Quantitative Analysis of Trade-offs and Model Input Sensitivities in Public Health

Proefschrift

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CHAPTER 1

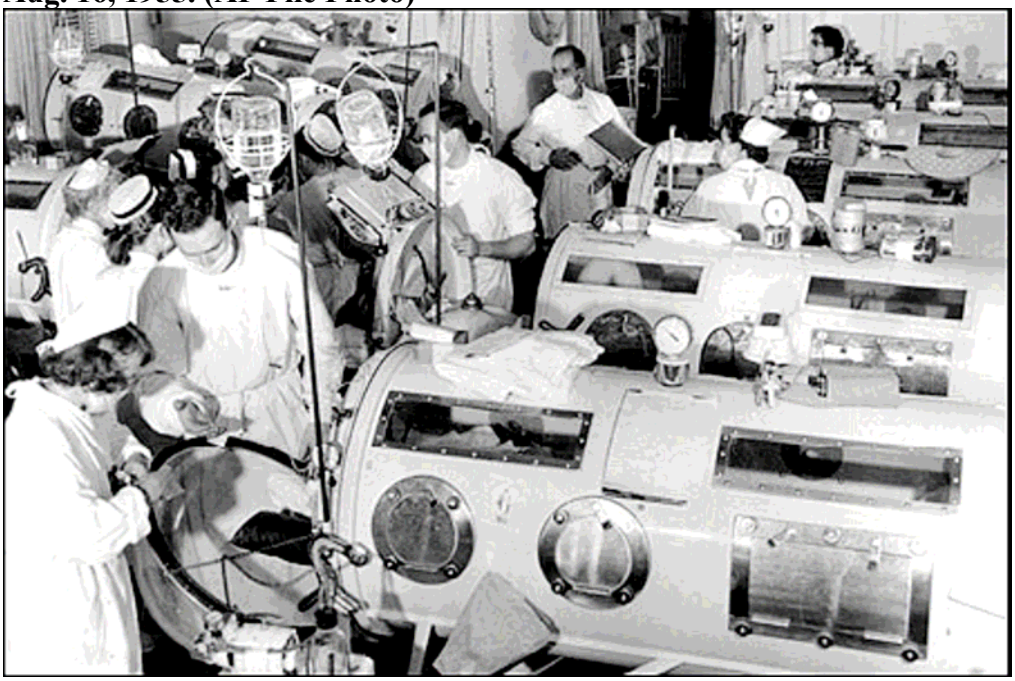
Introduction

Polio and the role of quantitative modeling in public health

After having enjoyed the pleasure of living several years in Boston, it is hard to imagine that 50 summers ago, in 1955, "Boston became a place to avoid." [1] A poliomyelitis (polio) epidemic terrorized the city that summer. Hospitals overflowed, people lined up outside, and the police worked hard to keep order. Despite the heat, worried parents urged their children not to use swimming pools to avoid infection with the poliovirus, which can cause permanent paralysis (in about 1 out of 200 infections; some people get milder, transient non-paralytic polio, and most infections go unnoticed) or even death. With some manifestations of the disease, patients relied on iron lungs to pump air through their paralyzed and damaged lungs (Figure 1). During a 10-week period, the state of Massachusetts reported 2,200 cases of polio. Polio outbreaks, like the one in Boston, happened frequently every summer in the United States and caused tremendous fear. Fortunately, the outbreak in Boston in 1955 was one of the last major polio outbreaks in the country, since on April 12, 1955, the federal government declared Jonas Salk's inactivated polio vaccine (IPV) safe and effective. This news unleashed a collective sigh of relief and optimistic faith in a victory of science against infectious diseases. Indeed, IPV, later followed by Albert Sabin's oral polio vaccine (OPV), controlled and then eradicated polio from the United States. With the fear that polio caused in the "pre-vaccine era" now mostly forgotten, public recognition of the benefits of the vaccination program also wanes, although the benefits continue to accrue by preventing polio cases and saving lives.[2]

One of the last large polio outbreaks in a Western country occurred during late 1992 and early 1993 in the Netherlands when a poliovirus, most likely imported from India, caused polio cases in places like Streefkerk, Nunspeet, Tiel, Rotterdam, Gouda and 's Hertogenbosch.[3] Although the outbreak remained confined to communities whose inhabitants frequently refused vaccination on religious grounds, panic caused a great rush on polio vaccines throughout the country.[4] The Netherlands, like all other countries that eliminated polio, still remains at risk for imported polio outbreaks until the achievement of global polio eradication.[3] Fortunately, the world made great progress towards global polio eradication since the World Health Assembly (WHA) resolved in 1988 to eradicate polio from the world.[5] Despite recent setbacks, global eradication remains an achievable goal within a few years. Since 2000, the global annual burden averaged only approximately 1000 polio cases.[6] However, during 2003-2004, an epidemic originating from Nigeria led to importation outbreaks, or in some cases even re-established wild virus transmission, in 13 previously wild polio-free African countries. The ease with which polioviruses can spread to polio-free countries underscored the importance for all countries to complete global polio eradication and to ensure maintenance and protection of this achievement through sound risk management policies in the post-eradication era.

Figure 1: "A scene in the emergency polio ward at Haynes Memorial Hospital in Boston on Aug. 16, 1955. (AP File Photo)"[1]



The cost of the polio eradication initiative amounts to billions of dollars in international monetary donations, and billions more in financial and other contributions from the developing countries.[7, 8] This investment already saved millions of children from polio and will continue to do so after successful eradication. The prospect of eradication raised expectations from the outset that vaccinations would stop soon after global eradication, eventually adding financial benefits to the health benefits.[8] However, experience in recent years demonstrated that simply ceasing all polio vaccinations may not emerge as the best exit strategy. The events of September 11, 2001, and the subsequent anthrax scare will most likely result in continuation of vaccination (with IPV) indefinitely in the US and other industrialized countries out of fear for the use of polioviruses as a bioweapon. Moreover, outbreaks of vaccine-derived polioviruses (VDPVs), like the 2000-2001 outbreak on the island of Hispaniola, made clear that OPV viruses (living viruses that normally confer immunity without causing paralysis) can continue to circulate among susceptible individuals in a population for years while gradually reverting back to a transmissible and neurovirulent form that can cause outbreaks. This implies that persisting OPV viruses remaining from the eradication era form a continued risk of polio outbreaks. In addition, scientists continue to learn more about the risks of poliovirus introductions after eradication through very rare immunodeficient long-term excretors of OPV viruses or through releases from a laboratory or polio vaccine manufacturing facility. Finally, recent detection of a wild poliovirus that circulated in Sudan for several years without detection by the surveillance system reinforces the need for maintaining high-quality polio surveillance to ensure that the virus truly disappeared after occurrence of the last polio case. The above risks raise important questions for the post-eradication policies. Should we stop the use of OPV? If so, when? What would it cost to move to IPV, and how will this affect the risks? How large of an outbreak might we see post-eradication?

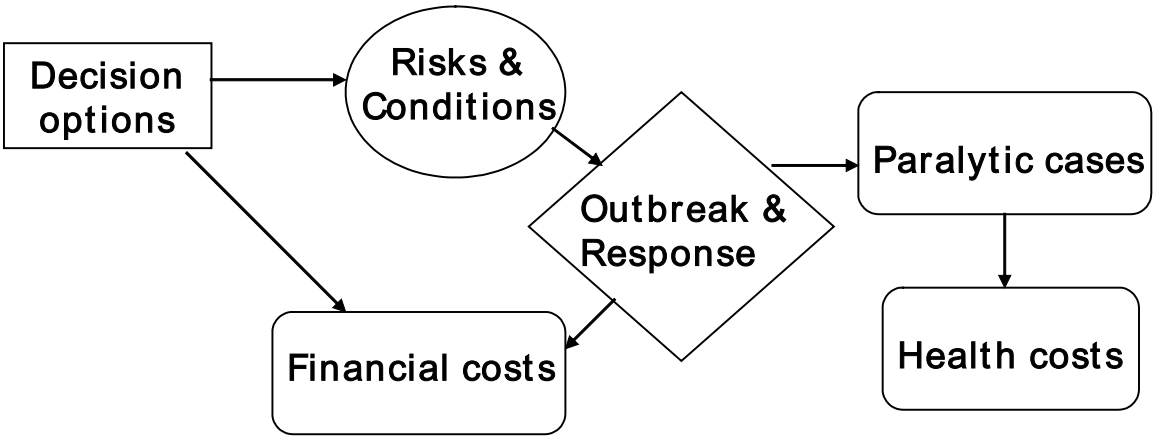
Remarkably, it "has been noted that some delegates to the [WHA] assembly in 1988 might not have made a truly informed decision on the launching of the initiative"[7, p. 913] No quantitative model existed to inform the decision makers about the costs, benefits, and risks of this enormous public health initiative. And yet, quantitative decision analysis methods, such as cost-effectiveness analysis and other economic evaluations, receive increasing recognition as important tools to inform public health decisions.[9] These methods continue to grow in level of sophistication as a result of the rapidly expanding processing speed of computers and the further development of the mathematical foundations of the models. For example, in the context of infectious disease control, analysts must factor in the population benefit of massive vaccination and not just the individual benefits; vaccines often not only protect the recipient against a disease but also reduce the prevalence of the agent (e.g., the virus), thereby protecting even unvaccinated persons. Dynamic infection transmission models factor in this concept (i.e., *herd immunity*) using non-linear sets of equations to produce a better representation of real transmission than simple, linear individual-based models.[2]

While models continue to improve, users also recognize that they will never be perfect, and that the quality of the results depends on the quality of the data that go into the model (also known as the principle of "garbage in, garbage out"). Unfortunately, the inputs of a model are very often uncertain. Ideally, the model should not only inform the decision maker about the most likely outcome of the model, but also about the likelihood and magnitudes of deviations from best estimates. Moreover, simply filling in the best estimates for each model input will generally not provide the best estimate of the model output (i.e., $E(f(X))\neq f(E(X))$ for most functions f of a random variable X). Uncertainty and sensitivity analyses address the impact of uncertainty in a given model. We can view the model as a function of k random variables $\{X_1,...,X_k\}$ that represent the uncertain inputs, which means the model output also becomes a random variable, i.e., $Y=Y(X_1,...,X_k)$. An uncertainty analysis aims to approximate the probability distribution of Y, while a sensitivity analysis investigates the impact of variations in inputs on the output distribution. Both types of analysis provide important information to modelers and decision makers. An uncertainty analysis provides the decision maker with more than one point estimate and gives an idea of the likelihood of different outcomes. A sensitivity analysis can help the decision maker understand how different inputs or interactions of inputs affect the model outcomes and get a sense of the robustness of the model to variations in the inputs. In addition, these analyses can provide the basis for a value-of-information analysis to identify inputs for which reduction of the uncertainty (e.g., through additional research such as clinical trials or structured expert judgment) might result in a better decision.

Thesis outline

This dissertation presents the components of a decision analysis model for polio risk management strategies after global polio eradication. The overall model analyzes different decision options for polio risk management from a global perspective. Figure 2 shows a simple schematic of the different components of the decision model. In this figure, the sharp-angled rectangular box represents a set of decisions, the oval reflects random events, the diamond stands for a dynamic outbreak and response sub-model, and the round-angled rectangular boxes represent health and financial outcomes.

Figure 2: Simplified schematic of the decision analytic model for polio risk management after eradication

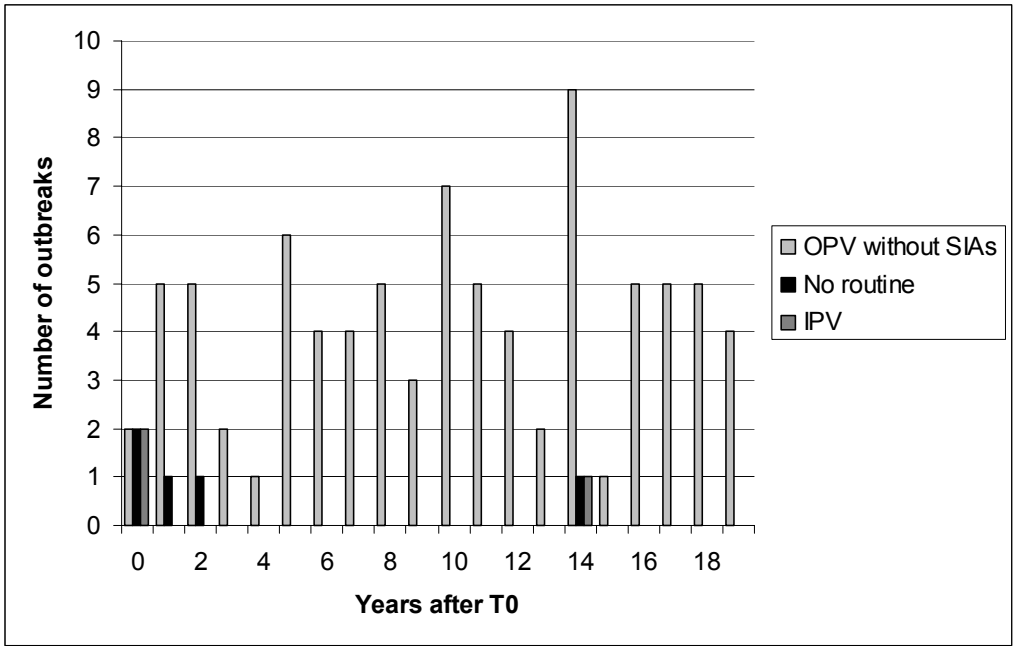


Chapter 2, taken from Sangrujee, Duintjer Tebbens, et al. (2003),[10] lays out the options after eradication. With global polio eradication approaching, the World Health Organization (WHO) will within the next few years propose resolutions and recommendations for the post-eradication era to the WHA. After endorsement by the WHA, these recommendations will substantially influence national decision makers, although ultimately countries will decide among their polio policy choices. The set of logically available options for supplemental immunization activities, outbreak response, vaccine stockpile, surveillance, laboratory and IPV manufacturing site containment, and management of chronic excretors depends on the chosen routine polio immunization policy. Options for vaccination include continued vaccination with OPV or IPV, or no vaccination at all (either with cessation synchronized with other countries or not). Due to differences in public health budgets, hygiene and sanitation, vaccination coverage, vaccine effectiveness and other factors, different countries may rationally prefer different policies. To factor in this variability to some extent, the model stratifies all countries according to their World Bank income level (2002 data[11]), and uses different values for many inputs in the model that depend on the stratification by income level.

