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Uncertainty and Sensitivity Analysis of Cost Assumptions for Global Long-term Poliovirus Risk Management

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Abstract

The world will stop the use of oral poliovirus vaccines (OPV) after certification of global wild poliovirus eradication, but investments must continue in long-term poliovirus risk management, including some level of use of the inactivated poliovirus vaccine (IPV). The health economic justification of these activities depends on their assumed costs and savings associated with prevented polio cases. We characterize probability distributions for economic inputs of an existing global model of long-term poliovirus risk management. Using a fixed set of 120 realizations of the stochastic model, we estimate the corresponding expected incremental net benefits (INBs) of OPV cessation compared to continued OPV use over a 40-year time period for a large sample of the uncertain cost inputs. We also explore the impact of some specific assumptions about future IPV costs. Cost-related uncertainty substantially influences the INBs for OPV cessation compared to continued OPV use, although nearly all simulations resulted in positive expected global INBs. IPV cost, OPV administration costs, and average treatment costs emerged as the most influential uncertainties. A potential drop in the IPV cost starting in the 2020's may result in an expected economic benefit of $1.5-4.5 billion mainly due to cost savings in higher-income countries, depending on the timing and magnitude of the cost decrease and on whether they apply to combination vaccine products. Cost-related uncertainties may lead to significantly higher or lower expected long-term benefits of polio eradication and OPV cessation, and efforts to further reduce costs, particularly associated with IPV vaccine cost and delivery, will likely yield significant benefits.

Keywords: Polio; Eradication; Risk management; OPV cessation; Dynamic modeling; Uncertainty analysis; Sensitivity analysis; Health economics

Abbreviations: cVDPV: circulating vaccine-derived poliovirus; DEB: differential equation-based; GPEI: Global Polio Eradication Initiative; HIGH: high-income; INB: incremental net benefit; IPV: inactivated poliovirus vaccine; IPV5: global minimum policy of IPV use for 5 years after cessation of the last OPV Serotype; iVDPV: immunodeficiency-associated Vaccine-derived poliovirus; LMI: lower middle-income; LOW: low-income; LPV: live poliovirus; OPV: oral poliovirus vaccine; OPV## cessation: globally-coordinated cessation of OPV containing the serotype(s) indicated by ##; oSIA: outbreak response SIA; pSIA: preventive SIA; RC: reference case; RI: routine immunization; SD: standard deviation; SIA: supplemental immunization activity; tOPV: trivalent oral poliovirus vaccine; UMI: upper middle-income; VAPP: vaccine-associated paralytic poliomyelitis; VDPV: vaccine-derived poliovirus; WPV(1,3): wild poliovirus (serotype 1 and 3, respectively).

Introduction

Following the 1988 resolution to globally eradicate polio [1], the world succeeded in preventing reported paralytic poliomyelitis (polio) due to serotype 2 wild poliovirus (WPV) since 1999 [2] and serotype 3 WPV (WPV3) since 2012 [3]. Indigenous transmission of serotype 1 WPV (WPV1), the only remaining WPV serotype, occurred in three countries (i.e., Pakistan, Afghanistan, and Nigeria) in 2016 [4]. While WPVs still caused hundreds of thousands of polio cases per year in the 1980s [5], the annual global incidence remained below 1,000 between 2011-2015 [6]. Accounting for the societal value of prevented disability and mortality, the Global Polio Eradication Initiative (GPEI) efforts to date to eradicate polio already resulted in tens of billions of dollars in health-economic benefits [5,7], which will continue to accumulate as future generations avoid the devastating consequences of polio outbreaks.

However, preventing polio and maintaining eradication requires continued effort and investment [7,8]. First, intense vaccination reaching all children in Pakistan, Afghanistan, and Nigeria must interrupt the last chains of WPV1 transmission and other countries must maintain sufficient polio vaccination coverage to prevent imported WPV1s from causing outbreaks. Second, oral poliovirus vaccine (OPV) use must stop to eliminate all polio disease [8,9], including vaccine-associated paralytic poliomyelitis (VAPP), circulating vaccine-derived polioviruses (cVDPVs), and long-term immunodeficiency-associated vaccine-derived poliovirus (iVDPV) infections in rare patients with primary immunodeficiency disease. However, stopping OPV use in the context of low population immunity to transmission will lead to continued transmission of OPV-related viruses and may allow those viruses to cause cVDPV outbreaks [10]. Consequently, countries must intensify homotypic OPV use before withdrawing any OPV serotype [7,10,11].

The GPEI coordinates the global partners and oversaw the globally-synchronized cessation of all serotype 2-containing OPV (OPV2 cessation) in April and May 2016. The GPEI plans to withdraw the other two serotypes (OPV13 cessation) after certification of WPV1 and WPV3 eradication [8]. Considering the suggestions from an earlier analysis [12], the GPEI developed several prerequisites for OPV cessation that it used for coordinated OPV2 cessation [13], and the GPEI will presumably do the same for OPV13 cessation. For OPV2 cessation, the prerequisites included certification of homotypic WPV eradication, confirmation of cessation of persistent serotype 2

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cVDPVs (cVDPV2s) , outbreak response and stockpile preparedness, appropriate biocontainment plans for all homotypic live polioviruses (LPVs, which includes WPV, cVDPV, iVDPV, OPV, and OPV-related polioviruses), surveillance capacity to detect any homotypic LPVs, and inclusion of at least one inactivated poliovirus vaccine (IPV) dose in national immunization schedules [8,13]. While the addition of IPV will not significantly reduce cVDPV risks after OPV cessation due to its limited impact on fecal-oral transmission [14], it will provide individual protection from polio to vaccine recipients and a relatively higher level of population immunity to transmission in populations with less intense fecal-oral transmission and a greater likelihood to experience iVDPV or other introductions [7,15]. Besides the stated prerequisites, long-term poliovirus risk management may require ongoing investments in polio antiviral drugs and/or safer poliovirus vaccines [7,15] and implementation of containment activities for facilities that continue to store any LPVS.

