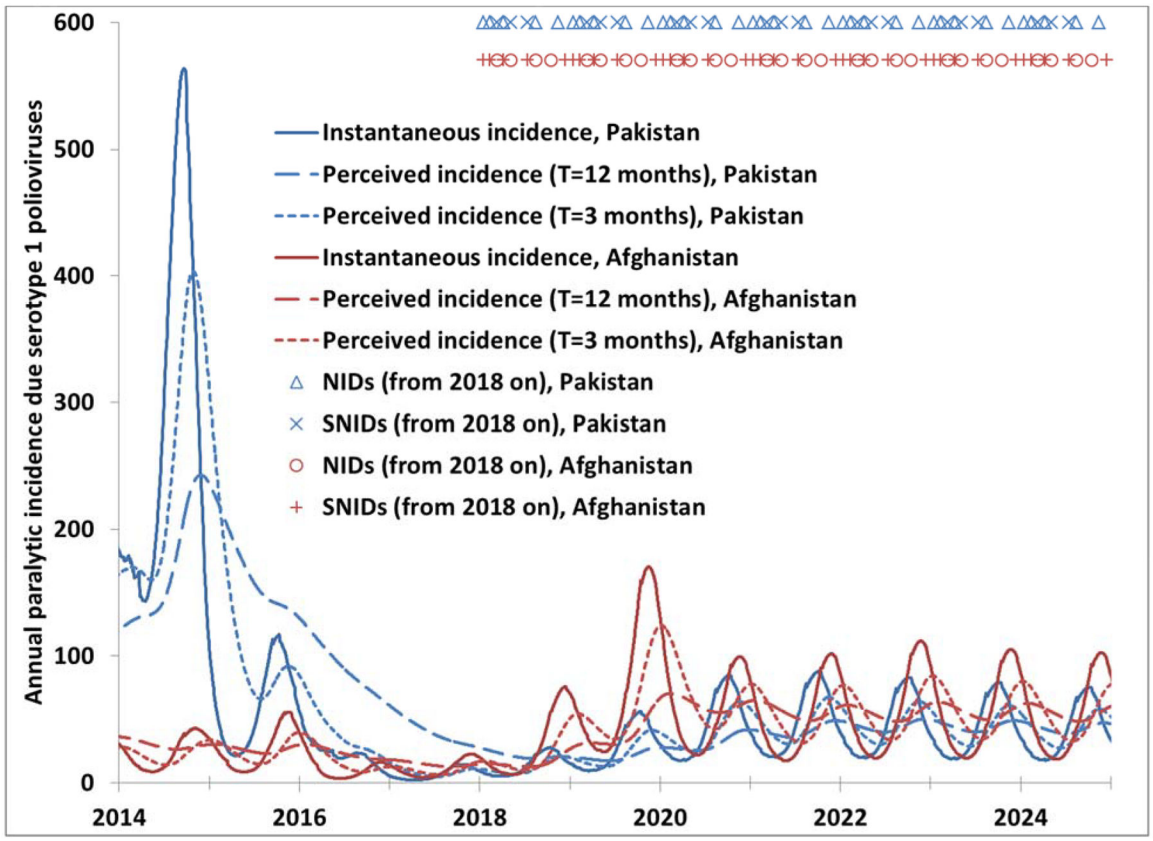


Figure 1: Base case model result for Pakistan and Afghanistan, with timing of supplemental immunization activities and perceived incidence in both countries

Abbreviations: NID, national immunization day (i.e., covering children in entire country); SNID, sub-national immunization day (i.e., covering only a fraction of children in each subpopulation); T, perception time