Each decision carries fixed costs (although they can change over time) for vaccine purchase and administration, surveillance and, other programmatic activities. Chapter 3, based on Duintjer Tebbens et al. (2005),[12] summarizes the available cost data to derive estimates for the fixed costs as a function of time. In addition to these fixed costs, in the event of an outbreak the authorities will likely respond with a mass vaccination campaign, which carries costs that depend on the outbreak and response characteristics.

The decisions also impact the level of immunity in a population as a function of time, which plays a substantial role in determining the size of the susceptible population and thus the potential occurrence of future outbreaks. Chapter 4, based on Duintjer Tebbens et al. (2005),[13] discusses the factors that influence the risk of polio cases after eradication and provides quantitative estimates for the risks as a function of policy, income level, and time. We describe the risks as Poisson rates and simulate the number of outbreaks in each year by sampling from the Poisson distribution with the appropriate rate. Figure 3 gives an example of one such simulation.

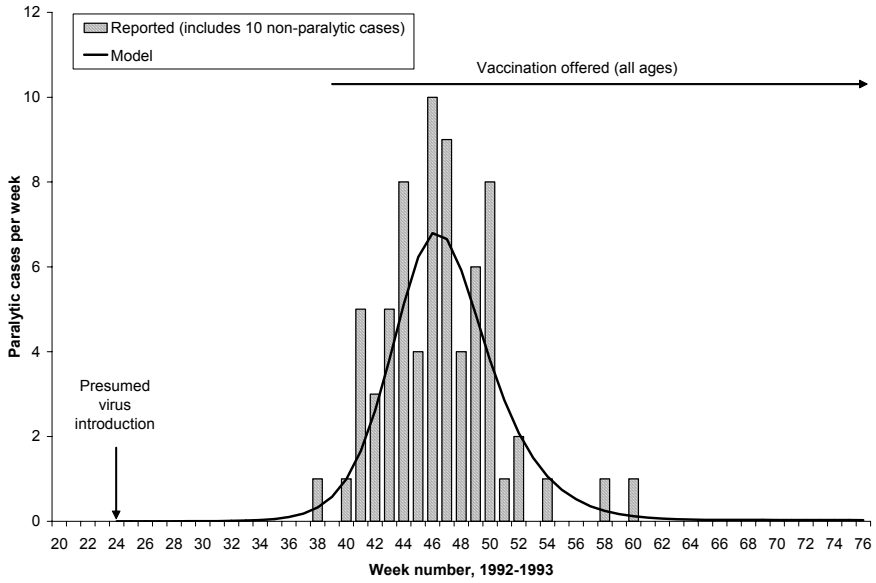
Figure 3: Example of one simulation of a possible future based on the Poisson outbreak rates. This figure shows the aggregate number of outbreaks in low, lower-middle, and upper-middle income countries by year and routine immunization policy. This assumes the "Realistic Population Immunity" profile at T_0 and bases the frequency of cVDPV outbreak on the recorded frequency of cVDPV and aVDPV events during 1999-2004 (see chapter 4).



Whenever an outbreak happens in the risk simulation (in the context of a given year, income level, and set of policies), a dynamic transmission model estimates the typical size of an outbreak in that situation. Chapter 5, based on Duintjer Tebbens et al. (2005),[14] describes this deterministic model and the results of three simulations of polio outbreaks in Albania in 1996, in the Dominican Republic in 2000-2001 and in the Netherlands in 1992-1993. Figure 4 shows the results of the dynamic model simulation of the Netherlands outbreak against the reported number of cases. Based on the experience of modeling these outbreaks and review of the evidence, we developed inputs for a prospective model to estimate the size and kinetics of outbreaks after eradication. The size of an outbreak depends on many factors, including the population immunity profile (and thus the time since OPV cessation if OPV use stops), the hygienic, climatic, and crowding conditions in a country, the quality of surveillance, and the timeliness of a vaccination response.

The outcomes of the overall model include the costs and number of paralytic cases for each permutation of the decision options. The decision analysis is a living model, evolving as events unfold (e.g., our understanding of VDPVs continues to grow as the number of VDPV detections increases) and iteration on the model continues (e.g., we use placeholder inputs for outbreak response until specific guidelines exist). Given that the risks, costs and dynamic model results are functions of sometimes very uncertain inputs, uncertainty exists in the overall model outcomes. While we cannot perform an uncertainty or sensitivity analysis on the overall model outcomes before obtaining agreement on the final model, we must eventually address the uncertainty in the model, and given the size and impact of the model it is important to choose appropriate methods to do so. Therefore, in Chapter 6 we tested methods on a simpler, dynamic decision model for a vaccination program against a hypothetical disease.[15]

Figure 4: Weekly incidence of polio cases in the 1992-1993 outbreak in the Netherlands; reported data from Ref. [3]



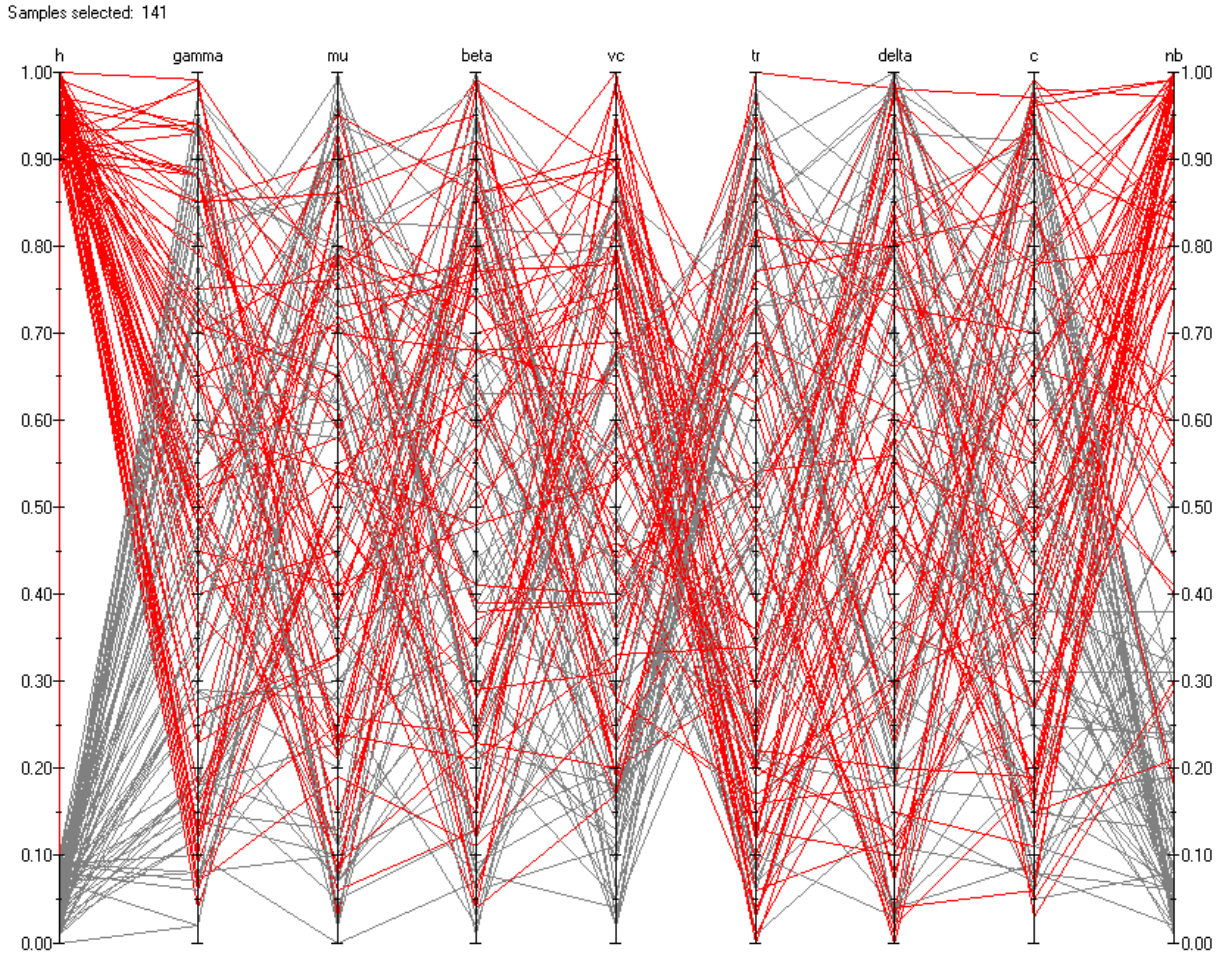
Chapter 6, based on Duintjer Tebbens et al. (2005),[16] describes a dynamic decision model for a hypothetical disease. It presents the methods, results, and insights we obtained from performing a selection of sensitivity analysis methods, including one-way sensitivity analysis, multi-way sensitivity analysis, design-of-experiments, Morris' method, and computation of local partial derivatives and a number of probabilistic sensitivity measures. While the chapter focuses on sensitivity analysis, we show that we can use the samples necessary to estimate the probabilistic sensitivity measures to complete the uncertainty analysis. This exercise serves the dual purpose of demonstrating the use of these methods to a public health decision analysis community and exploring the advantages and drawbacks of candidate methods for the polio decision analysis. Figure 4 shows an example of a graphical result of the probabilistic sensitivity analysis in the form of a cobweb plot.[1] In a cobweb plot, each horizontal line, which consists of piecewise straight segments, represents one sample from the input distribution. The location where a line crosses each vertical axis reflects the percentile of that sample with respect to the distribution of the input indicated above the axis. For the last axis, the location represents the resulting model output percentile (i.e., *nb* in this case, which stands for the net benefit of the vaccination program). The pattern of these lines graphically illustrates the relationships among the variables (both inputs and the output), resulting from their correlation structure, the shape of their marginal distributions, and their functional relationship. In

Figure **5**, we see that values in the highest 10 percentiles of the distribution of the first input (called *h*, which stands for the total costs associated with each disease case) almost always lead to output values in the upper 50 percentiles, regardless of the values of the other inputs. On the other hand, taking *n* in its lowest 10 percentiles results in values of *nb* in the lowest 50 percentiles. This demonstrates the importance of *h* in the model.

[1] Wegman (1990)[17] introduced parallel plots, of which cobweb plots are an independent implementation incorporating extended user interaction

Chapter 6 also discusses the choice of a sensitivity analysis method for the overall polio decision model. We highlight the important opportunity to use formal expert judgment in future refinements of the decision model to improve characterization of the model input uncertainties. The analytical tools developed in this thesis provide important assets for the decision makers charged with protecting public health by managing the risks of polio.

Figure 5: Graphical illustration of the importance of input *h* using cobwebs.



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CHAPTER 2

Policy Decision Options During the First 5 Years Following Certification of Polio Eradication

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Abstract

Policy makers face a number of difficult choices as they develop policies to ensure maintenance of a polio-free world following global eradication and certification. These policy decisions include choices about immunization, outbreak response (including whether to create a vaccine stockpile), surveillance, containment, management of chronic excretors, and investment in future research. This paper focuses on identifying the categories of decisions and characterizing the actual factors that country-level policy makers must weigh to manage polio risks during the first 5 years after certification. Building on a comprehensive literature review, we report the results of the first qualitative analysis to: (1) systematically characterize each type of decision and the relevant options during the first 5 years after certification, (2) clearly identify critical factors that influence the choices, and (3) specifically demonstrate the interdependence among the decisions to produce a reduced set of decision options. This paper explicitly focuses on the different perspectives of developed and developing countries in characterizing the options. While the management of polio risk in the postcertification period presents important challenges, this comprehensive approach helps simplify the process by focusing on critical decisions.

Introduction

Successful polio eradication efforts continue to move the world closer to eradication and certification as free of wild poliovirus. Global certification will occur once all 6 World Health Organization (WHO) regions report finding no wild poliovirus under high-quality surveillance for at least 3 years and the Global Certification Commission becomes satisfied that sufficient laboratory containment exists,[1,2] a milestone already achieved by 3 regions. The achievement of polio eradication and certification will soon lead policy makers to face difficult choices to ensure maintenance of a polio-free world. These choices primarily include policies related to: routine and supplemental immunization, outbreak response (including whether to create a stockpile), surveillance, and containment of wild and vaccine-derived polioviruses (VDPVs). The combination of discrete policy choices forms an overall strategy, with the best strategy from the policy maker's perspective striking an optimal balance among the risks, costs, and benefits. In the context of global discussions of postcertification risk management strategies, few efforts to date have comprehensively described the complexity of choices and placed them within the context of developing and evaluating an overall national strategy. This paper builds on prior work to help fill this void.