Although less significant than the financial investments to achieve polio eradication, long-term poliovirus risk management will require resource investments to reduce the probability and consequences of potential future poliovirus reintroductions, including surveillance and outbreak response. An integrated global model of long-term poliovirus risk management policies (i.e., the global model) suggested that under the base case assumptions, the benefits of these activities outweigh the costs due to the low risk of continued large outbreaks after OPV cessation if well-managed, leading to expected incremental net benefits (INBs) of approximately $16 billion (all $ amounts in year 2013 United States dollars) compared to continued OPV use between 2013-2052 [7]. However, OPV cessation leads to an unprecedented world without any LPV exposure and with widespread IPV use for which no direct data exist. Consequently, significant uncertainty exists about the costs of the risk management activities and their effectiveness. Better understanding the impact of uncertainties associated with different courses of action will help policy makers make more informed decisions. Several studies explored alternative assumptions related to the risks, including outbreak response options [16], OPV cessation logistics [17,18], iVDPV risks and polio antiviral drug use [19], and the impact of safer poliovirus vaccines [20]. However, no study comprehensively analyzed the impact of uncertainty in cost assumptions on current long-term poliovirus risk management decisions. This study focuses on characterization of the uncertainty in the cost assumptions and their implications for the INB estimates.

Materials and Methods

We focus on characterization of uncertainty in cost assumptions for a previously published global model that quantified the economic benefits of different policy options for poliovirus risk management for 2013-2052 (see appendix available at: http://www.kidrisk.org for details about the model) [7]. The global model integrates a previously developed and validated poliovirus transmission and OPV evolution model [21-23] with vaccination-related costs [5,24-26], random poliovirus reintroductions from various sources (e.g., iVDPVs, release from a laboratory or IPV production site) [14,27], and a global mixing structure involving 710 populations of approximately 10 million people each [7]. The global model assigns populations to different 2013 World Bank income levels (low, lower middle, upper middle, and high) and polio vaccine use (OPV-only, IPV/OPV sequential schedule, IPV-only) [28-30], with representative properties (cost inputs, poliovirus transmission potential, vaccine usage over time, surveillance) given to each of the 710 populations. Due to the stochastic nature of poliovirus reintroductions and exportations between populations, each (stochastic) iteration results in a different possible realization of the future [7].

The economic analysis of the main immunization policy choices computed expected INBs of an OPV cessation policy (*alt*) compared to a reference case (RC) of continued OPV use (*ref*) as:[7]

$$INB(alt\ vs.\ ref)=(T+S)\times(PP_{ref}-PP_{alt})-(FC_{alt}-FC_{ref})$$

where

S=average societal economic costs per polio case

T=average treatment costs per polio case

FC_{ref}=financial costs associated with the RC

FC_{alt}=financial costs associated with the alternative policy

PP_{ref}=polio cases with the RC

PP_{alt}=polio cases with the alternative policy

To characterize expected values, the FC_{ref}, FC_{alt}, PP_{ref}, and PP_{alt} represented the average cumulative, discounted financial costs and polio cases based on 100 iterations of the global model [7]. The baseline long-term global risk management policy assumed that all populations introduce at least one IPV dose in their routine immunization (RI) schedules in 2015 and continued to use IPV until at least 5 years after OPV13 cessation assumed to occur in 2019 (i.e., the IPV5 policy). The timing assumption reflected the understanding that OPV13 cessation would occur after successfully carrying out the GPEI Strategic Plan 2013-2018 [8], although this will depend on the actual timing of global WPV1 eradication, certification of WPV1 and WPV3 eradication, and other preparations for OPV13 cessation. Low- and lower middle-income populations followed this minimum global policy, but the IPV5 policy assumes that upper middle-income populations move from IPV/OPV (i.e., 2 IPV doses followed by 2 OPV doses) to IPV-only (i.e., 3 IPV doses) at the time of global OPV13 cessation and that they continue to use IPV-only through the end of the analytical time horizon (i.e., 2053). The IPV5 policy also assumed that high-income countries followed the same progression (if using IPV/OPV in 2013) or used IPV-only throughout (if already using IPV-only in 2013). Thus, substantial costs associated with IPV use continue throughout the time horizon regardless of the occurrence of outbreaks due to continued use in relatively higher income countries. The IPV5 policy further assumed sufficiently large vaccine stockpiles to conduct aggressive monovalent OPV (mOPV) outbreak response for the first five years after homotypic OPV cessation and IPV thereafter due to the risks associated with massive introduction of LPVs after a substantial decline in global population immunity to transmission. For the RC, we considered continued OPV use use in both RI and supplemental immunization activities (SIAs) (RC with SIAs) or continued OPV use only in RI from 2019 on (RC no SIAs) [7].

The financial costs included only vaccination-related costs based on the simplifying assumption that other global programmatic costs remain similar for OPV cessation and the RCs. The analysis revealed an important dichotomy in expected costs and cases for different iterations. In most iterations, aggressive outbreak response rapidly controlled all outbreaks, leading to small numbers of polio cases and stable costs principally associated with RI. However, in a few iterations, poliovirus reintroductions occurred long after OPV cessation and/or in places that did not sustain sufficient population immunity to transmission with IPV-only to allow outbreak control even with aggressive response. We assumed that a failure to control outbreaks would lead all populations that used OPV in 2013 to resume OPV RI instead of continued

unsuccessful and costly outbreak response, which we arbitrarily defined as occurring the year after the accumulation of 50,000 polio cases since the year 2016 [7]. For such iterations (i.e., OPV restart iterations), we assumed the costs and cases incurred for the RC after the OPV restart, either with or without SIAs. OPV restart iterations involve much higher costs than iterations without OPV restart due to outbreak response SIAs (oSIAs), resumed OPV use in populations that would otherwise stop all polio vaccination, and the economic impact of a large number of polio cases.

