APPENDIX for "Uncertainty and sensitivity analysis of cost assumptions for global long-term poliovirus risk management" by Radboud J Duintjer Tebbens and Kimberly M. Thompson, *Journal of Vaccines and Vaccination*, 2016.

Overview of the global model

Figure A1 provides a simplified schematic of the main components of the global model.[1] The policy choices determine how population immunity to poliovirus transmission evolves over time in the differential equation-based (DEB) model.[2] The policy choices further lead to fixed costs and cases associated with preventive activities. Poliovirus reintroductions occur randomly, and thus differ for each iteration of the global model. If an effective poliovirus reintroduction occurs after OPV cessation in a given subpopulation, then this results in new transmission of the reintroduced poliovirus in the DEB model for that subpopulation. Accumulation of polio cases leads to detection of the outbreak depending on the subpopulation-specific threshold number of cumulative cases per 10 million people (which depends on surveillance quality), and detection of the outbreak triggers oSIAs as defined by the pre-determined outbreak response choices (and potentially constrained by the number of vaccine doses in the stockpile). Accumulation of 200,000 effective infections triggers a virus exportation to another subpopulation, with the destination of the exportation determined randomly, but preferentially to relatively closer areas. The exportation destination probabilities assume that most exportations remain within blocks of 10 subpopulations with similar properties into which we grouped the 710 subpopulations. Effective infections of virus related to mOPV used for outbreak response can trigger exportations of the mOPV or OPV-related viruses, and use of mOPV can also start new iVDPV infections that could later reintroduce polioviruses. Thus, poliovirus reintroductions result in costs and cases related to outbreaks involving one of more subpopulations. In the event of uncontrolled outbreaks (i.e., approximated by over 50,000 cases), an OPV restart occurs, which results in costs and cases for all subsequent years. Combining the costs and cases related to both preventive activities and outbreaks yields economic estimates, including INBs, which in this analysis we calculated based on appropriately weighting the total costs and total cases of each of the 120 stratified iterations (see below). The computation of cost estimates, poliovirus reintroductions, DEB model outputs, and economic estimates involve the model inputs indicated by unboxed text with dashed arrows pointing to the components they affect in Figure A1. For the cost uncertainty analysis, we keep all of these model inputs fixed, except for the cost inputs, which we vary according to the distributions in Table 1. Table A1 lists the key model inputs that we held fixed, with complete lists of model inputs provided in comprehensive descriptions elsewhere.[1, 3-5]

Sampling from the uncertainty distributions

To sample from a triangular distribution, we draw a random standard uniform number U and find the corresponding realization R from the triangular distribution using the inverse cumulative distribution function:

$$R = \begin{cases} LL+(U(UL-LL)(M-LL))^{1/2} & \text{if } 0 \le U < (M-LL)/(UL-LL) \\ UL-((1-U)(UL-LL)(UL-M))^{1/2} & \text{if } (M-LL)/(UL-LL) \le U \le 1 \end{cases}$$

where LL = lower limit

M = mode
UL = upper limit

While we assumed independence between the 13 different cost inputs, we fully correlated the realizations of each input for the different indicated income levels by using the same realization from the standard uniform distribution to sample all income level-specific values of the corresponding input. For example, we used different random numbers U1 and U2 to sample the OPV cost in each income level and the IPV cost in each income level, respectively. Thus, a high value for U1 implies high OPV costs in all income levels, but does not affect the IPV costs in any income level, which independently take on different values according to U2. We performed 50,000 realizations of cost input realizations to construct cost-related uncertainty distributions of the INBs of IPV5 compared to the RCs. We used the first 10,000 realizations for the importance ranking of the cost inputs given similar results found using all iterations or different sets of 10,000.

Rank correlations as an importance measure of uncertain cost inputs

The (Spearman) rank correlation reflects the strength of a monotonic relationship between an uncertain model input and the model output (i.e., INBs), with values near 1 indicating a strong increasing relationship (i.e., higher values of the cost input correspond to higher INBs), values near -1 indicating a strong decreasing relationship, and values near 0 indicating that the input exerts little influence on the INBs.[6] We also computed the conventional (Pearson) product moment correlations between each cost input and the INBs, which reflect the strength of increasing (i.e., values near 1) or decreasing (i.e., values near -1) linear relationships between the inputs and the INBs and may disproportionately depend on outliers (i.e., rare observations may make the input look more important than it would be based on the rank correlation).[6, 7] However, given the minimal observed differences between the rank and product moment correlations, we report only the rank correlations. We repeated the probabilistic uncertainty and sensitivity analysis for discount rates of 0% and 10% to explore the importance of valuation of future outcomes (i.e., both costs and polio cases) and reported the summary statistics of the INB results for each discount rate value.