Recent discussions predominantly focused on stopping immunization as the ultimate goal of the eradication initiative and on characterizing related issues. In March 1998, a WHO meeting on the scientific basis for stopping polio immunizations identified 4 strategies for stopping immunization that depended on the then unanswered question of whether VDPVs could persist in populations.[3,4] If VDPVs could persist, the preferred options would be to replace the current trivalent oral polio vaccine (tOPV) for a transition period or replace the tOPV indefinitely with either the enhanced inactivated polio vaccine (eIPV) or a new vaccine. If VDPVs could not persist, the preferred option involved a coordinated cessation of tOPV use, possibly including sequential removal of eradicated strains from tOPV (ie, using bivalent OPV [bOPV] or monovalent OPV [mOPV]).

Following clear evidence of the persistence of VDPVs and associated outbreaks,[5] Wood and colleagues[6] concluded that "discontinuation of OPV in a synchronized way remains the most plausible" option. Subsequent publications presented similar vaccination options[7-13] and discussed whether and how immunization should be stopped,[14-16] with one study emphasizing the differences in decisions between developed and industrialized countries.[15] Another study summarized available data addressing the option of using monovalent vaccines as part of the immunization policy,[17] and a recent report noted the interdependence of countries' decisions.[18]

In spite of clear recognition of the need for surveillance strategies, stockpiles, and contingency plans to respond to potential outbreaks in the postcertification era,[3,4,9,10,13,19,20] few articles have elaborated on these issues and related decision options.[10,21] Fine and colleagues[10] estimated the impact in the posteradication era of an outbreak in a population assuming various immunization and surveillance conditions that might result from the implementation of different policies. From their analysis of the implications of delays in outbreak response, they recommended: (a) maintaining active surveillance for at least 5 years after ceasing all polio vaccination, (b) minimizing delays in diagnosis and confirmation of an outbreak, (c) restricting poliovirus work to a few high-level containment laboratories, (d) maintaining OPV manufacturing capacity, and (e) establishing a stockpile and a response protocol for outbreaks. Recently, Sangrujee and

colleagues[21] estimated the potential immunization policy costs for continuing tOPV, switching to eIPV, and stopping immunizations, and developed general cost estimates for global programmatic activities such as maintaining stockpile, laboratory network, and surveillance capabilities. Finally, Fine[22] suggested the need to refine the scenarios presented by Wood and colleagues,[6] recognizing that probably the most important choice facing policy makers remains which vaccine to use, if any.

While these papers represent important progress in informing decision makers, considerable work remains. The decision makers at the 1988 World Health Assembly (WHA) resolved to eradicate polio,[23] and this paper anticipates that the success of the eradication initiative will lead a future WHA to discuss and determine global polio policies to implement after global certification. Clearly, the current (precertification) time period represents a critical time for research efforts focusing on scientific uncertainties, economics, and logistics to provide sufficient information to decision makers about the implications of policy challenges after certification.

This paper describes the policy options during the first 5 years after certification from the perspective of the decision maker for an individual country. We focus on the first 5 years after certification because it represents a critical time period for decisions about continuing OPV use. During this time, we expect both the highest population immunity and the greatest risk of VDPVs. We characterize the currently debated policy options and discuss how various factors (eg, cost, risks, risk perception, neighboring countries' policies) influence policy decisions. Through qualitative analysis and with the objective of providing focus and context to the debate, we narrow the list of potential policy options to those most likely for decision makers of either developed or developing countries. Section 2 describes the methodology used, while section 3 describes each category of decisions and the current country-level options that exist within that category. Section 4 discusses several factors likely to influence policy makers as they evaluate the options and presents our expectations about the reduced set of options available to decision makers in developed and developing countries. Section 5 discusses critical issues (eg, time); and sections 6 and 7 present the conclusions and references, respectively.

Methods

We conducted a thorough review of the literature on policy options following certification of polio eradication. A PubMed search of relevant keywords (ie, polio post certification, polio post eradication, polio post-eradication, polio policy, polio certification strategy and strategies, polio eradication strategy and strategies, and polio endgame) identified 304 unique articles. Review of the titles and available abstracts led to selection of 21 articles for complete review, from which we identified 19 articles or letters that discuss postcertification decision options. We also reviewed unpublished reports and operational guidelines provided by the WHO and the Centers for Disease Control and Prevention (CDC).

Based on our synthesis of the existing literature, we identified categories of current and future policies after certification. We listed all possible decision options within those categories from the perspective of a country-level policy maker and developed decision trees to characterize the set of options for each category. From these options, we eliminated any that appeared economically and technically impractical within the time period starting from the point of certification and ending 5 years after certification (ie, those for which financing would not likely

exist and/or technical, regulatory, or other barriers suggested implausibility in the short-term). We also informally queried experts on several of the issues for more information and to ensure that we included relevant unpublished reports. We particularly benefited from helpful discussions with a number of experts involved with the Polio Eradication Initiative (PEI) at the WHO and the CDC. We further identified a number of critical factors that may influence a policy maker's choices. Finally, we conducted qualitative analyses of the decision options using the decision trees to identify any dependent relationships among the policy categories; this allowed us to eliminate any logically inconsistent policy combinations.

Categories of Policy Options for the First 5 Years Following Certification

We identified 8 categories of policy options that the following 8 subsections address independently. Each subsection identifies the current policies, to provide context for the unfamiliar reader, and the postcertification options. For each category, we provide a corresponding figure that shows the options in the form of a decision tree.

Routine Immunization

Current policies. The decision to vaccinate routinely requires choosing both the type of vaccine for use and the schedule for vaccine administration. Currently, the WHO recommends that each child receive 4 doses of tOPV (administered at 6, 10, and 14 weeks, with the fourth dose given either at birth or within the first year) in order to be fully protected against polio.[24,25] Consistent with this recommendation, most countries perform primary vaccination (defined as the first 3 doses of polio vaccination) with tOPV. However, currently, 16 developed countries use eIPV for primary vaccination (Andorra, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Iceland, Latvia, Lithuania, The Netherlands, Norway, Sweden, Switzerland and the United States).[24,25] In addition, 4 countries (Belarus, Croatia, Hungary, and Israel) currently use a primary sequential schedule of eIPV/tOPV.[24,25] Three countries (Andorra, Latvia, and Lithuania) give children a routine tOPV booster dose after the completion of the eIPV primary schedule,[24,25] and routine immunization schedules continue to change.

All countries currently using eIPV maintain high levels of routine coverage and good sanitation, resulting in no reported cases of wild polio in more than 10 years (The Netherlands last reported a case in 1993[26]). Most of these countries switched from tOPV to eIPV (some first transitioning with a sequential schedule) to avoid cases of vaccine-associated paralytic polio (VAPP), a rare adverse event associated with tOPV.[27] Given lingering concerns about the risk of importation from countries where the wild poliovirus still exists, not all industrialized countries have switched to eIPV, mainly due to the better intestinal immunity with tOPV and the benefit obtained from secondary spread of tOPV to maintain high levels of population immunity. Variation currently exists among countries in terms of the number or scheduling of doses given. Policy decisions on scheduling tend to focus on harmonizing the vaccination schedule with other vaccinations. For example, in the United States, the current Advisory Committee on Immunization Practices recommends administering eIPV in a 4-dose schedule at 2, 4, 6-18 months, and 4-6 years of age, coordinating polio vaccination with the recommended schedules for DT(a)P and Hib vaccines.[27] Currently, Cuba relies only on mass immunization campaigns twice a year for its routine delivery of tOPV instead of regularly scheduled visits to a clinic.

Postcertification options. In the postcertification era, routine immunization policies include stopping vaccination altogether, using the same or a different vaccine, and changing or maintaining the vaccination schedule. Currently, tOPV is used to vaccinate against 3 types of wild poliovirus (types 1, 2, and 3), but policy makers may at some point in the future choose to use bOPV or mOPV as the different types are eradicated. Fine and colleagues[10] discussed some of the potential motivations and issues related to using mOPV or bOPV, with thorough discussions of both the risks and the benefits. Alternatively, countries may choose the current eIPV vaccine, available alone as a single vaccine (ie, single-antigen) or in a combination form (ie, combined with other antigens, such as in DTaP-IPV, DTaP-Hib-IPV, DTaP-Hep B-IPV, DTaP-Hep B-Hib-IPV). A new potential alternative IPV/Sabin vaccine, produced using the Sabin poliovirus strains instead of the wild strains now used, is being developed for bulk production. The choice of IPV/Sabin may offer some benefits related to containment during production, although licensing of an IPV/Sabin vaccine within the first 5 years after certification appears unlikely. Similarly, licensing of bOPV or mOPV for routine immunization appears unlikely. Finally, at some point, policy makers may benefit from research efforts leading to a new vaccine, although the complexities of evaluating such vaccine make the probability of licensure and production within the first 5 years after certification remote.

Figure 1 illustrates the set of decision options for routine immunization, with the options that we assume to be practical within the first 5 years after certification indicated in bold. The main decision countries face is whether to use OPV, IPV, or no vaccine. If the WHO recommends cessation of all vaccinations in a coordinated fashion, countries must decide whether to join the coordinated cessation or not. We assume that in the first 5 years following certification, only tOPV and eIPV are realistic vaccines for routine immunization, and those countries that continue to vaccinate will maintain their current vaccination schedules. Countries that plan to stop tOPV vaccination may also need to decide whether to conduct a mass immunization campaign just prior to stopping to boost population immunity.[6] Although some countries might decide to switch to a sequential schedule from an all-tOPV schedule immediately after certification, we treat this as a transitional choice to an all-eIPV schedule and do not include it explicitly in this analysis.

Supplemental Immunization Activities (SIAs)

Current policies. SIAs include national immunization days (NIDs), sub-NIDs (SNIDs), and mop-up campaigns that rapidly interrupt poliovirus transmission. The WHO Technical Consultative Group (TCG) on Polio Eradication recommended the maintenance of high-quality SIAs in all polio endemic countries and developed criteria for determining when to conduct NIDs.[28] The WHO recommends NIDs at least annually in polio-endemic or recently endemic countries. Currently, all SIAs use tOPV, targeting all children under the age of 5 years (regardless of the child's immunization history). Two rounds of SIAs are conducted over a 4- to 6-week period. Other countries that border endemic countries may also conduct NIDs or SNIDs. Countries may target SNIDs in areas with particularly low routine vaccination coverage, and large, populous countries (eg, China, India) may conduct SNIDs on the scale of smaller countries' NIDs to target specific regions. During mop-up campaigns, vaccinators go door-to-door to immunize children in areas that are difficult to reach with a (fixed post) (S)NID campaign, have low immunization coverage, or are at highest risk. Finally, in the context of the PEI, countries often collaborate

with neighboring countries to conduct synchronized regional NIDs to interrupt transmission in larger geographic areas.[29]

In April 2002, the TCG also recommended that: (1) polio-free countries that either border an endemic area or have routine coverage of 70% or less should continue to conduct NIDs or SNIDs, as appropriate, on an annual basis; and (2) countries that maintain polio-free status for at least 3 years but fail to achieve or maintain a level of 90% routine immunization coverage with 3 doses of tOPV among infants should continue to conduct NIDs at least every 3 years to prevent the accumulation of susceptible individuals and protect against the importation of wild polioviruses.[28] The WHO also recommends, where appropriate, that larger countries conduct SNIDs to cover those states or provinces with lower than 90% coverage. These recommendations support the goals of interrupting any continued transmission of the poliovirus and maintaining high levels of population immunity in areas with insufficient routine coverage.

Postcertification options. In the postcertification era, countries must decide whether to conduct NIDs, SNIDs, or no SIAs, as shown in Figure 2. If they continue SIAs, they must also decide how frequently to conduct them, the number of rounds, and the type of vaccine to use. We assume that the target group consistently remains children under 5 years of age and that the NID includes 2 vaccination rounds. We assume that the vaccine used in SIAs will be the same as the vaccine used for routine vaccination. However, due to regulatory constraints mentioned previously for bOPV, mOPV, and IPV/Sabin as well as potential supply constraints on eIPV, we assume that immediately after certification, only tOPV is used during SIAs. Immediately after certification, conducting NIDs may become the optimal choice for developing countries to prevent re-emergence of wild poliovirus or circulating VDPVs (cVDPVs), although some countries may opt to conduct only SNIDs based on WHO TCG recommendations.

Outbreak Response

Current policies. An outbreak response, as defined in the WHO guidelines,[30] consists of 2 parts: intensified surveillance (to detect new cases and identify subpopulations at high risk), and immunization response (currently with tOPV). Current guidelines aim to intensify acute flaccid paralysis (AFP) surveillance by introducing active case investigation and increased efforts to isolate additional polioviruses.[31-33] The immunization response generally consists of house-to-house mopping-up campaigns in the districts of the confirmed outbreak (or even in some cases prior to isolation of poliovirus, for example, in China[34]), followed by NIDs or SNIDs depending on the number of cases found and the size of the country (eg, NIDs in Albania[31] and Bulgaria,[33] SNIDs in China[34]). The WHO recommends notification of an outbreak to both the WHO and UNICEF within 48 hours of detection.[30] The WHO, in turn, can offer recommendations and assistance to countries in the context of the global PEI. Countries must decide how to respond to an outbreak at the national level.