Due to the high computational resource demands to run the global model, the previously published economic analysis performed only 100 iterations, which yielded 2 OPV restart iterations (i.e., OPV restart probability of 0.02) and 98 iterations without OPV restart [7]. For this cost analysis, we performed an additional 1,000 iterations to obtain more robust estimates of the OPV restart probability, mechanisms, and the expected INBs, which resulted in an OPV restart probability of 0.057 (i.e., suggesting that the initial 100 runs by chance yielded a relatively low OPV restart probability, as discussed in the appendix). To represent the findings from the 1,000 iterations while limiting the computational resources, we performed subsequent analyses for this study based on a stratified subset of the 1,000 iterations, consisting of all 57 OPV restart iterations and 63 iterations without OPV restart (see appendix), consistent with other recent analyses [19,20]. Throughout, we assume OPV restarts involve OPV RI with SIAs whenever we compare against RC with SIAs and involve OPV RI

Model input [unit]	Base case value [7]	Parameters of assumed triangular uncertainty distribution		
		Lower limit	Mode	Upper limit
OPV cost per dose [$/dose]				
- LOW and LMI	0.12	0.05	0.12	0.20
- UMI	0.13	0.10	0.13	0.50
- HIGH	0.16	0.10	0.16	1.0
IPV cost per dose [$/dose]				
- LOW	1.3	0.75	1.3	2.0
- LMI	2.3	1.0	2.3	4.0
- UMI	3.2	2.0	3.2	5.0
- HIGH	13	5.0	13	25
Effective wastage of OPV in RI				
- LOW or LMI	50%	30%	50%	60%
- UMI	30%	10%	30%	40%
- HIGH	10%	5%	10%	15%
Effective wastage of IPV in IPV-only RI				
- UMI	25%	10%	25%	35%
- HIGH	5%	3%	5%	10%
Effective wastage of IPV in IPV/OPV RI				
- LOW or LMI	40%	20%	40%	50%
- UMI	30%	15%	30%	40%
- HIGH	10%	5%	10%	15%
Effective wastage of OPV or IPV in SIAs (any income level)[a]	44%	20%	44%	50%
OPV in RI administration costs per dose [$/dose]				
- LOW or LMI	0.86	0.50	0.86	1.5
- UMI	2.3	1.5	2.3	3.5
- HIGH	2.9	2.0	2.9	4.0
Incremental cost for OPV+IPV co-administration in LOW or LMI [$/dose]	0.30	0.10	0.30	0.50
OPV in pSIAs administration costs per dose [$/dose]				
- LOW or LMI	0.60	0.30	0.60	1.0
- UMI	3.3	1.0	3.3	5.0
- HIGH	4.2	2.0	4.2	10
IPV single-antigen in RI administration costs per dose[b] [$/dose]				
- LOW or LMI	1.1	0.50	1.1	2.0
- UMI	2.9	2.0	2.9	4.0
- HIGH	10	5.0	10	15
IPV combo in RI administration costs per dose[c] [$/dose]				
- UMI	0.72	0.25	0.72	1.5
- HIGH	2.6	1.0	2.6	10
Relative administration costs oSIAs *vs.*pSIAs	1.5	1.0	1.5	2.0
Treatment cost per (paralytic) polio case [$/case]				
- LOW	650	50	650	1,000
- LMI	6,500	500	6,500	10,000
- UMI	65,000	5,000	65,000	100,000
- HIGH	650,000	50,000	650,000	1,000,000
Difference in annual global programmatic costs (from 2019 forward for IPV5 compared to RC) [$/year]	Not included	0	200 million	400 million

Abbreviations: HIGH, high-income; IPV, inactivated poliovirus vaccine; IPV5, global minimum policy of IPV use for 5 years after cessation of the last OPV serotype; LMI, lower middle-income; LOW, low-income; OPV, oral poliovirus vaccine; oSIA, outbreak response SIA; pSIA, preventive SIA; RC, reference case; RI, routine immunization; SIA, supplemental immunization activity; UMI, upper middle-income

Notes:

[a]Uncertainty distribution also reflects demographic uncertainty about the number of children targeted in SIAs, which can significantly impact the effective discrepancy between doses distributed and estimated number of children reached [11]

[b]In the absence of better information, we assume that this IPV cost per dose also applies in the event of IPV use during an SIA

[c]Not applicable for low- and lower middle-income countries because the modeled policies assume only single-antigen IPV use in those countries

Table 1: Cost inputs with base case values used in an economic analysis of long-term poliovirus risk management policies [7] and assumed uncertainty distributions for the probabilistic cost uncertainty and sensitivity analysis.

without SIAs whenever we compare against RC no SIAs.

We conducted several analyses. First, we explored the breakdown of the costs into major categories for the IPV5 policy option using the base case cost input values from Table 1. Second, we conducted a probabilistic uncertainty and sensitivity analysis using Monte Carlo simulation of 50,000 independent draws of all cost inputs, including vaccine costs, vaccine administration costs, vaccine wastage, and average treatment costs per polio case, with the assumed uncertainty distributions indicated in Table 1. For all cost inputs, we assume triangular uncertainty distributions with modes equal to the base case values and lower and upper limits based on informed judgment. We selected the bounds of the distributions to reflect comparable degrees of uncertainty across the different inputs and ranges of values seen in the literature or deemed realistic based on our judgment. For example, the lower limits of the OPV costs reflect the possibility of substantially lower costs than recent UNICEF prices [31], due to sizeable domestic OPV production in some countries that historically produced OPV domestically at lower costs [32]. We also added a new cost input to reflect the possibility of differential global programmatic costs with OPV cessation compared to the RCs, which we did not include in the original analysis [7]. The GPEI Strategic Plan 2013-2018 [8], budgeted $1.4 billion (i.e., annual average of $230 million) in resources not attributed to individual countries, which reflect costs for surveillance, the Global Polio Laboratory Network, technical assistance, and other regional- and global-level activities [7]. To include these costs, we assume that the RCs would not incur most of these costs from 2019 forward since countries would either rely on OPV RI only without conducting surveillance to respond to outbreaks or continue to conduct sufficient OPV SIAs to prevent outbreaks and thus not need significant investments in surveillance. For the IPV5 option, we assume that the incremental annual global programmatic costs after 2019 equal $100 million (range $0-$200 million) to reflect a substantial shift from intensive eradication efforts to long-term risk management.