Construction of the stratified set

The set of 1,000 iterations suggested an OPV restart probability of 5.7% (95%CI 4.3% to 7.1%) for the IPV5 policy. Assuming that OPV restarts represent independent realizations of Bernoulli random variables with probability 5.7%, then the probability of observing ≤2 OPV restarts among 100 iterations equals 7.1%, and thus the original set of 100 iterations represented a relatively rare but possible outcome from the global model with higher INBs for OPV cessation compared to the set of 1,000 iterations. The stratified subset includes all 57 OPV restart iterations and the first 63 iterations without OPV restart. We verified that the choice of the 63 iterations without OPV restart did not significantly affect the results (see Table A2). In computing averages, we weigh the iterations with or without OPV restart by the probability of each type of iteration based on 1,000 iterations (i.e., weights of 1/1000 for each of the 57 OPV restart iterations and greater weights of $(1/63)\times 943/1000 \approx 0.015$ for each of the 63 iterations without OPV restart that represent all 943 iterations without OPV restart in the full set). This

stratified set yields expected INBs with all inputs at their base case values of $15.6 billion for IPV5 vs. RC with SIAs and $12.2 billion for IPV5 vs. RC without SIAs.

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Table A1: Overview of key numerical assumptions of the models used to estimate polio incidence, adapted from Duintjer Tebbens et al. (2016).[8]

Assumption	Value	Source [a]
DEB model (Values based on expert review [3, 9, 10] and model calibration[2, 4] process)		
Relative contribution to transmission compared to fully susceptible, by immunity state[b]		[2, 11]
Maternally immune	0.66;0.48	
1 successful IPV dose, recent	0.74;0.41	
1 successful IPV dose, last waning stage	0.90;0.36	
2 successful IPV doses, recent	0.42;0.06	
2 successful IPV doses, last waning stage	0.81;0.13	
≥ 3 successful IPV doses, recent	0.28;0.04	
≥ 3 successful IPV doses, last waning stage	0.72;0.06	
1 LPV infection, recent	0.07;0.05	
1 LPV infection, last waning stage	0.20;0.20	
≥ 2 LPV infections or IPV and LPV (any # or order), recent	0.01;0.01	
≥ 2 LPV infections of IPV and LPV (any # or order), lastwaning stage	0.08;0.06	
Average time for maternally immune newborns to wane to fully susceptible [months]	3	[2]
Average time for other immunity states to wane from recent to fifth and last waning stage [years]		[2]
Serotypes 1 and 2	4	
Serotype 3	3	
Paralysis-to-infection ratio for WPV[c]		[2]
Serotype 1	1/200	
Serotype 2	1/2000	
Serotype 3	1/1000	
Relative R_0 compared to serotype 1 R_0		[2]
Serotype 2	0.9	
Serotype 3	0.75	
Relative R_0 for OPV compared to homotypic WPV		[2, 4]
Serotype 1	0.37	
Serotype 2	0.55	
Serotype 3	0.25	
Average time to reach last of 20 reversion stages (i.e., fully-reverted VDPV, with same properties as homotypic WPV) [years]		[2, 4]
Serotype 2	1.1	
Serotypes 1 and 3	1.7	
Transmission threshold, i.e., minimal prevalence (weighed by contribution to transmission) for non-zero force-of-infection [effective infectious proportion]	5 per million	[2]
Global model [1]		
Timing of major events		
bOPV introduction for some SIAs	2010	
IPV introduction (in populations using OPV-only in 2013)	2015	
tOPV intensification (until OPV2 cessation)	2015	
OPV2 cessation (in April)	2016	
OPV13 cessation (in April)	2019	
Last year of IPV use in all populations	2024	
Last full year of analytical time horizon (T_{end})	2052	
Average per-dose take rate for OPV[d] [%]		[1, 12]
tOPV, serotype 1	35-65	
tOPV, serotype 2	60-75	
tOPV, serotype 3	27-55	
mOPV, serotype 1	45-90	
mOPV, serotype 2	60-95	
mOPV, serotype 3	45-85	