Postcertification options. In the postcertification era, the likely immediate surveillance response includes performing a comprehensive outbreak investigation and surveillance enhancement (intensified AFP surveillance, active case search, retrospective hospital record reviews, etc.) until evidence shows the interruption of transmission. This effort essentially corresponds to a classical epidemiologic outbreak investigation, and we expect future WHO guidelines for postcertification outbreak response to include these efforts. We assume that each country would follow any WHO

guidelines for the outbreak surveillance response, and we anticipate that the WHO would develop guidelines for the postcertification era before certification.

Given the current experience with outbreaks, we expect future guidelines to suggest some scale of mass immunization response. Countries may choose the size of the response, ranging from no response at all to a focal immunization response (eg, immunization of contacts to house-to-house immunization of children in the district or area of the outbreak), to SNIDs or NIDs, and finally to participation in a regional or global NID. We expect decisions about the appropriate size of the response to depend on time, with greater responses needed with lower levels of population immunity, and all response strategies depending on the scale-up required to successfully interrupt transmission. We assume that the choice of outbreak response in any country increases in a discrete manner, and it depends on the size and characteristics of the outbreak, as shown in Figure 3. We assume that in the first 5 years after certification, evidence of an outbreak of circulating poliovirus will lead at least to an SNID if not an NID. Further, at some threshold, the scale of the response will rapidly increase to an NID to ensure interruption of transmission. We assume a very low threshold for a national response following certification of eradication, given the global repercussions of failing to contain the outbreak.

From the country perspective, Figure 4 summarizes the vaccination options for responding to an outbreak, although we emphasize the likely role of the WHO and its guidelines in determining the size of the response. Figure 4 shows that the choices for those countries that stop routine immunization after certification include resuming routine immunization in addition to conducting response NIDs. Restarting routine immunization assumes resuming polio vaccination indefinitely using the country's current immunization schedule, whether with tOPV or eIPV, possibly with regularly conducted NIDs. We emphasize that the scale of the response may also depend on the availability of sufficient quantities of vaccine from suppliers or stockpiles, but we assume that during the first 5 years after certification, a sufficient supply of vaccines exists. We further assume that outbreak response will use tOPV, mOPV, or eIPV, and it will target children under the age of 5 years. As Fine and colleagues[10] discussed, the use of mOPV might become desirable in the postcessation era so as not to reintroduce nonoutbreak-related poliovirus serotypes into the environment.

Stockpile

Current policies. The WHO and UNICEF currently have vaccine reserves, through the maintenance of funds and arrangements with manufacturers to purchase vaccine for outbreak response, but no formal global stockpile of polio vaccine currently exists. The TCG recommended that a global stockpile exist prior to discontinuation of OPV immunization.[9] Stockpile policy decisions must be made well before certification in order for cessation of immunization to be a realistic policy option at the time of certification. The WHO is currently researching the stockpile design and specifications and exploring issues related to governance and financing. The United States is considering the components of a US national stockpile and is reviewing critical regulatory issues. For example, tOPV needs relicensing in the United States because the prior license lapsed once the United States switched to eIPV for routine vaccination in 2000, and the facilities that manufacture tOPV for the stockpile must meet US Food and Drug Administration production regulations.

Postcertification options. Figure 5 shows the high-level stockpile choices that countries face. Note that the decision to create a stockpile necessitates a number of other critical decisions related to the design, specifications, and governance of a stockpile (not shown in Figure 5, but currently the subject of WHO and US research as noted above). If the WHO creates a global stockpile, then countries could presumably negotiate for explicit access to the global stockpile in the case of an outbreak. For some countries, this access would be implicitly assumed (ie, they assume that the WHO would give them access to the global stockpile in the event of an outbreak). We make the analogy here to the option of purchasing insurance, and we assume that arranging for coverage by the global stockpile essentially provides insurance in case of an outbreak, while not doing so essentially leaves a country uninsured. Some countries may decide to establish a national stockpile only or in addition to arranging for access to the global stockpile.

For countries that create their own stockpile, a number of important design decisions arise, including determination of the: (1) number of doses of 1 or more types of vaccine to keep in the stockpile, (2) number of locations in which to house the stockpile, (3) amount of vaccine to keep readily available in packaged form vs bulk, and (4) appropriate management policies related to cycling the inventory and ensuring that the stockpile size increases in accordance with changing risks and potential demands (ie, growth in the susceptible population). At the global level, for example, a stockpile during the period immediately after certification may in one scenario consist of sufficient doses of tOPV to cover 3 global birth cohorts with 3 doses,[10] although the existence of the global stockpile and numerous possible scenarios related to design issues currently remain under debate. At the national level, we treat the design questions as secondary decisions and we assume that the primary stockpile decisions include arranging for coverage by the global stockpile and/or building a national stockpile (which would include choosing the vaccine type and all other secondary decisions).

Surveillance

Current policies. The current surveillance system for polio started when the Pan American Health Organization initiated a regional laboratory network for AFP surveillance in 1986.[35] In 1989, the WHO Plan of Action (endorsed by the World Health Assembly in 1990 and revised in 1996) expanded this system globally under the WHO PEI.[36] AFP results from multiple causes, including infection by a poliovirus. However, even in the absence of poliovirus circulation, cases of AFP occur at a minimum background incidence rate of approximately 1 per 100,000 children under 15 years of age.[37] This surveillance system analyzes stool specimens from cases of AFP for the presence of poliovirus. Currently, the AFP surveillance system includes the placement of personnel dedicated to finding any wild poliovirus through the identification and investigation of cases of AFP and a global laboratory network of virologic laboratories.[37] The global polio laboratory network includes "7 global specialized laboratories, 15 regional reference laboratories, 83 national laboratories, and 40 subnational laboratories (in large countries)."[38] Currently, surveillance also includes characterization of strains as wild, vaccine, or vaccine-derived (ie, genetic variations of a vaccine strain, of most concern when they revert to virulent forms). A few industrialized countries, including the United States, do not conduct AFP surveillance, although they have laboratories that participate in the global polio laboratory network, choosing instead to include reporting of poliomyelitis as part of ongoing systems of passive and enterovirus surveillance.

Some experience exists with using alternative methods (eg, environmental surveillance) to enhance surveillance; in the future, countries or regions may also consider these alternatives as options. The report of the 6th TCG report stated that: "experience gained from environmental surveillance projects in Egypt, Georgia, India (Mumbai) and Turkey has demonstrated that it is possible to detect wild virus in the absence of AFP cases (Egypt, Mumbai)."[32] One recent study concluded that aseptic meningitis-based surveillance appears impractical as a substitute for AFP surveillance, but suggested the potential utility of environmental and enterovirus surveillance (eg, routine clinical diagnosis of cell cultures of stool specimens) as supplements to AFP surveillance.[39] As recommended at the 6th TCG meeting,[32] the WHO has developed global guidelines for environmental surveillance.[40]

Currently, no policy exists for the routine use of serologic surveillance. Serologic surveillance provides evidence of poliovirus population immunity, but it cannot distinguish between previous vaccine-related or wild poliovirus infections. Serosurveys provided additional evidence of the limited persistence of vaccine-derived polioviruses in an unvaccinated and polio-free population in Cuba[41] and may prove to be a useful tool for the PEI.[42] In a growing susceptible population (ie, following cessation of vaccination), serologic surveillance may offer an additional method for detecting exposure to poliovirus in the population.

Postcertification options. From the country perspective, Figure 6 shows the main options for the first 5 years after certification, including passive surveillance, which relies on the national routine passive disease reporting system, and dedicated AFP surveillance, which represents the current policy now used essentially globally (with the exception of a few developed countries). In some countries, AFP surveillance could eventually get incorporated into a national Integrated Disease Surveillance system, and we assume that such integration would not change the quality of the AFP surveillance, although the costs and details related to implementation require further study. In addition to a passive or dedicated surveillance system, countries may also opt to conduct some form of enhanced surveillance, including environmental surveillance, enterovirus surveillance systems, or serologic surveillance, either nationally or limited to targeted high-risk areas. In the short term, serologic surveillance is not useful following cessation of routine vaccination, given the presence of antibodies from previous vaccinations in most of the population in the 5 years after certification. Similarly, screening for enteroviruses also appears to be a limited option because few countries have the infrastructure to provide routine diagnostic services for the whole population, although this could be initiated. Thus, environmental surveillance remains the only realistic enhanced surveillance policy option for countries immediately following certification.

Containment Strategies

Current policies. Containment strategies focus on reducing the risk of reintroduction of poliovirus into the environment, notably through vaccine manufacturing facilities and laboratories that handle materials that could contain poliovirus (wild or vaccine-related). The WHO recommends that laboratories handle wild poliovirus infectious or potentially infectious materials under biosafety level (BSL-2/polio) procedures.[2] Current WHO policy requires countries to complete a national inventory of wild poliovirus infectious materials and potentially wild poliovirus infectious materials before global certification of eradication.[43] The WHO defines wild poliovirus infectious materials as clinical materials collected from persons with wild or VDPV infections, or materials that contain wild poliovirus isolates (ie, those treated and

stored to preserve the virus). Potentially wild poliovirus infectious materials include "respiratory secretions, feces, and environmental samples collected for any purpose at a time and in a geographic area where wild poliovirus was known or suspected to be present."[44]

One year after detection of the last wild poliovirus, the WHO plans to ask countries to begin the implementation of procedures for containment of wild polioviruses. This process includes contacting all agencies and institutions on the national inventory to do one of the following with the materials: (1) implement laboratory containment procedures (BSL-3/polio for all laboratories with wild poliovirus infectious materials or laboratories that "perform activities involving poliovirus permissive cells or animals" for wild polioviruses and potentially poliovirus infectious materials, or BSL-2/polio for laboratories handling only potential poliovirus infectious materials and performing no such activities[2]); (2) transfer wild poliovirus infectious and potentially infectious materials to WHO-designated repositories; or (3) render such materials noninfectious or destroy them under appropriate conditions. These actions require completion prior to consideration of global certification of polio eradication. In the case of a global decision to cease tOPV administration, the WHO anticipates an increased stringency in the containment requirements for wild and vaccine-derived polioviruses for those countries that choose not to immunize, although the degree of increase remains under discussion.[2]

Postcertification options. As shown in Figure 7, given the condition of meeting containment requirements in order for global certification to occur, the policy decision after certification for each country essentially becomes whether to enforce the WHO-suggested containment requirements.

Management of Chronic Excretors of Polioviruses

Current policies. No known cases exist of chronic excretion of wild poliovirus.[6] As of early 2003, WHO reports have catalogued a cumulative experience consisting of a total of 19 immunodeficient chronic excretors of vaccine-derived polioviruses (iVDPV) globally in more than 40 years of OPV use. These individuals live(d) in mid- to upper-level income countries, primarily in the United States and Europe. Of these 19 chronic excretors, 2 continue to excrete, while the others died or stopped excreting virus. Poliovirus type 2 represents the most frequently isolated serotype. Virtually all of these individuals suffered from severe primary (congenital) antibody deficiency diseases. Preliminary studies estimated extremely low (ie, on the order of 0.1% to 1%) upper limits of prevalence of chronic poliovirus excretion among patients with primary immunodeficiency.[45] The poor access to appropriate medical care and treatment dramatically limits the survival beyond early childhood of patients with primary immunodeficiency in developing countries.

An informal survey of prominent immunologists attending the 2002 Federation of Clinical Immunology Societies meeting gauged their support of a "standard of practice" recommendation that would lead to routine screening (for poliovirus excretion) of patients with primary immunodeficiencies. The immunologists declined endorsement of such a screening policy given the absence of adequate therapy for identified chronic excretors.

We did not identify any current global or country level policies for the specific surveillance of iVDPV. The existing AFP surveillance network has identified all iVDPV cases since 1998, but

the sensitivity of the AFP surveillance system for detecting iVDPV remains unknown, given that prolonged excretion may occur prior to the development of paralysis.

Postcertification options. Figure 8 shows the options for managing chronic excretors. We expect that global and country level options for specific surveillance of iVDPVs may become more feasible with the identification of effective therapeutic measures. However, to manage the risk of reintroduction of poliovirus to the community from identified patients, countries may choose whether to conduct screening and/or offer education about strategies for minimizing exposure to others.

Investment in Research

In any risk management process, ongoing research continues to play an important role in resolving important uncertainties and in creating new (and often better) options (eg, safer, cheaper, and/or more effective vaccines). Although this section does not identify any specific research options, we note that countries may choose to invest some of their resources in research, although currently the WHO and the CDC have funded most research.

Characterizing the Set of Decision Options

Figure 9 combines decision categories and options discussed above as realistic during the first 5 years after certification to represent them in the form of a summary decision tree. This section begins by explicitly recognizing that several critical factors influence the relative attractiveness of the different options to various countries. Then, the following section focuses on identifying the interdependence among some of the options in Figure 9, enabling further narrowing of the decision tree to a realistic set of options.