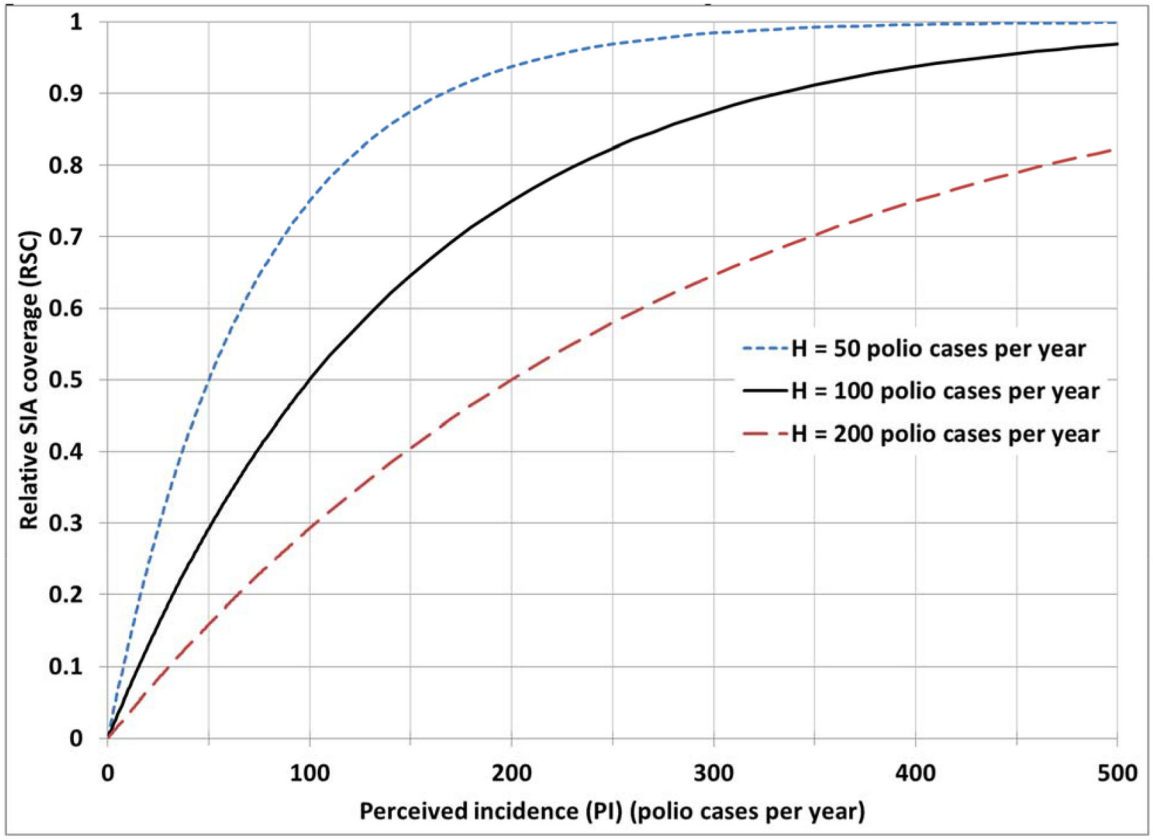


Figure 2:

Assumed relationship between perceived incidence and relative SIA coverage in the under-vaccinated subpopulation for reactive strategies, for different values H of the perceived incidence that results in a relative SIA coverage of 0.5.