We independently sampled values for each cost input from the uncertainty distributions (see appendix) and recalculated the costs for the IPV5 policy and the two RCs (i.e., with SIAs or no SIAs) for all 120 runs (polio cases remain unchanged), and the resulting INBs of IPV5 compared to both RCs. We rank the cost inputs that most contribute to the overall cost-related uncertainty based on the absolute values of their rank correlations with the global INBs of IPV5 *vs.* the RCs, with higher values indicating greater influence of the cost input on the INBs (see appendix) [33].

Finally, we varied the assumption about the future IPV costs

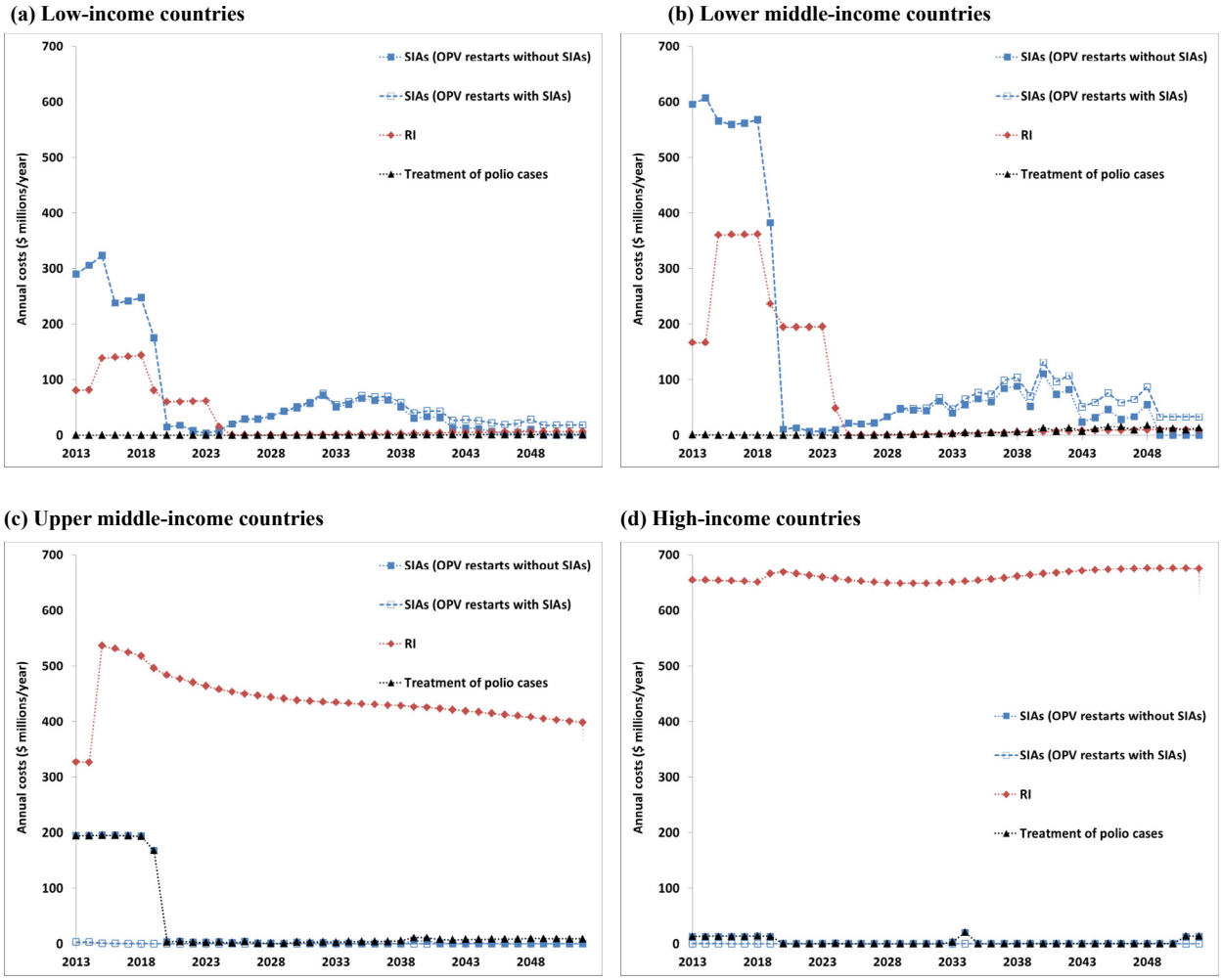

Figure 1: Annual costs over time (undiscounted and based on weighted average of a stratified set of 120 global model iterations) with base case cost inputs (Table 1) for the baseline IPV5 policy option, broken down by major cost categories and income level. (Abbreviations: IPV5, global minimum policy of inactivated poliovirus vaccine use for 5 years after cessation of the last OPV serotype; OPV, oral poliovirus vaccine; RI, routine immunization; SIA, supplemental immunization activity).

because ongoing research to reduce IPV production costs (particularly high-yield seed strains and/or adjuvants for fractional dosing without loss of immunogenicity) may eventually lead to lower IPV costs. Focusing on the uncertainty about the success and lead times of these IPV innovations, we assumed that the IPV costs per dose either drop to the lower limits in Table 1, or drop to $0.50 per dose in low- and lower middle-income countries and to $1.00 in other countries starting in 2022, 2026, or 2030. These cost scenarios assume that innovation in IPV production will spill over to the IPV-containing combination products used in most upper middle- and high-income countries, although this remains uncertain. Given that the IPV5 policy assumes that low- and lower middle-income countries stop IPV RI in 2024 [7], a late drop in IPV costs would imply costs savings based only on IPV use for outbreak response for these countries. We performed this analysis with all other cost inputs kept at their base case values.

Results

Figure 1 shows the breakdown of the costs for the IPV5 policy with all cost inputs at base case values (Table 1), based on the weighted averages from the stratified set of 120 iterations. In low- and lower middle-income countries, Figures 1a and 1b show the RI cost increases associated with IPV introduction in 2015. However, OPV13 cessation in 2019 and the assumed cessation of IPV use 5 years later yield substantial future reductions in RI and SIA costs. Beyond 2019, Figures 1a and 1b show increasing SIA costs due to the low probability but high cost of uncontrolled outbreaks that require expensive oSIAs and lead to OPV restarts in 5.7% of iterations. OPV restarts result in some new RI and SIA costs that depend on whether the OPV restart policy reinstates OPV SIAs or not, and consequently Figure 1 includes both curves. Despite the possibility of large numbers of polio cases in the event of uncontrolled outbreaks, the low probability of this occurring implies relatively low average numbers of polio cases and small expected treatment costs relative to the immunization costs.