bOPV, serotype 1	42-80	
bOPV, serotype 3	42-80	
Average per-dose take rates for IPV (any serotype)[e] [%]		[1]
Low- and lower-middle income populations	63	
Upper middle-income populations	70	
High-income populations	75	
Number of subpopulations with given R_0 for WPV1[f] (N=710)		[1, 5]
4	20	
5	77	
6	43	
7	250	
8	90	
9	30	
10	30	
11	120	
12	20	
13	30	
Number of subpopulations with given proportion of transmissions via oropharyngeal route[g] (N=710)		[1]
0.3	290	
0.5	40	
0.6	233	
0.8	107	
0.9	40	
RI coverage and schedules	Varies[h]	[1]
Preventive SIA impact and schedules	Varies[i]	[1, 13]
Cumulative effective infections needed to trigger a potential exportation from a subpopulation (exportation threshold)	200,000	[1]
iVDPV prevalence	Varies[j]	[5]
Average time between contacts of long-term iVDPV excretors with the general population [days]	150-600	[1]
Global rate of WPV and Sabin seed strain releases from randomly determined IPV production sites [per year]	1/5	[1]
Other poliovirus releases (i.e., inadvertent OPV use, unintentional release from laboratory, intentional release)	Varies[k]	[1]

Abbreviations: bOPV, bivalent oral poliovirus vaccine of serotypes 1 and 3; DEB model, differential equation-based poliovirus transmission and OPV evolution model; IPV, inactivated poliovirus vaccine; iVDPV, immunodeficiency-associated vaccine-derived poliovirus; LPV, live poliovirus; mOPV, monovalent OPV; OPV, oral poliovirus vaccine; OPV## cessation, globally-coordinated cessation of OPV containing the serotype(s) indicated by ##; PID, primary immunodeficiency disease; RI, routine immunization; R_0, basic reproduction number; SIA, supplemental immunization activity; T_{end}, end of the analytical time horizon (i.e., December 31, 2052); tOPV, trivalent OPV; WPV(1,2,3), wild poliovirus (serotype 1, 2, or 3, respectively)

[a] Publications that list the numerical assumption and/or provide methodological details

[b] Numbers separate by semi-colons indicate contribution to a fecal-oral and oropharyngeal transmission, respectively

[c] Model assumes half of these ratio for maternally immune individuals and full and permanent protection from paralysis in all other immunity states

[d] Values vary by population and correlate with higher R_0 values

[e] Includes priming response without seroconversion for first IPV dose

[f] R_0 values for OPV and VDPV/WPV of each serotype follow from relative R_0 values in top section of table

[g] Lower values correlate with higher R_0 values

[h] See sources for values by subpopulation; technical details about characterization of RI provided in [2, 14]

[i] See sources for values by subpopulation; technical details about characterization of SIAs provided in [4]

[j] Generated by discrete-event simulation model of all global PID patients[5]