Critical Factors

Costs. Clearly, cost implications arise with each decision, and the implications of these resource requirements warrant serious consideration. In some cases, cost considerations may make some policy options unfeasible for countries with competing health and budget priorities. The cost of tOPV has ranged from $0.02 ($US, 2002) in China, which self-produces,[46] to $0.09 ($US, 2002) when purchased by UNICEF,[47] and $16.50 ($US, 2002) in the UK private market.[48] In the US public sector, eIPV vaccine costs $9.67 ($US, 2002) per dose and a DTaP-HepB-IPV combination vaccine costs $31.80 ($US, 2002) per dose; the price doubles in the private sector.[49] Additional costs for eIPV include needle, syringe, trained personnel, and disposal. SIAs represent large operations that involve high costs for planning, personnel, transport, and social mobilization. The cost of a response, including planning, cold chain, and training, could influence the size of the outbreak response, but we assume that, to some degree, the required size of the response will follow WHO recommendations. For countries that do not currently conduct enhanced surveillance, the establishment of an environmental surveillance system/program may potentially prove too costly in terms of human and financial resources.

Certain activities in developing countries currently benefit from support by external funders such as operational costs of NIDs and maintenance of an AFP surveillance system. Financing of these costs will play a large role in a national decision maker's policy choices.

Risk. The decision makers' perceptions of the risk of adverse events also influences their vaccine choice for routine immunization, SIAs, and outbreak response. Continued tOPV use implies a small (but measurable) risk of VAPP and the potential risk of emergence of cVDPVs into the population. Using mOPV may become increasingly desirable to eliminate the risk of reintroduction of particular poliovirus types.[10] eIPV use carries the risk of adverse events related to injection safety and greater impact of potential outbreaks because the level of individual immunity induced by eIPV when administered at the current WHO 6, 10, 14-week schedule appears lower than that induced by tOPV.[50] The option to stop all vaccinations inherently carries the risk of potentially large outbreak scenarios in the longer term, particularly with the impact of the outbreaks increasing as the size of the unvaccinated population increases. The level of risk aversion (where risk perception of an intentional release or catastrophic outcome influences decisions) will affect a country's containment policy decision to support the WHO's biosafety requirement guidelines. An increase in susceptible individuals over time may raise the relative importance of laboratory containment efforts.

Differing perceptions of the risk of an outbreak and likely consequences will affect a country's decision to rely on a global stockpile and/or develop a national stockpile. The change in the number of susceptible individuals and the changing perception of the risks of reintroduction may also influence how the size of the stockpile changes over time. For example, changes in the perception of current risks of bioterrorism recently led US policy makers to re-establish a stockpile of smallpox vaccine. As seen in the case of smallpox, the decision to reduce and eventually abandon the global stockpile followed from changes in perceptions of the relative benefits of a stockpile compared with the costs of its maintenance.

Other countries' policies. The policies of neighboring countries also play an important role. For example, a country bordering a tOPV-using or eIPV-manufacturing country might face an increased risk of reintroduction of vaccine-associated poliovirus strains compared with countries in regions where all tOPV vaccination stops and no eIPV production occurs. Recent polio endemicity may increase the country and neighboring countries' desire for high-quality surveillance to provide additional evidence of continued maintenance of the country as polio free.

The establishment of a global stockpile with access for all countries clearly influences a country's choice to build a national stockpile. Although it remains unclear how countries would participate in a global stockpile, this participation will likely differ between developed and developing countries. For example, wealthier countries may contribute a vast majority of the funds, ensuring stocks for their own country as well as other countries.

Interdependence of Policy Decisions

The previous section provided a glimpse of some of the factors that influence national choices within the comprehensive perspective of the complexity of the set of choices that policy makers will face after certification. The significant differences between developed and developing countries play an important role in limiting the set of options that any single country would consider. In addition, the interdependence of policy decisions leads to a significantly narrowed set of realistic decision options, since some options make little sense when combined. This section summarizes what we find as the realistic set of options when considering interdependent options jointly for the first 5 years after certification. We discuss the narrowed set of options first

for developed countries where we assume routine vaccination with eIPV continues, and then for developing countries where continued routine vaccination remains an open question.

Developed Countries

Clearly, a country's vaccine history and current policy provide important context for its future vaccine policy choices. In the context of developed countries (ie, those that switched from tOPV to eIPV to avoid the burden of VAPP), we do not foresee that these will either return to tOPV or stop vaccination during the first 5 years after certification. Further, we do not expect that developed countries will conduct SIAs (using tOPV), as their current policy also does not include SIAs. Policy makers in a developed country also face a smaller set of options associated with managing an outbreak. While outbreaks of different magnitudes will lead to a varying scale of responses, developed countries do not face the choice of restarting routine vaccination because they will already be routinely vaccinating with eIPV. Based on previous outbreaks, we assume that developed countries would use either tOPV, mOPV, or eIPV as vaccine options in outbreak response efforts.[10,26,51] We include eIPV as a policy option given that some countries may not wish to vaccinate with a live vaccine, or because regulatory hurdles may preclude the use of tOPV or mOPV. This implies that they must maintain access to supplies of tOPV, mOPV, or eIPV either from current supply production or from a stockpile. Thus, from a national perspective, each country will face the choice of either having a national stockpile or participating in any agreements related to the creation and maintenance of a global stockpile. Figure 10 reflects the more restricted set of decisions we expect policy makers in developed countries to face. Note that no reduction occurs in the decisions related to surveillance, laboratory containment, and management of chronic excretors and that the list of options for these decision categories is essentially independent of other choices.

Developing Countries

Currently, all developing countries rely on tOPV for routine vaccination. While the eradication initiative began with the full expectation that all countries would stop vaccination following certification, that assumption no longer exists. Developing countries will choose between continuing routine vaccination with tOPV, switching to eIPV, or stopping routine vaccination (in coordinated fashion or not) during the first 5 years following certification.

For countries that decide to switch to eIPV, the reduced set of options is similar to the scenarios described for developed countries (shown in Figure 10). Although the set of options remains the same, the critical influencing factors for a developing country policy, and thus the likelihood of choosing an option, may differ.

Figure 11 shows the more restricted set of options for those countries that choose to continue vaccination with tOPV, assuming access to a supply of tOPV exists. We assume that with continued routine use of tOPV, these countries would not see a need to participate in a global stockpile, although they might decide to build a national stockpile to help ensure vaccine supply. We eliminate outbreak response options that include restarting routine immunization. WHO recommendations, current SIA policies, coverage rates, and other factors will affect the choice about whether to conduct SIAs. However, we assume that the vaccine used for SIAs and for outbreak response will be the same as the vaccine used for routine vaccination. As in the case of

developed countries, all options for surveillance, laboratory containment, and management of chronic excretors remain possible.

Figure 12 shows the more restricted set of options for those countries that choose to stop all routine polio vaccination. If countries decide to stop routine immunization, we assume that they would not continue to conduct SIAs, so we eliminate this set of options from the tree. However, additional choices arise in the set of outbreak response options to allow for the possibility of restarting routine vaccination. The country's policies with respect to vaccination may affect their choice of surveillance policy, with the potential need for a higher intensity and quality of surveillance than that used by a country with high levels of routine coverage.[10] In developing countries that stopped all immunizations, the policy makers must decide among all options for building a stockpile, surveillance, containment, and management of chronic excretors.

Discussion

The previous section focused on identifying the realistic set of decisions for policy makers in developed and developing countries over the limited period of 5 years after certification. The purpose is to help policy makers develop much needed communication tools as they evaluate and discuss their options within their countries and with the leaders of other countries. Although management of national and global polio eradication activities remains relatively complex, it is important to provide characterizations now of critical issues and the implications of various choices.

Future studies will need to consider the implications of the framework presented here and whether additional time periods following certification should be examined. After certification, manufacturers may stop producing tOPV, anticipating that the demand for the vaccine will greatly diminish. However, this may lead to initiatives to increase the production of eIPV. Finally, the licensing of mOPV, bOPV, and IPV/Sabin and/or the development of a new vaccine may present a more desirable future routine immunization or stockpiling options that avoid the need for containment of large stocks of wild poliovirus in the production of eIPV. The supply of vaccines and consequently the pricing of vaccines will also change over time. Given that a policy maker has a limited budget, these changes in prices and hence costs of different decision options (eg, vaccination, maintenance of stockpile) may change the likelihood of choosing certain options. Further out from certification, OPV use may become suboptimal because of high health-related and financial costs associated with greater numbers of VAPP cases and continued cVDPV risks.

In any country, the time elapsed since eradication influences the level of alarm caused by an outbreak and, therefore, the probability of a public demand for vaccination outside the indicated response boundaries. For countries that stop vaccination, the increasing cohort of susceptible individuals may influence the size of the response. Moreover, the priority of polio surveillance may decline as the risk of cVDPVs decreases over time. However, the potential consequences of an outbreak will increase over time with the growing susceptibility of the population, indicating an increasing importance of maintaining sensitive surveillance and timely detection of potential outbreaks (eg, perhaps shifting the relative attractiveness of environmental or serologic surveillance to detect polioviruses before they caused paralysis).

For countries using tOPV, the switch to eIPV becomes more likely after interruption of transmission or certification of global eradication. However, some countries in certified polio-free regions may begin to switch to eIPV as tOPV becomes the primary source of polio cases within the population. Although stopping routine immunization altogether in countries before certification seems unlikely, countries may in some cases decide to do so if they perceive that the risk and costs of VAPP or unsafe injections exceeds that from wild poliovirus.

The optimization of future options depends on current investments in research and analysis of current program data. For example, if the risks associated with cVDPVs appear significant after certification, then research conducted now to characterize the circumstances that increase or decrease the risk of cVDPV outbreaks can help identify appropriate efforts to minimize these conditions in the future. Research to identify more cost-effective ways to conduct environmental or serologic surveillance might make these options more attractive, particularly with respect to managing the potential risks of re-emergence due to a break in laboratory containment or bioterrorism. Anticipating that outbreak responders will face dilemmas about potentially reintroducing VDPVs into the population (ie, through responding with live vaccine), research done now that might improve the ability to understand the trade-offs could also be helpful.

The fact that neighboring countries' policies will influence a country-based policy maker's decision emphasizes the need for open discussion and coordination of policy making. The meeting in Annecy, France in April 2002 was the first forum for an open discussion that included individual country perspectives and the factors that influence their decisions (eg, costs, risk perception).[52] Without explicit coordination and commitment of containment, a country neighboring an eIPV-manufacturing country could perceive itself to be at increased risk for importations due to break in containment and choose to continue to vaccinate. The opportunity cost of those resources used to maintain a vaccination policy could exceed the cost of maintaining laboratory containment. Given that actions by a neighboring country affect a country's risk of reintroduction, coordinating country implementation of policy changes emerges as a critical issue for consideration and discussion. Finally, efforts to develop models that aid policy makers as they weigh the different alternatives and evaluate the risks, costs, and benefits of their choices will provide a means for stimulating dialogue and discussion of key issues and promote more informed decisions.

Conclusions

Although policy makers will face a complex set of choices in managing polio risks after certification, considering the logical relationships and feasibility leads to a more restricted set of practical options for the specific time period of 5 years following certification. We believe that our paper provides the first comprehensive synthesis of all potential choices at the country level and the factors that influence these choices. Policy makers must weigh these sets of policy options jointly. Moreover, discussions between countries regarding the implications of their policy choices for each other and globally must occur for policy makers at all levels to make the best policy decisions. Additional efforts to provide information to decision makers about the expected relative risks, costs, and benefits of these options and the trade-offs associated with making these choices are needed to inform the global policy discussions about polio risk management after certification.

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Figure 1. Routine vaccination decision options.

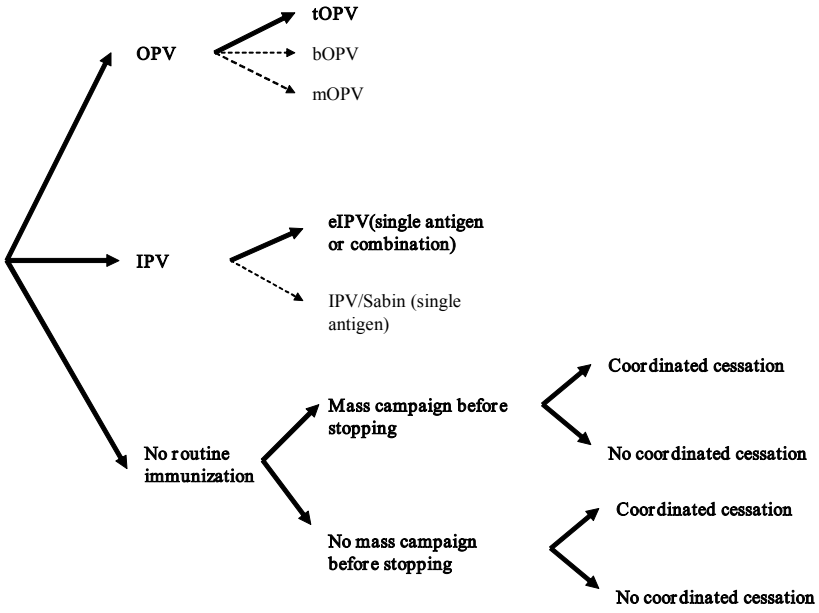


Figure 2. Supplemental immunization activities decision options.