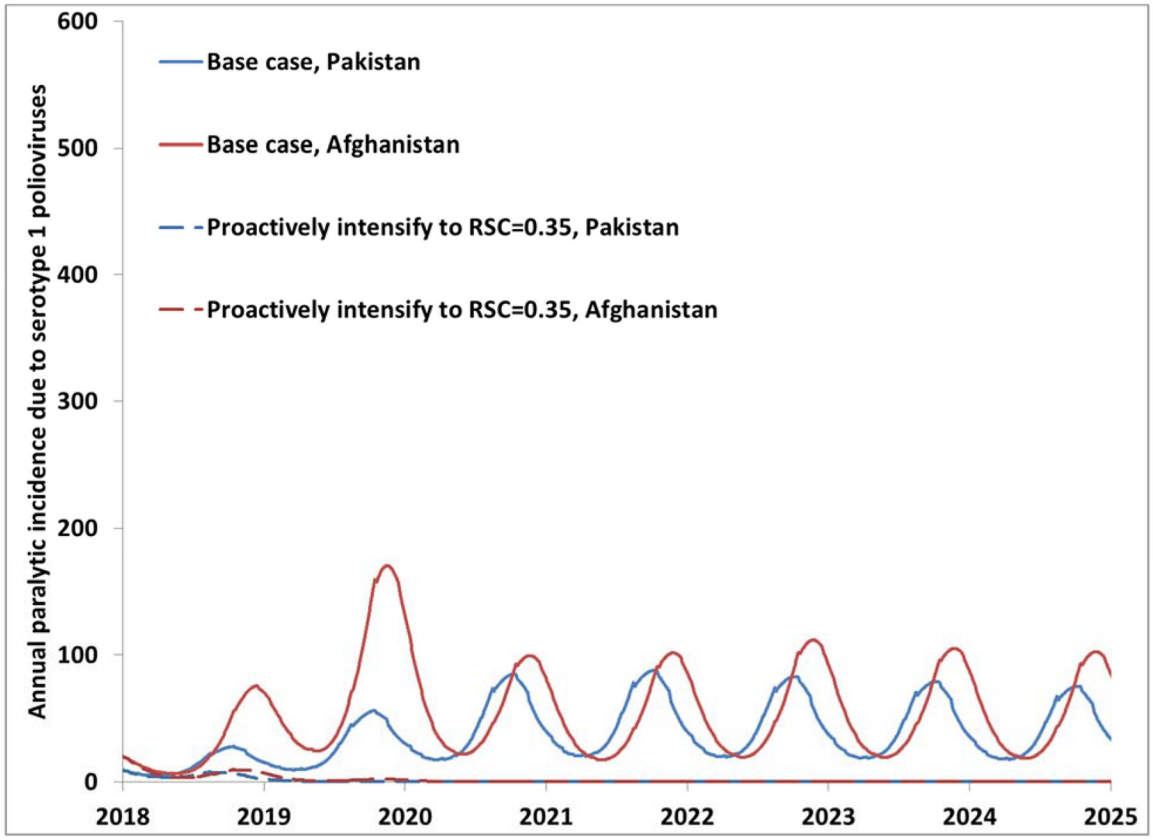
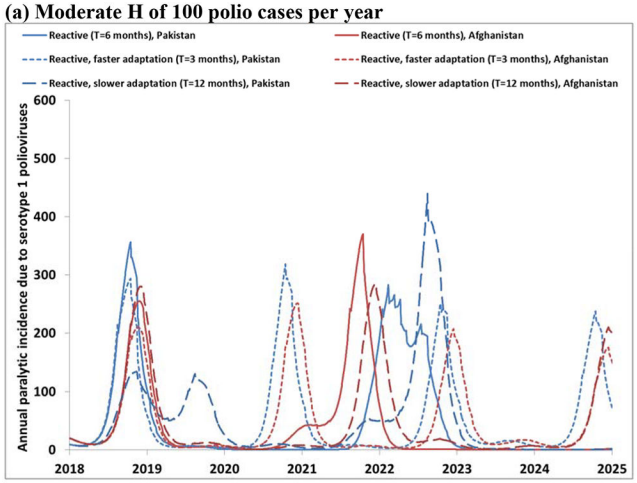
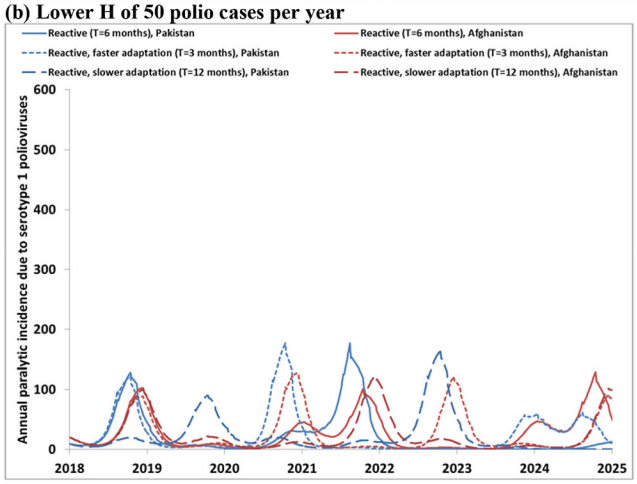


Figure 3:
Comparison of the base case to a proactive strategy increases the relative SIA coverage (RSC) in both under-vaccinated subpopulations to 0.35