Figure 1c shows different cost dynamics for the upper middle-income countries than the two lower income levels. IPV introduction in 2015 in upper middle-income countries that still used OPV-only in 2013 leads to a large RI cost increase, and continued IPV RI in these countries implies continued RI costs not seen in the lower two income levels (Figures 1a and 1b). In contrast, the SIA costs almost vanish after OPV13 cessation, with relatively small outbreaks and resulting oSIAs causing negligible SIA and treatment costs. In high-income countries, the policies hardly change over time; so that the costs remain largely constant (Figure 1d).

Figure 2 shows the cost-related uncertainty distributions based on 50,000 realizations from the cost input uncertainty distributions (Table 1). Overall, the global INBs of IPV5 *vs.* each RC remain positive, except for 13 of 50,000 realizations of IPV5 *vs.* RC with SIAs and 1 of 50,000 realizations of IPV5 vs. RC no SIAs (both <0.1%) if we include the possible global programmatic cost difference between OPV cessation and the RCs after 2019. The large global INBs arise mainly due to the high expected INBs in low- and lower middle-income countries that can prevent large numbers of polio cases and/or large continued costs compared to the RCs. However, in upper middle- and high-income countries that change their policy with global OPV cessation (i.e., those that still used OPV in 2013), the costs of replacing OPV with IPV remains high relative to the expected number of cases prevented by this change (primarily VAPP cases). Consequently, the expected INBs become negative, consistent with earlier findings about the high costs to prevent relatively few VAPP cases in industrialized countries [7,34].

Table 2 provides summary statistics from the distributions shown in Figure 1 and shows the impact of different discount rates, applied equally to financial costs and health outcomes [7,15,35]. Overall, the expected INBs with cost uncertainty remained very similar to the base case expected INBs without cost uncertainty despite the asymmetric distributions in Table 1. However, the possibility of a substantial difference in global programmatic costs for IPV5 *vs.* the RCs implies a reduction in the global INBs by approximately $1.8 billion. Without discounting of future outcomes, the expected INBs generally increase because most of the undesirable outcomes associated with any failures to control outbreaks typically occur long after 2013 [19]. Conversely, a very high discount rate implies lower expected INBs because of the increased weight of the earlier costs of global IPV introduction. All INBs in the analysis represent prospective estimates that exclude the very large value of polio cases prevented in the past by the introduction of polio vaccination [5,36], and they reflect only the differences in economic benefits of future policy options given the state of the world

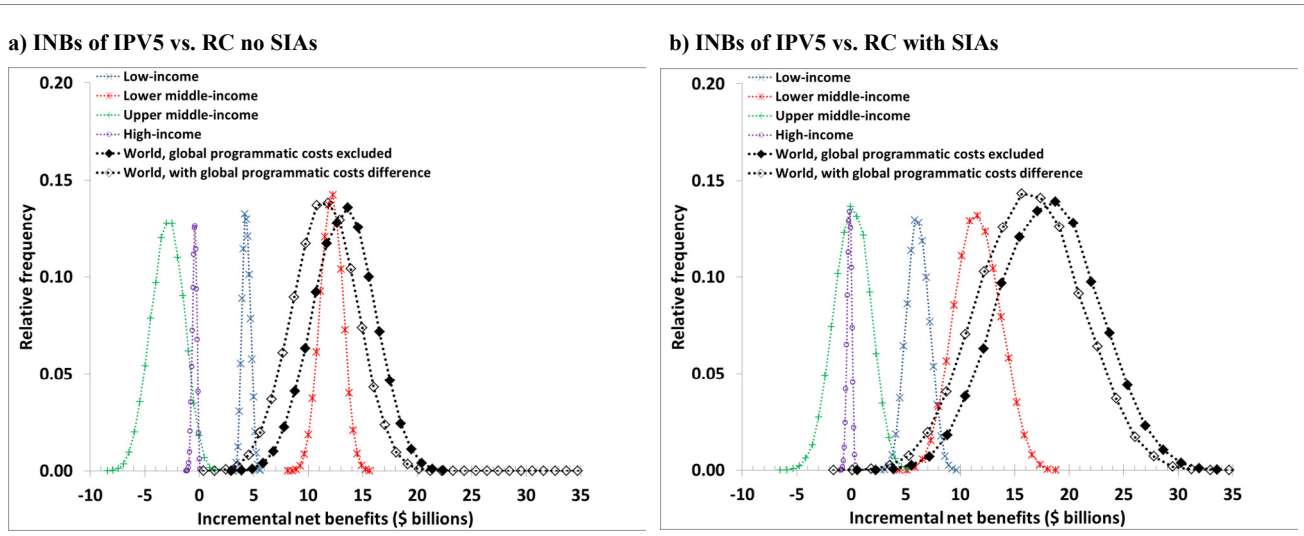

Figure 2: Cost-related uncertainty distributions for the INBs from the probabilistic uncertainty and sensitivity analysis, based on 50,000 realizations from the cost input uncertainty distributions in Table 1 (3% discount rate). (Abbreviations: INB, incremental net benefit; IPV, inactivated poliovirus vaccine; IPV5, global minimum policy of IPV use for 5 years after cessation of the last oral poliovirus vaccine serotype; RC, reference case; SIA, supplemental immunization activity).