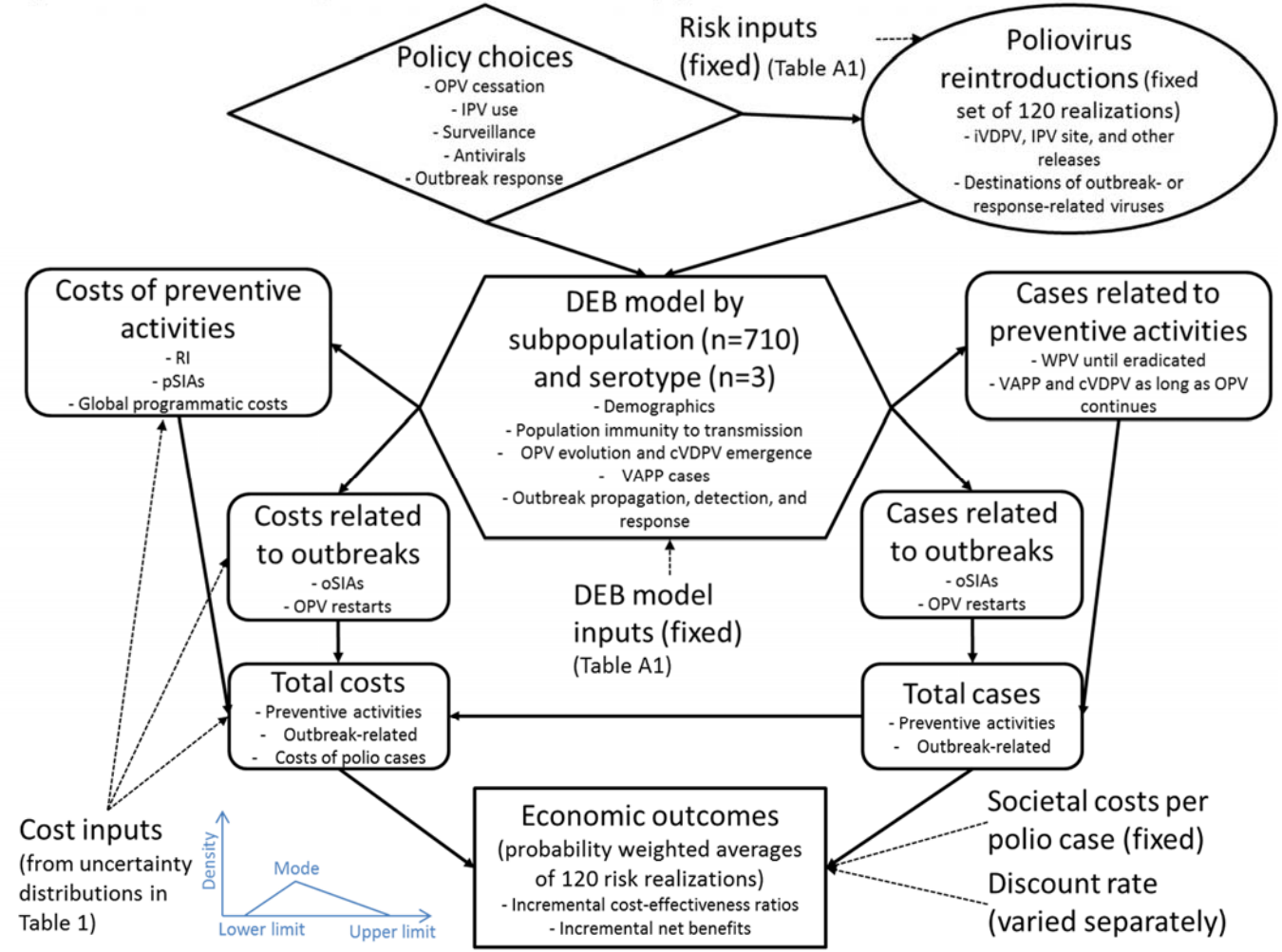
[k] Depends on nature of release, income level, and time

Table A2: Comparison of global INB results using either the first 63 iterations without an OPV restart (as used for all other analyses in this paper) or 5 sets of randomly selected iterations without OPV restart. All results use the same 57 OPV restart iterations.

Selected set of 63 iterations without OPV restart	Global INBs[a] of IPV5 vs. OPV no SIAs ($ billions)	Global INBs[a] of IPV5 vs. OPV with SIAs ($ billions)
First 63	12.2	15.6
Random set 1	12.2	15.6
Random set 2	12.2	15.5
Random set 3	11.7	15.1
Random set 4	12.2	15.6
Random set 5	12.2	15.6
Average of 5 random sets	12.1	15.5

[a] Excluding global programmatic costs difference

Figure A1: Influence diagram of the global model.[1]



Abbreviations: cVDPV, circulating vaccine-derived poliovirus; IPV, inactivated poliovirus vaccine; iVDPV, immunodeficiency-associated vaccine-derived poliovirus; OPV, oral poliovirus vaccine; oSIA, outbreak response supplemental immunization activity; pSIA, preventive supplemental immunization activity; RI, routine immunization; VAPP, vaccine-associated paralytic poliomyelitis; WPV, wild poliovirus

Legend: Bold arrows = direction of influence; dashed arrows = dependence on indicated model inputs; diamond = long-term poliovirus risk management decisions; hexagon = submodel; oval = random events; rounded rectangles = intermediate outcomes; straight rectangles = main outcomes; unboxed text = model inputs