(a) Moderate H of 100 polio cases per year



(b) Lower H of 50 polio cases per year



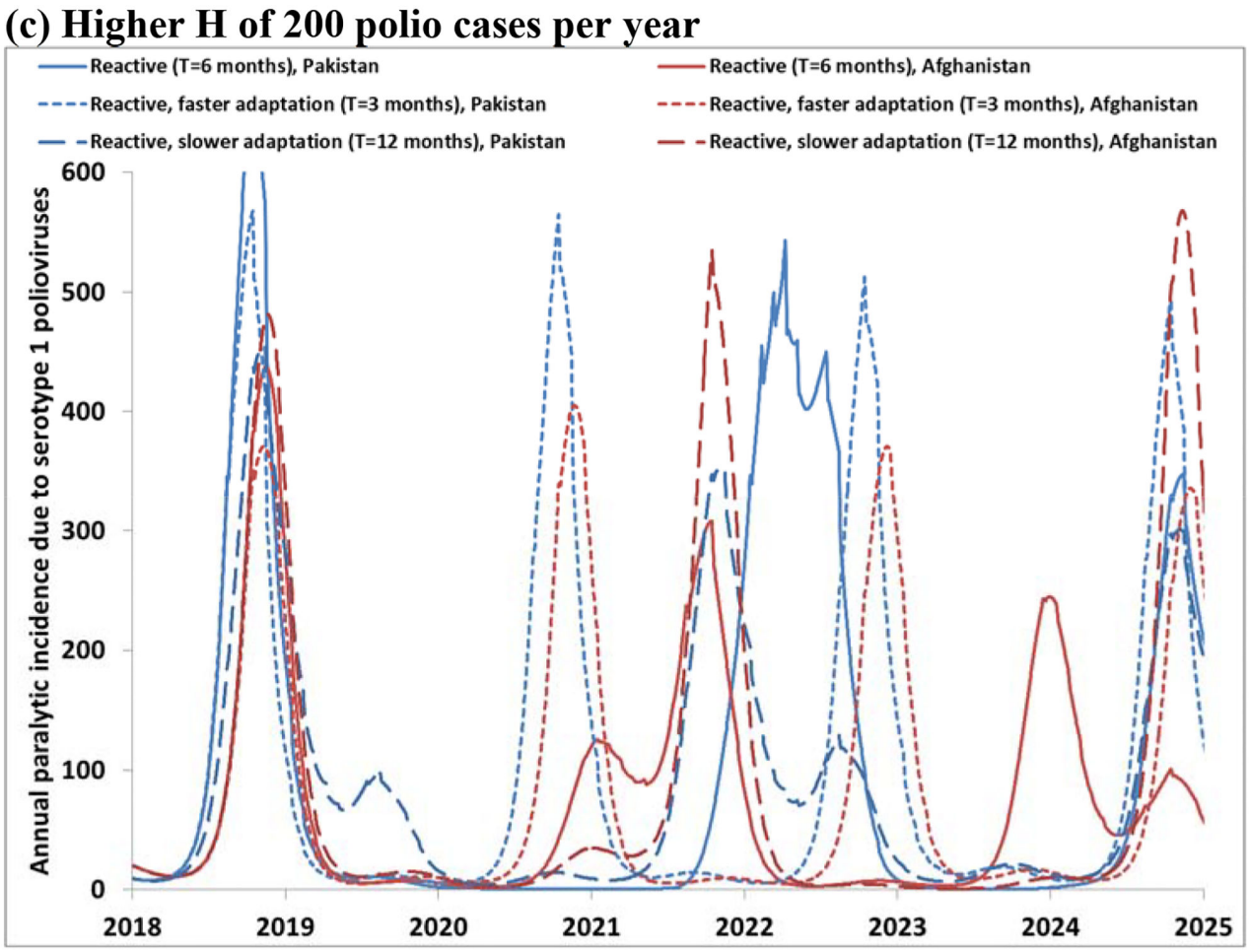


Figure 4:

Results for reactive strategies that adapt independently to the perceived incidence in each subpopulation. T denotes the perception time and H the perceived annual incidence for which the relative SIA coverage becomes 0.5