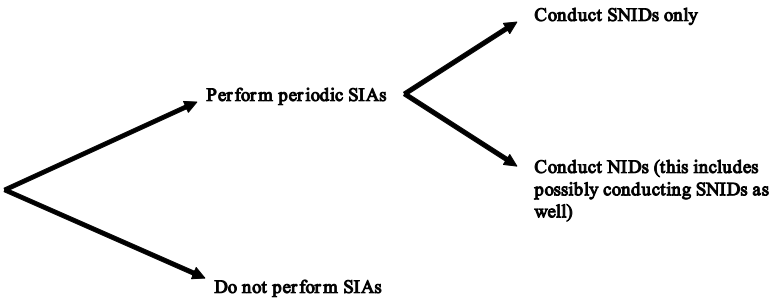


Figure 3. Size of outbreak immunization response as a function of outbreak magnitude.

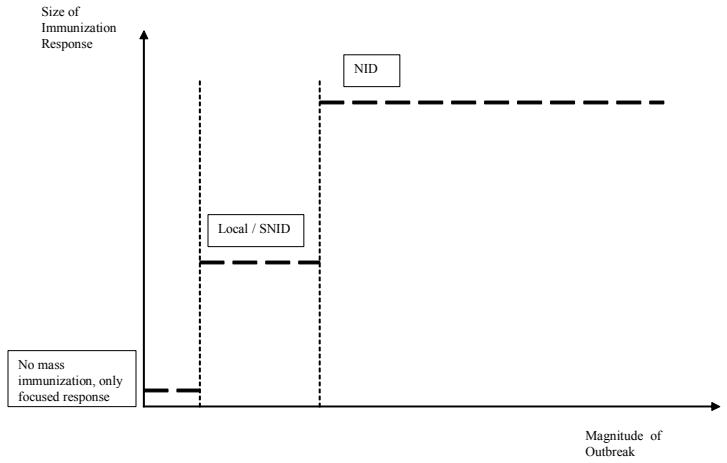


Figure 4. Outbreak response strategies decision options.

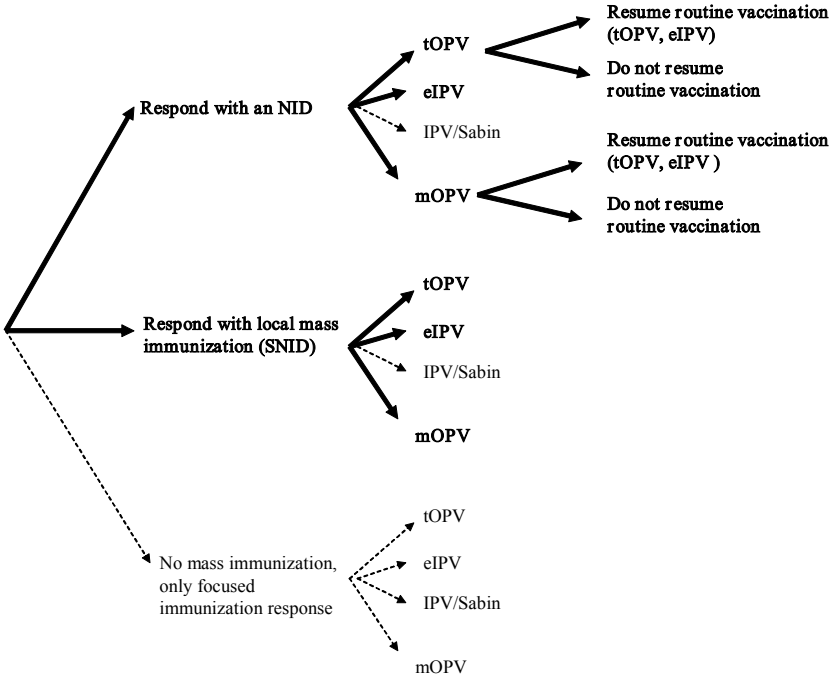
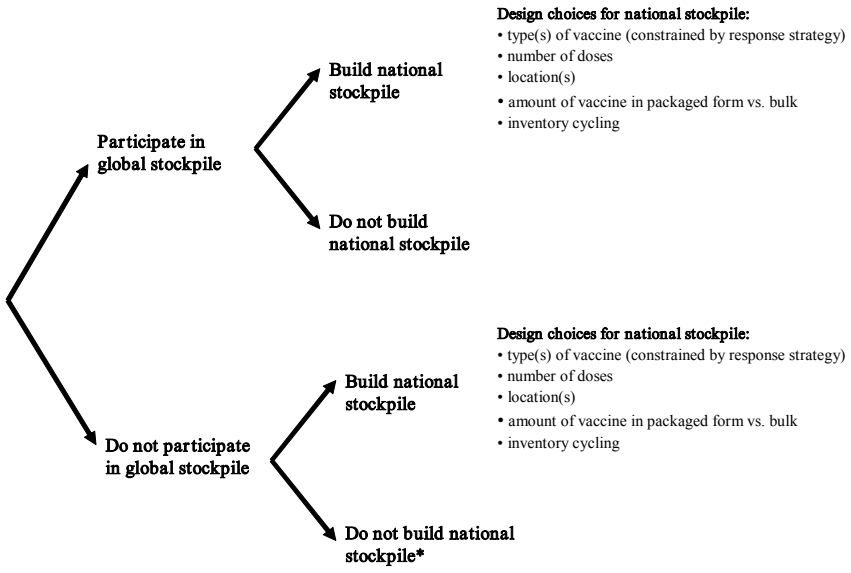


Figure 5. Stockpile decision options.



*Developing countries may assume access to a WHO stockpile

Figure 6. Surveillance decision options.

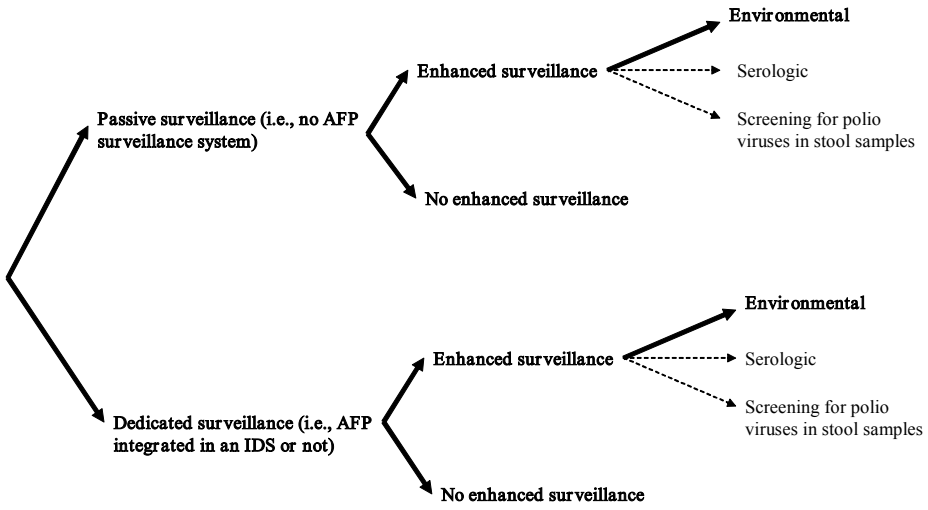


Figure 7. Containment decision options.

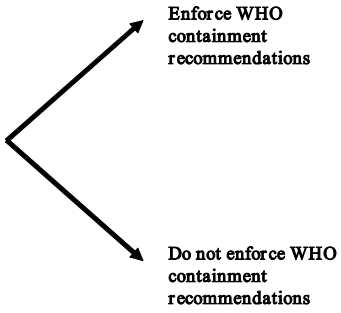


Figure 8. Management of chronic excretors decision options.

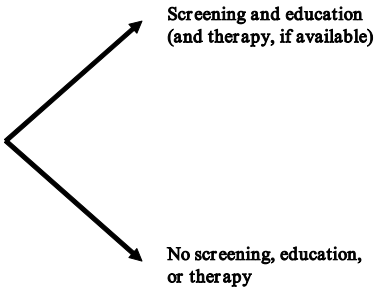


Figure 9. Country decision options -- first 5 years following certification

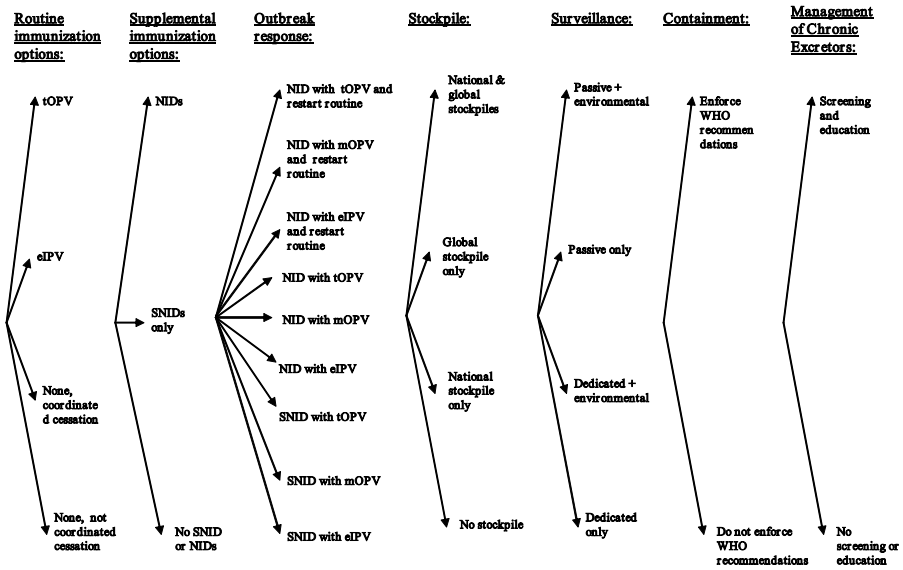


Figure 10. More restricted set of decision options for developed countries choosing routine IPV vaccination.

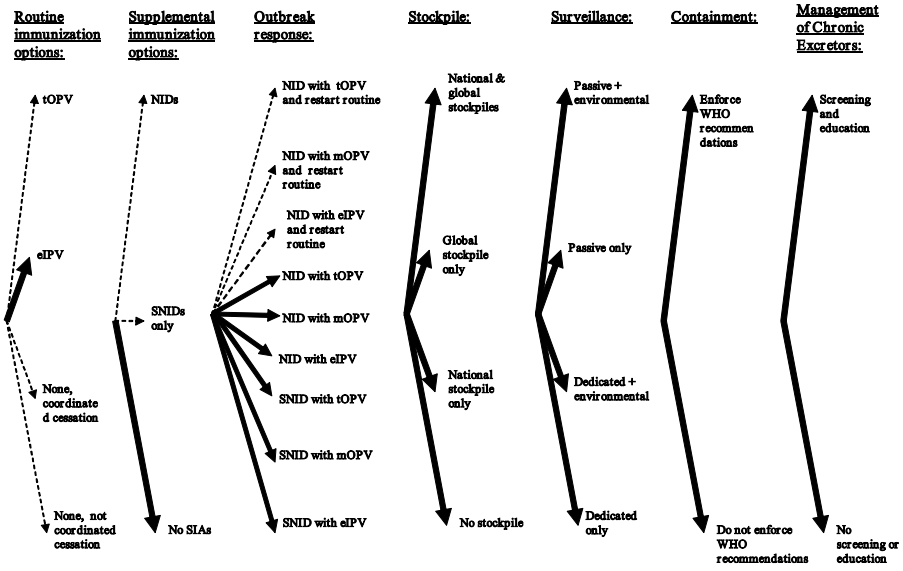


Figure 11. More restricted set of decision options for developing countries choosing routine OPV vaccination.

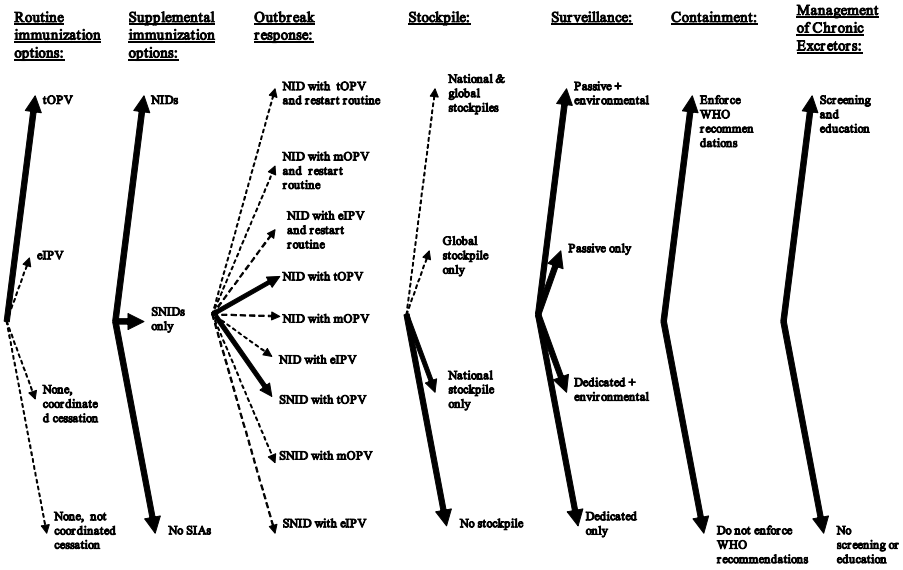
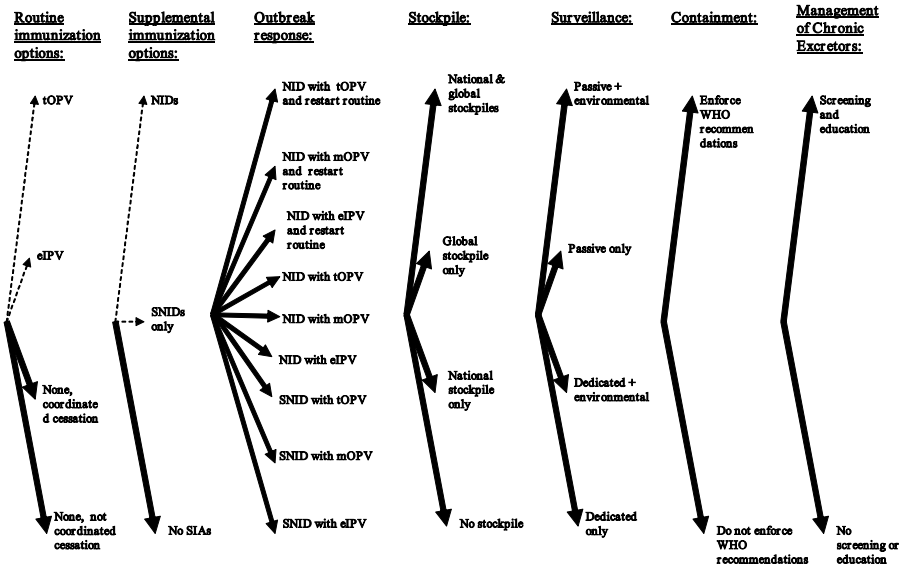


Figure 12. More restricted set of decision options for developing countries choosing to stop routine vaccination.