Income level	Base case without cost uncertainty (3% discount rate)	With cost uncertainty, showing Mean (SD) [5th,95th]		
		3% discount rate	No discounting	10% discount rate
IPV5 *vs*.RC no SIAs				
Low-income countries	4.2	4.3 (0.38) [3.7,4.9]	9.0 (0.70) [7.9,10]	0.95 (0.13) [0.74,1.2]
Lower middle-income countries	12	12 (1.0) [10,14]	26 (1.9) [22,29]	2.5 (0.39) [1.9,3.2]
Upper middle-income countries	-3.6	-3.4 (1.5) [-5.9,-1.1]	-5.7 (2.6) [-10,-1.6]	-1.6 (0.57) [-2.5,-0.63]
High-income countries	-0.37	-0.49 (0.19) [-0.82,-0.18]	-0.92 (0.36) [-1.5,-0.35]	-0.16 (0.064) [-0.27,-0.059]
World, global programmatic costs excluded	12	12 (2.8) [7.7,17]	28 (4.8) [20,36]	1.8 (1.1) [-0.085,3.5]
World, with global programmatic costs difference	10	10 (2.9) [5.7,15]	25 (5.0) [16,33]	1.2 (1.1) [-0.73,3.0]
IPV5 *vs*.RC with SIAs				
Low-income countries	5.7	6.0 (1.0) [4.3,7.7]	11.8 (1.9) [8.7,15]	1.7 (0.31) [1.2,2.2]
Lower middle-income countries	11	11 (2.1) [7.9,15]	22 (3.8) [16,29]	3.1 (0.70) [1.94,4.25]
Upper middle-income countries	-0.61	-0.52 (1.6) [-3.3,2.1]	-0.32 (2.9) [-5.2,4.4]	-0.57 (0.62) [-1.6,0.42]
High-income countries	-0.18	-0.23 (0.21) [-0.59,0.10]	-0.44 (0.39) [-1.1,0.18]	-0.077 (0.069) [-0.19,0.032]
World, global programmatic costs excluded	16	16 (4.5) [9.0,24]	33 (8.3) [20,47]	4.1 (1.6) [1.5,6.7]
World, with global programmatic costs difference	14	15 (4.6) [7.1,22]	30 (8.4) [16,44]	3.5 (1.6) [0.85,6.1]

Abbreviations: INB, incremental net benefit; IPV, inactivated poliovirus vaccine; IPV5, global minimum policy of IPV use for 5 years after cessation of the last OPV serotype; OPV, oral poliovirus vaccine; RC, reference case; SIA, supplemental immunization activity.

Table 2: Summary statistics of the cost-related uncertainty distributions of the INBs (in $ billions) for different discount rates.

Cost input	Rank correlation with the global INBs[a]	Rank correlation between income level-specific input value and INBs			
		Low-income	Lower middle-income	Upper middle-income	High-income
IPV cost per dose	-0.68	-0.32	-0.46	-0.81	-0.86
OPV in RI administration costs per dose	0.52	0.86	0.54	0.41	0.16
Treatment cost per polio case	0.25	0.19	0.63	0.02	0.01
Difference in annual global programmatic costs	-0.24	N/A	N/A	N/A	N/A
Effective wastage of IPV in IPV-only RI	-0.18	-0.09	-0.12	-0.22	-0.14
IPV combo in RI administration costs per dose	-0.16	0.00	-0.01	-0.26	-0.40
OPV cost per dose	0.15	0.22	0.14	0.13	0.10
Effective wastage of OPV in RI	0.06	0.11	0.08	0.04	0.01
Effective wastage of OPV or IPV in SIAs	-0.03	-0.08	-0.04	0.00	0.00
Incremental cost for OPV+IPV co-administration in LOW or LMI	-0.03	N/A	N/A	N/A	N/A
Effective wastage of IPV in IPV/OPV RI	0.02	0.01	0.01	0.02	0.15
Relative administration costs oSIAs *vs*.pSIAs	-0.01	N/A	N/A	N/A	N/A
OPV in pSIAs administration costs per dose	-0.01	-0.05	-0.02	0.00	0.00
IPV single-antigen in RI administration costs per dose	0.01	0.01	0.00	0.00	0.00

Abbreviations: INB, incremental net benefit; IPV, inactivated poliovirus vaccine; IPV5, global minimum policy of IPV use for 5 years after cessation of the last OPV serotype; OPV, oral poliovirus vaccine; oSIA, outbreak response SIA; pSIA, preventive SIA; RC, reference case; RI, routine immunization; SIA, supplemental immunization activity.

Notes: [a] Global INBs with global programmatic costs difference.

Table 3: Sensitivity of the INBs of IPV5 vs. RC no SIAs to uncertain cost inputs based on the rank correlation between each input and the INBs (ranked by absolute values of the rank correlation with the global INBs)

in 2013.

Tables 3 and 4 rank the cost inputs by their contribution to the cost-related uncertainty about the global INBs. The ranking depends on whether we assume that the RC includes continued SIAs beyond 2019. If not, then the IPV cost emerges as the most important cost input, followed by the OPV RI administration costs and the treatment cost per polio case (Table 3). If the RC includes SIAs, then the OPV administration costs in preventive SIAs (pSIAs) represent the most influential cost input, followed by the IPV and OPV costs (Table 4). Thus, perhaps somewhat surprisingly, the economic value of OPV cessation depends strongly on the uncertainty about OPV vaccination costs for the counterfactual 2013 baseline. However, regardless of the assumed RC, Table 2 Tables 3 and 4 underscore the importance of current and future IPV costs, and the uneven importance of this and other inputs in the different income levels, with the strongest relationship in the highest

Cost input	Rank correlation with the global INBs[a]	Rank correlation between income level-specific input value and INBs			
		Low-income	Lower middle-income	Upper middle-income	High-income
OPV in pSIAs administration costs per dose	0.72	0.83	0.83	0.40	0.32
IPV cost per dose	-0.42	-0.13	-0.23	-0.73	-0.80
OPV cost per dose	0.32	0.30	0.26	0.36	0.15
OPV in RI administration costs per dose	0.32	0.38	0.36	0.19	0.15
Difference in annual global programmatic costs	-0.15	N/A	N/A	N/A	N/A
Effective wastage of IPV in IPV-only RI	-0.12	-0.04	-0.06	-0.20	-0.13
IPV combo in RI administration costs per dose	-0.10	-0.01	-0.01	-0.23	-0.37
Effective wastage of OPV or IPV in SIAs	0.05	0.07	0.07	0.01	0.00
Effective wastage of OPV in RI	0.04	0.04	0.04	0.03	0.01
Incremental cost for OPV+IPV co-administration in LOW or LMI	-0.02	N/A	N/A	N/A	N/A
Treatment cost per polio case	0.01	0.00	0.00	0.02	0.02
IPV single-antigen in RI administration costs per dose	<0.01	0.00	0.00	0.00	0.00
Relative administration costs oSIAs *vs.*pSIAs	<0.01	N/A	N/A	N/A	N/A
Effective wastage of IPV in IPV/OPV RI	<0.01	-0.01	-0.01	0.01	0.14