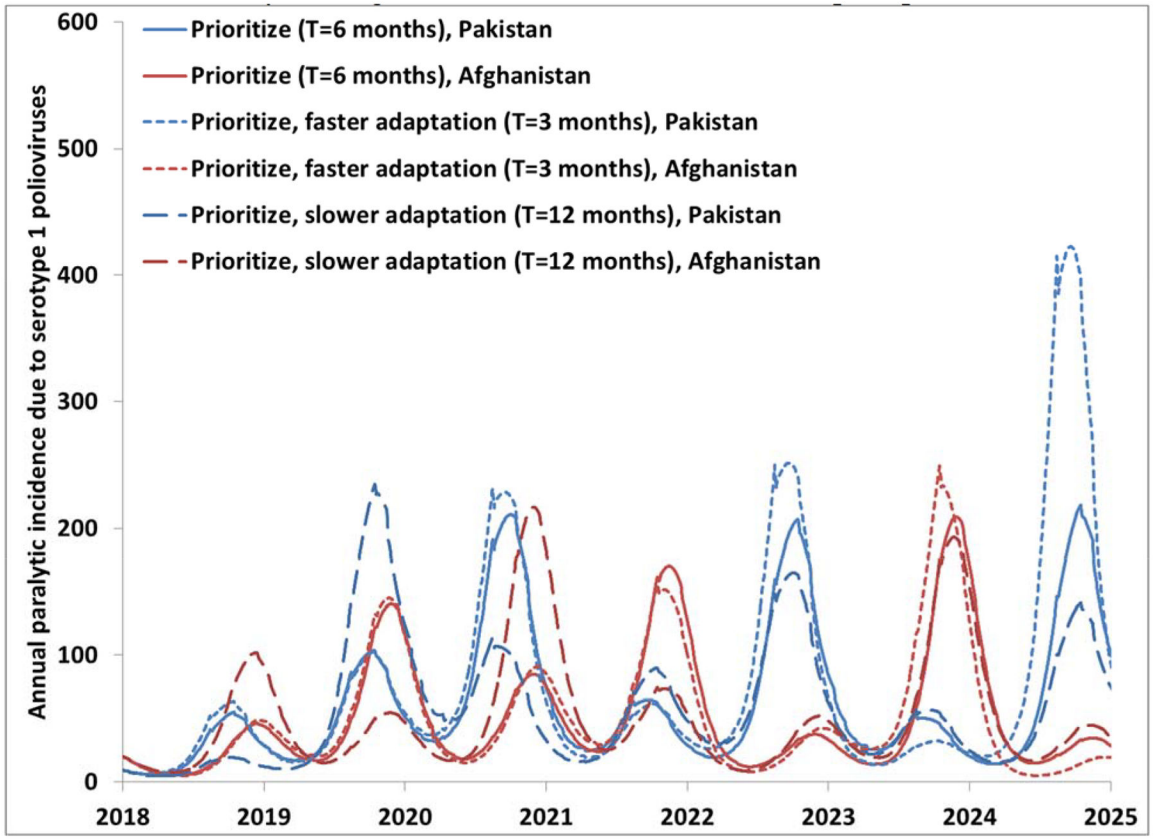


Figure 5:

Results for reactive strategies based on priority, as determined by the perceived incidence in each subpopulation, that maintain the same total relative supplemental immunization activity coverage as for the base case. T denotes the perception time.