CHAPTER 3

The Costs of Future Polio Risk Management Policies

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ABSTRACT

Decision makers need information about the anticipated future costs of maintaining polio eradication as a function of the policy options under consideration. Given the large portfolio of options, we reviewed and synthesized the existing cost data relevant to current policies to provide context for future policies. We model the expected future costs of different strategies for continued vaccination, surveillance, and other costs that require significant potential resource commitments. We estimate that a global transition from oral polio vaccine (OPV) to inactivated polio vaccine (IPV) would increase the costs of managing polio globally, and that even combined with other antigens, current cost projections make global IPV an expensive option. However, the costs of supplemental immunization activities required to maintain adequate OPV coverage represent an important consideration in future vaccination policy. Given the lack of existing specific policies for a stockpile and for responding to potential outbreaks after eradication, we emphasize the need for additional analyses that further develop specific plans and assessments of their costs. We find that the costs of surveillance, while small compared to vaccine costs, represent important considerations in overall costs. Finally, we estimate the costs of different potential policy portfolios for low-, middle-, and high-income countries to demonstrate the variability in these costs.

Keywords: Polio Eradication, Decision Analysis, Economic Evaluation, Cost Analysis

INTRODUCTION

With global polio eradication approaching,[1] discussions regarding polio risk management policies after eradication continue to evolve.[2-10] While current WHO policy focuses on cessation of OPV use,[11] economic evaluation of the available policies remains a critical area of research as part of the global Polio Eradication Initiative's (PEI) Strategic Plan for 2004-2008[10] to provide quantitative context regarding the trade-offs between economic costs and health outcomes associated with each option. Earlier efforts focused on estimating the cost and benefits of regional eradication in Latin America,[12] the entire global eradication initiative,[13-15] the economic costs for three scenarios of immunization policies after eradication,[16] and on the costs and benefits of two possible future immunization strategies.[17] None of these studies comprehensively addressed the costs of all policy categories: routine and supplemental immunization, surveillance, stockpiles, outbreak response, maintenance of containment of poliovirus stocks in laboratories and IPV-manufacturing sites, and management of chronic poliovirus excretors.[8]

This paper provides estimates of the future costs associated with a range of different options in each policy category. We present the methods and data sources for this cost analysis and then focus on modeling the future costs associated with each category. We review available data, propose simple models to estimate the costs as a function of time and policy option, and present best estimates of inputs for the calculation of the future costs.

METHODS

We reviewed the existing literature on polio costs and we collected and synthesized data from the PEI by surveying program managers. We used cost projections from available sources for vaccines, and analyzed trends over time. Recognizing the uncertainty inherent in estimating future costs, we provided ranges along with best estimates, and in some cases we discuss potential scenarios. We focus on policy at the global and national level, and stratify the world into four different income levels (i.e., low, lower-middle, upper-middle and high) according to the 2002 classification from the World Bank[18] in an effort to capture some of the real and important variability that might lead to different costs and policy choice preferences for different countries.[8] Consistent with current guidance for economic evaluation studies,[19] we take a societal perspective in characterizing costs, although we excluded the indirect costs of vaccination for patients and parents/caregivers (i.e., travel to clinic, opportunity costs of time spent for vaccination).

Given the risks associated with continued OPV use,[20, 21] coordinated transition to the post-OPV era should occur as soon as possible after assurance of the eradication of wild polioviruses.[22] We refer to the year of implementation of policies for the post-eradication era as T_0 and use an analytical time horizon from T_0 until 20 years later. We discount costs at a rate of 3% (range 0-5%),[19] and we take the perspective of a societal decision maker in year T_0. We report all costs in 2002 US dollars (notation US$2002). Before converting amounts to US$2002 using the Consumer Price Index,[23] we used rates of exchange from the year of any non-US currency data to express these in US dollars for that year. We rely on current population estimates from UNICEF[24] and projections from the United Nations Population Division[25] to derive linear interpolation functions for the total population and breakdown (younger than 1, younger than 5, and younger than 15 years of age) of the four income levels. For purposes of this analysis, we rely on population estimates for the years 2009 to 2028, although we emphasize that the actual value of T_0 remains uncertain.

COSTING OF POLICY OPTIONS

Routine immunization

We considered three routine immunization options. These include routine immunization with enhanced inactivated polio vaccine (IPV) (i.e., the *status quo* in most high income countries), routine immunization with trivalent oral polio vaccine (OPV) (i.e., the current vaccine of choice of the PEI and *status quo* in low and middle-income countries), or no routine immunization.[8] Cessation of immunization implies no on-going costs for polio immunization, which represents a significant savings over the *status quo*, but carries a greater risk of incurring important costs in the event of an outbreak. We assume that countries choosing to use OPV maintain the current vaccination schedule (i.e., they deliver OPV independent of vaccinations for other diseases), but for countries that continue or switch to IPV, we assume that they may deliver IPV as a single antigen or in a combination vaccine. Given the important difference between the cost of administering IPV as a single antigen and the incremental costs of administering it as part of a combination vaccine, we estimate the costs of both options separately. While middle and low-income countries may opt for any of the three policies, we assume that all high-income countries will continue routine IPV immunization for the foreseeable future.[8]

Available routine immunization cost data

Table 1 lists vaccine prices from selected publications in the peer-reviewed literature or from other published or unpublished sources.[13, 16, 17, 26-32] Prices vary between the public and private sectors, with much higher private sector prices where they exist (e.g., in the United States). For OPV, we focus on the public sector prices in developing countries, since these appear most appropriate for most of the world. Recent price quotes for OPV range from 0.012 (for domestically produced OPV in China) to 0.11 US$2002 per dose (for imported OPV), [27] with most developing countries purchasing their OPV from UNICEF at a price of 0.10 US$2002 per dose.[29] Recent price quotes for IPV as a single antigen range from 6.15[31] to 20.69[30] US$2002 per dose, all reflecting prices in high-income countries. Projections assume a range of costs for IPV with the lowest costs in developing countries.[16, 17, 28, 32] Routine immunization policies of all countries may significantly impact the vaccine price, which suggests that simple extrapolations of the current prices into the post-eradication era may lead to errors given potentially large changes in production volumes and the numbers and locations of suppliers. Prices in the US, Australia, and Belgium in Table 1 suggest somewhat similar prices for IPV in a single antigen form compared to its incremental cost in a combination vaccine.

Table 2 shows that non-vaccine costs also vary by the country's income level, with estimates in high-income countries substantially higher than in other countries.[13, 14, 16, 17, 26, 28, 33] However, the highest estimates (from the US) include indirect costs to the patient such as travel and opportunity costs (≈45% of the non-vaccine costs),[26] while the other sources do not include these.

Wastage for different vaccines around the world equals 50% according to WHO, although recent guidelines aim to reduce this to 15% over the next 3 years.[34] Wastage depends on many factors, including the use of vaccine vial monitors, a country's multi-dose vial policy, and the quality of the cold chain, and it occurs at all stages in the delivery process (transport, distribution, storage, administration).[34] It appears that few published studies retrospectively assessed wastage during routine OPV immunization, with one study in the United States

estimating OPV wastage as low as 8.4%.[35] However, cost studies commonly used higher estimates between 16.5% and 40% for base case analyses.[13, 26, 28, 36] The US reported only 1.5% wastage for IPV in 1999 (offered in 10-dose vials),[35] a prospective study estimated 7% wastage for IPV in Australia,[28] while a prospective study used 30% wastage for another injectible vaccine (measles) in Latin America.[37]

Future routine immunization costs

We use the following formula to estimate the total routine immunization costs $Routine^{i}_{j}(t)$ as a function of time (while discretized in years, we denote time-dependence of a variable x by $x(t)$) in income level i (i = *low*, *lower-middle*, *upper-middle*, or *high*) with routine immunization policy j (j = *OPV*, *IPV single antigen (IPV single), IPV in combination vaccine (IPV combo),* or *none*):

$$Routine^{i}_{j}(t) = b^{i}(t) \times POL3^{i} \times \left(nd \times vp^{i}_{j}(t) / (1 - w^{i}_{j}) + nvcpic^{i}_{j} \right)$$

where $b^{i}(t)$ = the birth cohort size in income level i,
$POL3^{i}$ = the average routine immunization coverage with three or more doses of polio vaccine in income level i,
nd = the average number of doses that a fully polio-immunized child (PIC) receives,
$vp^{i}_{j}(t)$ = the price of the vaccine of policy j in income level i,
w^{i}_{j} = the wastage associated with the vaccine of policy j in income level i, and
$nvcpic^{i}_{j}$ = the non-vaccine cost per PIC associated with the vaccine of policy j in income level i.

The top section of Table 3 lists values of the constants used for the estimation of the future routine immunization costs by income level. We assume that the routine immunization coverage, wastage, number of doses in the schedule and non-vaccine cost per fully polio-immunized child (PIC) all remain constant over time. Given the current small differences in the income level averages of the coverage for OPV and injectible childhood vaccines (Diphteria-Tetanus-Pertussis, DTP),[18, 24] we assume that equal coverage with OPV and IPV. Furthermore, we assume that currently OPV-using countries will collectively decide to continue or discontinue OPV routine immunization (i.e., a country will not choose to stop routine OPV use when its neighbors continue), and they will coordinate to minimize the risk of importations.[21] Given that these countries currently represent approximately 85% of the global birth cohort,[18, 24] if they decide to continue OPV use then the volume of OPV consumption will probably remain large enough to maintain the current low price in low and middle income countries, regardless of whether they continue to conduct supplemental immunization activities (SIAs). We use the UNICEF price of approximately 0.1 US$2002[29] as the best estimate for imported OPV in low and lower-middle income countries and the Chinese OPV price of 0.012 US$2002[27] as the best estimate for domestically produced OPV. With approximately 10% of vaccine in those income levels purchased from domestic manufacturers,[27, 38] we estimate an average price per OPV dose of $vp^{low}_{OPV} = vp^{lower\text{-}middle}_{OPV} =$ 0.0912 US$2002 (i.e., $0.9 \times 0.1 + 0.1 \times 0.012$). Assuming that upper-middle income countries cannot offer domestically produced OPV for less than the UNICEF price, we estimate the average price of OPV at $vp^{upper\text{-}middle}_{OPV} = 0.1$ US$2002 in those countries.

If many countries decide to switch to IPV, then the increased demand for IPV could significantly increase production and lead to an associated decline in price due to economies of scale in production. For example, the prices of both *Haemophilus influenza* type b (Hib) and *Hepatitis* B (HepB) vaccines dropped substantially for the Pan-American Health Organization

(PAHO) as PAHO's revolving fund started buying the vaccine for all countries in the region (i.e., Hib vaccine dropped from approximately 4.40-9.40 US$2002 in 1998 to approximately 2.50 US$2002 in 2000[39] and HepB from approximately 10 US$2002 before 1997 to approximately 1 US$2002 in 1999[40]). Although increased global production of IPV may drive costs down, the exact shape of the price curve will depend on many factors and remains difficult to predict. Consequently, we consider various prices scenarios but proceed with unpublished price estimates of $vp^{low}_{IPV} = 1$, $vp^{lower\text{-}middle}_{IPV} = 1.50$, and $vp^{upper\text{-}middle}_{IPV} = 2.50$ US$2002 US$2002 for all years for the base case.[41] We estimate that $vp^{high}_{IPV} = 10$ based on the quotes in Table 1. For the alternative scenarios, we assume that the price may decrease to half of the base case estimate (scenario 1), increase to 1.5 times the base case estimate (scenario 2), or decrease from 1.5 times the base case estimate to the base case estimate (scenario 3) over 3 years (all in US$2002, see Figure 1). Based on the quotes in Table 1, we assume that the price of IPV in a single antigen equals the incremental cost of the IPV component in a combination vaccine, although this assumption also comes with uncertainty, in particular in developing countries where questions regarding feasibility of IPV in combination vaccines remain.