Abbreviations: INB, incremental net benefit; IPV, inactivated poliovirus vaccine; IPV5, global minimum policy of IPV use for 5 years after cessation of the last OPV serotype; OPV, oral poliovirus vaccine; oSIA, outbreak response SIA; pSIA, preventive SIA; RC, reference case; RI, routine immunization; SIA, supplemental immunization activity

Notes: [a] Global INBs with global programmatic costs difference

Table 4: Sensitivity of the INBs of IPV5 vs. RC with SIAs to uncertain cost inputs based on the rank correlation between each input and the INBs (ranked by absolute values of the rank correlation with the global INBs)

Income level	Base case	IPV costs drop to lower limits of uncertainty ranges in			IPV costs drop to $0.50 (LOW+LMI) and $1.00 (UMI+HIGH) in		
		2022	2026	2030	2022	2026	2030
IPV5 *vs.*RC no SIAs							
Low-income countries	4.2	4.3	4.3	4.2	4.4	4.3	4.3
Lower middle-income countries	12	12	12	12	13	12	12
Upper middle-income countries	-3.6	-1.8	-2.1	-2.5	-0.30	-0.95	-1.5
High-income countries	-0.37	-0.10	-0.15	-0.19	0.039	-0.039	-0.10
World, global programmatic costs excluded	12	15	14	14	17	16	15
World (with global programmatic costs difference)	10	13	12	12	15	14	13
IPV5 *vs.*RC with SIAs							
Low-income countries	5.7	5.8	5.8	5.8	5.9	5.8	5.8
Lower middle-income countries	11	11	11	11	11	11	11
Upper middle-income countries	-0.61	1.2	0.81	0.50	2.7	2.0	1.4
High-income countries	-0.18	0.092	0.039	-0.0039	0.23	0.15	0.084
World, global programmatic costs excluded	16	18	18	17	20	19	18
World (with global programmatic costs difference)	14	16	16	15	18	17	17

Abbreviations: HIGH, high-income; INB, incremental net benefit; IPV, inactivated poliovirus vaccine; IPV5, global minimum policy of IPV use for 5 years after cessation of the last OPV serotype; LMI, lower middle-income; LOW, low-income; OPV, oral poliovirus vaccine; RC, reference case; SIA, supplemental immunization activity; UMI, upper middle-income

Table 5: Effect of a potential drop in IPV costs on the global INBs, with all other inputs kept at their base case values.

two income levels explained by their continued IPV use through 2052.

Given the importance of the IPV cost assumptions, Figure 3 shows the relationship between the assumed IPV cost and the INBs. Figures 3a and 3b show that higher IPV costs lead to lower INBs in each income level, with the biggest impact on the INBs in the upper middle-income countries and some chance of positive INBs in those countries for low IPV prices. At the global level, the expected INBs (i.e., accounting for the uncertainty about other cost inputs) for IPV5 *vs.* RC no SIAs range from ~$9 billion for the upper limit IPV cost to ~$16 billion for the lower limit IPV cost. For IPV5 *vs.* RC with SIAs, the expected INBs range from ~$14 billion for the upper limit IPV cost to ~$20 billion for the lower limit cost. Thus, varying IPV costs over a realistic uncertainty range yields a $6-7 billion change in INBs.

The importance of the IPV cost motivates significant GPEI-coordinated efforts to further lower these costs. Table 5 shows that such efforts may yield significant increases in the expected global INBs. While the benefits of lower IPV costs may come too late for most IPV RI use in low- and lower middle-income countries in the assumed IPV5 policy, these countries would still benefit from reduced costs in the event of needed IPV oSIAs after mOPV oSIAs become undesirable due to the risks. Greater benefits of lower IPV costs would occur in upper middle and high-income countries as they would continue to use IPV routinely (Figure 1). Overall, a drop in 2026 to the lower limit IPV cost from Table 1 would yield an approximately $2 billion increase in global INBs. A drop in 2026 to IPV costs as low as $0.50 per dose in low and lower middle-income countries and $1.00 per dose in other countries would yield an approximately $3.4 billion increase in global INBs.