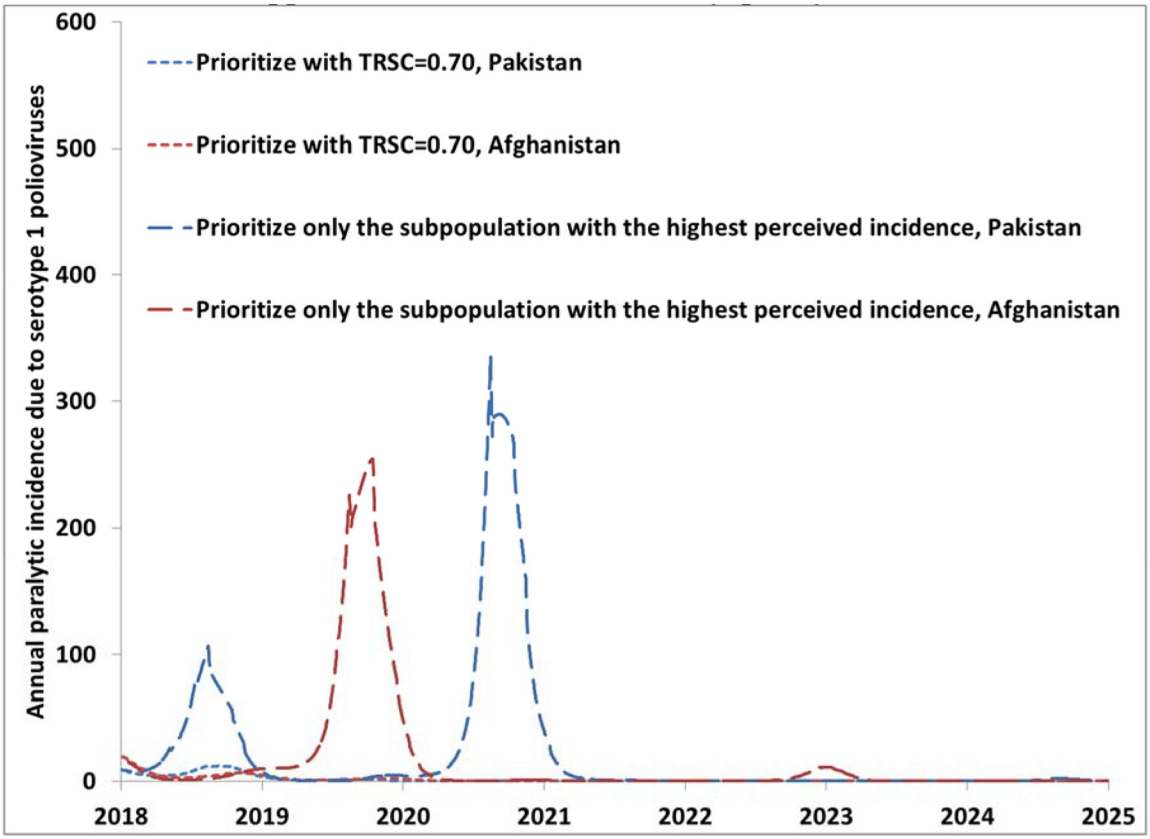


Figure 6:
Results for reactive strategies based on priority that involve an overall intensification of supplemental immunization activity quality.

Table 1:

Constant inputs specific for the Pakistan and Afghanistan model (adopted directly from Duintjer Tebbens et al. (2018) to facilitate review of the numerical assumptions)

Model input	Best estimate	Notes and sources
Number of subpopulations	4	Two each in Pakistan and Afghanistan (see Methods)
Size of under-vaccinated relative subpopulations relative to total population		Judgment, informed by size of border provinces and Pashtun populations (Library of Congress, 2008; Pakistan Bureau of Statistics, 2017)
- Pakistan	0.05	
- Afghanistan	0.10	
Number of age groups	11	0–2; 3–11 months; 1; 2; 3; 4; 5–9; 10–14; 15–24[a];25–39[a]; ≥ 40 years
Number of mixing age groups	3	0–4;5–15; ≥ 15 years, consistent with most modeled situations(Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013; Kalkowska, Duintjer Tebbens, Grotto, et al., 2015)
Proportion of contacts reserved for individuals within the same mixing age group	0.35	Measure of strength of preferential mixing between age groups; value similar to other high-risk settings(Duintjer Tebbens et al., 2014; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013)
Average R0 for WPV		Ratios by serotype based on generic model inputs, values between previously assumed values for northwest Nigeria (7.5 for serotype 1 WPV) and northern India (13)(Duintjer Tebbens et al., 2014; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013)
- Serotype 1	11	
- Serotype 2	9.9	
- Serotype 3	8.25	
R_0 amplitude	0.15	Based on judgment and calibration within ranges used for other populations (Duintjer Tebbens, Pallansch, Cochi, Wassilak, & Thompson, 2015; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013; Duintjer Tebbens & Thompson, 2014) to match incidence pattern
R_0 peak day (day of year)		Broadly consistent with typical precipitation patterns and non-polio enterovirus isolation rates in both countries and with range of values used in a global model(Duintjer Tebbens et al., 2015); calibrated to match incidence patterns
- Pakistan	180 (June 30)	
- Afghanistan	240 (Aug 29)	
Proportion of transmissions via oropharyngeal route	0.3	Value used for high R0 developing country settings(Duintjer Tebbens, Pallansch, et al., 2013b; Duintjer Tebbens et al., 2015; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013)
Average per-dose take rates (serotype 1;2;3)		Value based on review of seroconversion studies (Thompson et al., 2013) and consistent with ranges from a global model (Duintjer Tebbens et al., 2015) and between assumed values for northwest Nigeria and northern India (Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013; Duintjer Tebbens & Thompson, 2014)
- tOPV	0.40;0.60;0.32	
- mOPV	0.52;0.60;0.52	
- bOPV	0.48;NA;0.48	
- IPV	0.63;0.63;0.63	
Time of IPV introduction in RI		(World Health Organization Regional Office for the Eastern Mediterranean, 2015 a, 2015b)
- Pakistan	Aug. 20, 2015	
- Afghanistan	Sep. 30, 2015	
Time of switch from tOPV to bOPV	April 30, 2016	(World Health Organization, 2017)
Demographics	Time series	Surviving birth rates and age-specific mortality rates over time computed(Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013) from UNestimated medium variant annual number of surviving infants and population(Population Division of the Department of Economic and

Model input	Best estimate	Notes and sources
		Social Affairs of the United Nations Secretariat, 2017) in each age group and country using existing methods(Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013)

Abbreviations: bOPV, bivalent oral poliovirus vaccine; IPV, inactivated poliovirus vaccine; mOPV, monovalent oral poliovirus vaccine; NA, not applicable; R_0, basic reproduction number; RI, routine immunization; tOPV, trivalent oral poliovirus vaccine; UN, United Nations; WPV, wild poliovirus

Notes:

[a]Denotes age groups whose immunity profiles determine the fraction of newborn born with maternal antibodies.(Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013)

Table 2:

Summary of results for the evaluated strategies

Strategy	Perception time (*T*, months)	*H* (polio cases per year)	WPV1 cases, 2018–2025	Time of interruption of WPV1 transmission (if not continuing into 2025)
Base case (continuation of *status quo)*	N/A	N/A	650	None
Proactively intensify to RSC=0.35 (in each under-vaccinated subpopulation)	N/A	N/A	15	2020 (April)
Independently reactive	3	50	292[a]	None[b]
Independently reactive	6	50	335	None
Independently reactive	12	50	309	None
Independently reactive	3	100	723	None
Independently reactive	6	100	575	None[b]
Independently reactive	12	100	645	None
Independently reactive	3	200	1,277	None
Independently reactive	6	200	1,207	None[b]
Independently reactive	12	200	1,188	None[b]
Reactive based on priority (no increase in total RSC)	3	N/A	902	None
Reactive based on priority (no increase in total RSC)	6	N/A	797	None
Reactive based on priority (no increase in total RSC)	12	N/A	770	None
Reactive based on priority, with total RSC increased to 0.70	6	N/A	16	2020 (May)
Reactive only in subpopulation of highest priority, with RSC of 0.70	6	N/A	248[c]	2021 (August)

[a]Not including an additional 28 serotype 1 cVDPV cases in the under-vaccinated subpopulation of Pakistan during 2024–2025

[b]Elimination occurs in one of the two under-vaccinated subpopulations, but WPV1 reintroductions, indigenous cVDPV1 emergences, and/or partially-reverted serotype 1 OPV-related viruses that do not meet the VDPV definition lead to continued incidence from serotype 1 transmission

[c]Not including an additional 4 expected cases due to partially-reverted serotype 1 OPV-related viruses during 2022–2023 in the under-vaccinated subpopulation in Afghanistan