Discussion

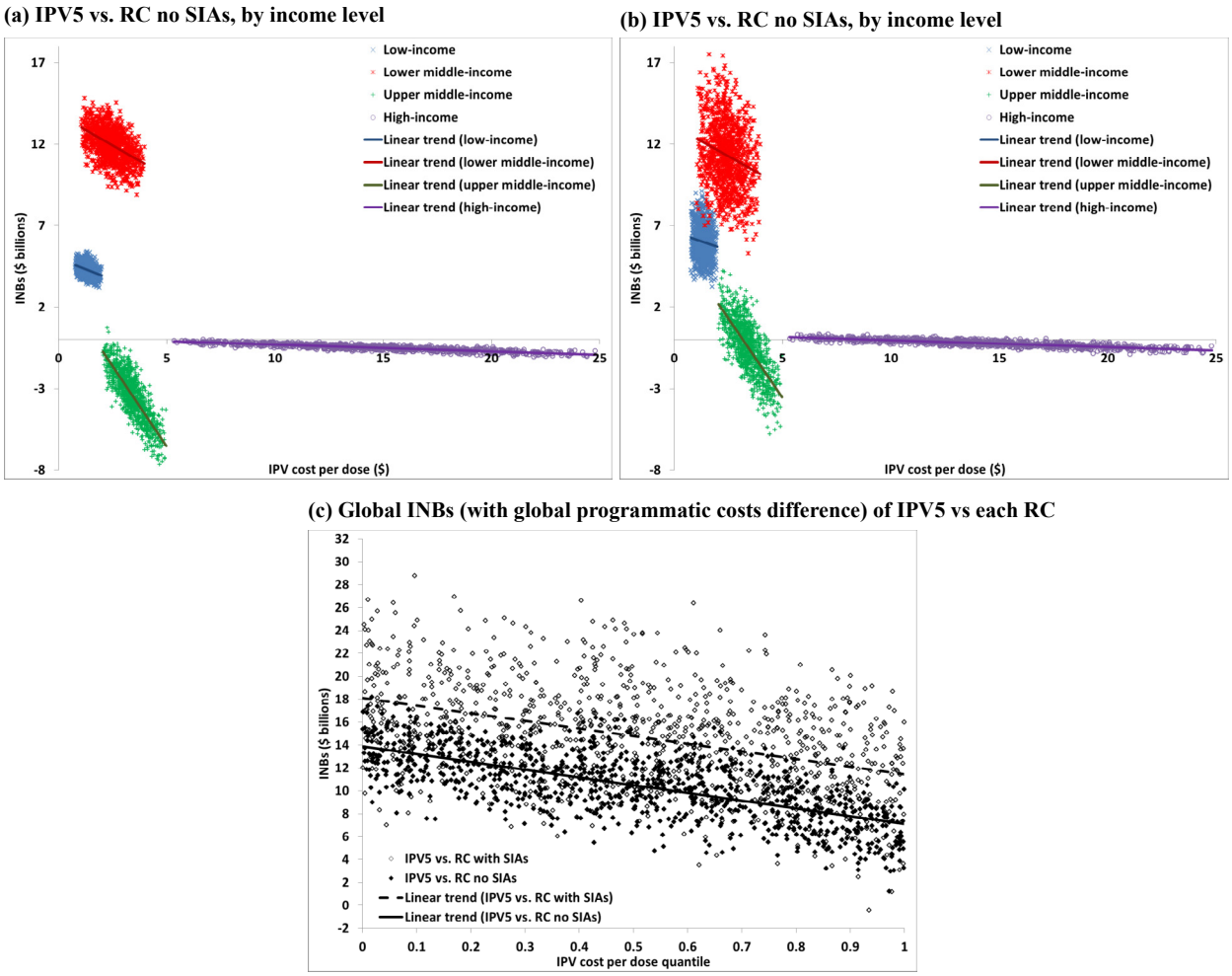

Figure 3: Relationship between IPV cost assumptions and the INBs of IPV5 *vs.*each RC (1,000 realizations from cost uncertainty distributions shown). (Abbreviations: INB, incremental net benefit; IPV, inactivated poliovirus vaccine; IPV5, global minimum policy of IPV use for 5 years after cessation of the last oral poliovirus vaccine serotype; RC, reference case; SIA, supplemental immunization activity)

Despite the higher probability of uncontrollable outbreaks compared to an earlier analysis based on fewer iterations [7], probabilistic uncertainty and sensitivity analysis confirmed the expected positive INBs of the current OPV cessation strategy compared to continued OPV use across a wide range of cost assumptions. Upper middle- and high-income countries may not experience much change in outcomes and by continuing to use IPV they implicitly place a high value on preventing VAPP cases and/or relatively rare events. Assumptions about future IPV costs, costs associated with continued OPV use for the counterfactual policy, and treatment costs emerged as the most influential uncertainties considered, while assumptions about wastage and the incremental costs for reactive outbreak response compared to current SIAs emerged as less important.

Further investments to bring down IPV costs could result in $2-4.5 billion in savings between the mid-2020's and 2052, although low and lower middle-income countries would benefit comparatively little from these cost reductions unless they continue IPV RI for over 5 years after OPV cessation of the last serotype. However, due to the possibility of delayed OPV cessation of the last OPV serotypes, longer IPV use, and/or IPV needs for outbreak response, further investments in IPV affordability may pay off for developing countries. The availability of a more affordable IPV would also increase the chances that lower-income countries would continue to use IPV for more than 5 years after OPV cessation of the last serotype. Specifically, scenarios of lower IPV future costs may not prove compatible with a potential reduction in global IPV demand 5 years after IPV cessation, such that the scenarios of lower IPV costs may only emerge as realistic if global IPV use continues for longer. Some possibility exists that currently lower expected future IPV demands may not justify investments in developing lower cost IPV if a new and safer OPV vaccine becomes available or if the long-term poliovirus risks turn out lower than expected. In contrast, longer IPV use increases the risk of uncontrollable outbreaks if IPV production occurs in settings that will not sustain sufficient population immunity to transmission with IPV-alone to prevent any inadvertently released Sabin or WPV seed strain viruses used for IPV production from establishing transmission [7]. We further emphasize that it remains uncertain whether efforts to reduce the costs of IPV production will lead to cost reductions for the existing combination vaccines with IPV that most upper middle- and high-income countries use. If not, then the global savings with more affordable IPV would remain much smaller and only affect the developing countries that may or may not use IPV long-term. Thus, investments in more affordable IPV come with risks and benefits that require careful considerations and balancing. As

research further develops, future studies will need to explore potential innovations in IPV delivery options, including vaccine patch delivery devices [37,38], that may further contribute to increased INBs.

Our analysis focused on a single baseline long-term poliovirus risk management policy, although numerous variations exist [7,39], and preferences may change over time as uncertainties resolve and reintroduction events do or do not occur. Moreover, the timing of eradication of serotype 1 WPV in Pakistan , Afghanistan, Nigeria, and the surrounding Lake Chad Basin will affect when OPV13 cessation occurs, which will affect the INBs and the uncertainty associated with the different cost inputs. The analysis reflects outcomes averaged over a finite number of iterations with some associated statistical uncertainty. This analysis does not vary uncertain inputs related to the risks, although it considers the stochastic nature of the risks. This analysis did not account for dependencies among cost uncertainties (e.g., IPV cost and wastage) or between these uncertainties and other uncertain model inputs (e.g., IPV cost and RI coverage or duration/schedule of IPV RI). All limitations from the global model [7], and its underlying models [14,21] carry over to this analysis.

Conclusion

This analysis underscores the important role of cost-related uncertainties on the expected long-term benefits of polio eradication and OPV cessation, and demonstrates the large potential benefits of efforts to further reduce costs, particularly associated with IPV use.

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