We rely on WHO data[36, 42] to estimate the non-vaccine costs per PIC for routine immunization in low and lower-middle income countries. The database[42] lists detailed actual expenditures (i.e., recurrent costs including personnel, transportation, maintenance and overhead, training, social mobilization, monitoring and surveillance, community participation, and capital costs including cold chain equipment, building, vehicles, equipment, research, steam sterilizers and incinerators) from all funding sources on routine immunization programs in 13 low-income countries during 2002. Given that administration of an oral vaccine requires about one-fourth of the time and skill needed for the administration of an injectible vaccine,[33] we attribute $N^{OPV}/(N^{OPV} + N^{other\ vaccines} \times 4)$ of the personnel cost to OPV immunization, where N stands for the number of doses in the routine immunization schedule. We did not include tetanus vaccines in $N^{other\ vaccines}$ given that the childhood immunization schedule generally does not include them. Using this approach, we found that the proportion of personnel costs attributable to OPV ranged from 0.07 to 0.17 (unweighted average 0.12) for the different schedules of the 13 countries studied. To estimate the personnel costs of immunization with IPV as a single antigen vaccine, we first subtract the OPV-related personnel costs from the total personnel cost and then we divide the result by the number of non-OPV doses in the schedule to obtain an estimate of the personnel cost per injectible vaccine. We then multiply the estimated personnel cost per injectible vaccine by the number of IPV doses in the schedule (assumed equal to the current number of OPV doses) to get to the personnel cost per fully IPV-immunized child.

For the other costs (i.e., non-personnel, non-vaccine costs also excludes reported injection supply costs), we start with the total routine immunization program costs and multiply by the fraction of the polio vaccine doses to total vaccine doses to obtain the costs attributable to OPV. We do the same for IPV, and then we add 0.0875 US$2002 per dose for injection supplies for IPV based on the WHO study.[36] To estimate the non-vaccine costs for IPV in a combination vaccine, we divide non-vaccine costs attributed to IPV by the number of antigens in the combination vaccine (ranging from 4 to 6 depending on the current combination vaccines of the 13 low-income countries).[42, 43]

To obtain the average non-vaccine costs per PIC ($nvcpic^{j}_{j}$) in an income level, we divided the aggregate polio-attributed routine immunization costs of the countries by the number of children receiving three or more routine polio vaccine doses in each income level.[43, 44] Given that additional data between 1997 and 2002[36] yielded a lower estimate for 2 lower-middle

income countries than for 16 low-income countries (presumably as a result of the small sample size), we used the average non-vaccine costs during 2002 of the low-income countries in the WHO database[42] as the estimate for both income levels ($nvcpic^{low}_{OPV} = nvcpic^{lower\text{-}micldle}_{OPV}$ = 2.08 US$2002, and $nvcpic^{low}_{IPV\ single} = nvcpic^{lower\text{-}micldle}_{IPV\ single}$ = 3.25 US$2002 for IPV in single antigen, and $nvcpic^{low}_{IPV\ combo} = nvcpic^{lower\text{-}micldle}_{IPV\ combo}$ = 0.71 US$2002 for IPV in combination) as shown in Table 3. Given the absence of recent data for routine immunization costs in upper-middle income countries, we estimate the costs in upper-middle income countries using Purchasing Power Parity (PPP) factors available from the World Bank (year 2002)[45] to convert the low and lower-middle income cost to the upper-middle income equivalent. This results in our estimates of $nvcpic^{upper\text{-}micldle}_{OPV} \approx$ 5.46 US$2002, and $nvcpic^{uppeer\text{-}micldle}_{IPV\ single} \approx$ 8.53 US$2002 for IPV in single antigen, and $nvcpic^{upper\text{-}micldle}_{IPV\ combo} \approx$ 1.86 US$2002 for IPV in combination. For IPV in high-income countries, we adopt a prior estimate of the administration costs of 12.05 per dose US$2002.[26] For consistency with the estimates in the other income levels we exclude the estimated indirect clinic visit costs to the child or caregiver (i.e., travel and time loss) of that study.[26] We multiply this by three (i.e., the number of IPV after T_0, see below) to obtain an estimated cost of $nvcpic^{high}_{IPV\ single} \approx$ 48 US$2002, while for the combination vaccine DTaP- Hep B-IPV we divide $nvcpic^{high}_{IPV\ single}$ by five for an estimated $nvcpic^{high}_{IPV\ combo}$ ≈10 US$2002.

We assume that after T_0 each PIC receives on average three doses of polio vaccine (nd = 3), consistent with current vaccination schedules in countries that sustained polio-free status for several years.[43, 44] For the coverage, we use income-level dependent averages based on WHO projections for DTP as a proxy for IPV or OPV,[46] or $POL3^{low}$ = 68%, $POL3^{lower\text{-}middle}$ = 90%, $POL3^{upper\text{-}middle}$ = 92%, $POL3^{high}$ = 94%. We assume that OPV wastage will tend towards the targeted global average of 15%,[34] but remains higher in developing countries than in developed countries, or $w^{low}_{OPV} = w^{lower\text{-}middle}_{OPV}$ = 20% and $w^{upper\text{-}middle}_{OPV}$ = 15%. For IPV, we assume the use of single-dose vials implies lower wastages of $w^{low}_{IPV} = w^{lower\text{-}middle}_{IPV}$ = 10% and $w^{upper\text{-}middle}_{IPV} = w^{high}_{IPV}$ = 5%, although IPV may come in multi-dose vials as well.[30]

Supplemental immunization activities (SIAs)

The term SIAs commonly represents a generic term for national immunization days (NIDs), subNIDs (SNIDs), and mop-up campaigns. The latter occur in the context of the last phases of wild polio eradication in hard-to-reach areas or for outbreak response. In this paper, we reserve the term mop-up for outbreak response, while we use the term SIAs to refer to (S)NIDs aimed at maintaining population immunity. In 2002, the TCG recommended that countries with less than 90% routine immunization coverage conduct NIDs at least once every three years.[47] Despite the small likelihood that countries decide to conduct NIDs after eradication, we assume that countries continuing routine OPV immunization may choose to supplement their routine immunization programs with NIDs. For purposes of this analysis, we define the SIA policy option as a policy to conduct one NID (i.e., two rounds administering 1 dose each to all children younger than 5 years of age) per three years.

Available supplemental immunization cost data

Generally countries pay the same price per OPV dose for routine immunization and SIAs. Table 4 lists estimates of the non-vaccine costs per dose during SIAs from various studies.[13, 14, 16, 17, 33, 48-51] While the WHO tracks resource requirements and expenditures from external funding sources,[52] no institution systematically tracks the (sub)national-level contributions to

SIAs for all countries. Aylward et al. (2003) estimated that if continued through 2005, polio NIDs conducted during 1988-2005 as part of the PEI would cost 2.35 billion US$2002 (assuming data in US$2002) in volunteer time alone (valued at hourly labor market rates), compared to $3 billion total external donor contributions (for all polio eradication activities) to polio-endemic countries during that same period.[15] In addition, country governments and the private sector contribute to social mobilization, transportation, training, and other costs.[15]

A study during OPV NIDs in Egypt in 1993 found roughly equal costs per dose for vaccinating a child with a fixed-post versus a house-to-house delivery strategy.[53] These campaigns showed wastage of OPV of approximately 25% with both delivery strategies in urban areas, but much higher wastage with fixed-post delivery in rural areas (41.5% for fixed-post delivery vs. 23.5% with house-to-house delivery in rural settings). Studies of immunization campaigns in Cambodia and Turkey found no substantial increase in cost per dose for a mixed delivery strategy compared to a fixed-post-only strategy,[48] but they found a substantial increase for response immunization or mop-up campaigns.[48] This study reported 20% wastage in Cambodia, but no wastage estimate for Turkey.[48] A recent study on OPV wastage during NIDs in India estimated a wastage of only 14.5% at vaccination booths.[54] Overall, wastage during SIAs appears somewhat lower than during routine immunization, perhaps because vaccinators administer the doses from a vial in a shorter period of time.

Future supplemental immunization costs

We use the following formula to calculate the total supplemental immunization costs $SIA^i(t)$ in income level i (i = *low*, *lower-middle*, or *upper-middle*) as a function of time:

$$SIA^i(t) = pop5^i(t) \times nr \times cov^i_{NID}\left(vp^i_{OPV}/(1 - w^i_{NID}) + nvcdose^i\right)$$

where $pop5^i(t)$ = the number of children younger than 5 years of age in income level i,
nr = the average number of NID rounds per year (i.e., the number of doses administered annually to children younger than five years of age),
cov^i_{NID} = the proportion of children younger than 5 years of age reached by each NID round in income level i,
vp^i_{OPV} = the price of OPV in income level i,
w^i_{NID} = the wastage associated with OPV NIDs in income level i, and
$nvcdose^i$ = the non-vaccine cost per OPV dose during NIDs in income level i.

Table 3 provides the inputs for this formula. As mentioned, we assume that countries will conduct one NID per 3 years, or $nr = 2/3$, and that the price of OPV during SIAs equals the price of OPV for routine immunization. For the wastage, we assume slightly lower estimates than during routine immunization, or $w^{low}_{NID} = w^{lower\text{-}middle}_{NID} = 15\%$ and $w^{upper\text{-}middle}_{NID} = 10\%$. We assume coverage levels of $cov^{low}_{NID} = 80\%$, $cov^{lower\text{-}middle}_{NID} = 85\%$, and $cov^{upper\text{-}middle}_{NID} = 90\%$ based on current experience[55-57] and the expectation that coverage may decrease after eradication.

We base our estimates for $nvcdose^i$ on the available cost estimates of NIDs during the PEI. Table 4 includes four studies of specific NIDs in Brazil,[33] China,[17] Cambodia,[48] and Turkey.[48] While those studies provide the most accurate and complete information, they may not fully represent the entire set of countries of their income level. Our analyses of recent WHO data (last two entries in Table 4) and three other studies[13, 14, 16] in Table 4 estimate the average cost per dose based on data for multiple countries (stratified by income or development level) from the Expanded Program on Immunization, the WHO, or its regional offices.

However, the complicated financing structure of NIDs, shared costs with surveillance and routine immunization, and incomplete information about the numbers of NID rounds or children covered during SNIDs for some countries make the estimates less accurate than the country-specific studies. The study by Liu et al. (2002)[17] used a stratification by routine immunization coverage levels and took the approach of costing out the different components of vaccination instead of looking at actual budgets or expenditures. Their study yielded much lower estimates of the cost per dose[17] because they focused on the difference between OPV and IPV and consequently they did not include capital costs or overhead costs. To estimate the average cost per administered dose, we took the simple average of the country-specific NID cost studies and the multiple-country analyses, but we excluded the study by Liu et al. (2002)[17] because of the different stratification they used and other limitations. Table 5 shows the point estimates for $nvcdose^{i}$ that we included and the averages for the three income levels of interest. Finally, we multiply the average by a correction factor to account for real costs that none of the sources included, such as volunteer time and hidden nationally-funded costs. We estimate this factor at 2 (range 1-3) for all three income levels, based in part on the study by Aylward et al. (2003)[15] and our own judgment. This factor results in estimates for the total non-vaccine costs per dose administered during SIAs of $nvcdose^{low}$=0.46, $nvcdose^{lower\text{-}middle}$=1.28 and $nvcdose^{upper\text{-}middle}$=3.74 US$2002.

Surveillance

We assume that after polio eradication countries face the options to conduct passive surveillance (i.e., rely on reporting of (suspected) polio cases) or to continue acute flaccid paralysis (AFP) surveillance,[58] with or without environmental surveillance.[8, 59] Except for a limited number of high-income countries in Europe and North America, all countries currently conduct AFP surveillance, while environmental surveillance happens in a limited number of sites. We did not include the cost of passive surveillance since it relies on an existing national reporting infrastructure and does not require routine analysis of samples. In contrast, AFP and environmental surveillance both involve routinely analyzing samples (from children with AFP or from sewage) and carry substantial costs. We recognize that environmental surveillance will ultimately represent a country-level decision once guidelines or recommendations for implementation exist.[8] However, given the lack of information to characterize the implementation and costs of future potential environmental surveillance options, we model the costs of environmental surveillance here as a placeholder by including only a global annual cost with significant uncertainty. We model AFP surveillance costs as country-level costs (i.e., stratified by income level) given their important international variability and allowing for the possibility that countries/income level groups opt to discontinue AFP surveillance.

Available surveillance cost data

AFP surveillance involves costs of personnel, data collection, case investigation, sample collection and transportation, social mobilization, training, supplies and equipment, and administrative work. In addition, the current AFP surveillance system includes a global polio laboratory network consisting of 145 global, regional, national, and sub-national laboratories that analyze samples from AFP patients.[10] To our knowledge, no published studies specifically focused on AFP surveillance costs. However, the WHO financial resource requirement estimates include nearly 40 million US$2002 annually for AFP surveillance and the laboratory network for 2004-2005 and approximately 25 million US$2002 annually for 2006-2008.[60] They estimate

roughly an additional 50 million $US2002 per year in technical assistance for polio eradication during 2004-2005, decreasing to little over 35 million $US2002 per year for 2006-2008, some of which may support AFP surveillance. Sangrujee et al. (2003) assumed annual costs of 70 million US$2002 globally for the laboratory network and surveillance.[16] Both sources include only externally financed costs.

A closer look at the WHO resource requirements combined with population data[60, 61] reveals a much higher externally financed cost per child younger than 15 years of age (i.e., the target group of AFP surveillance) in different regions of generally lower income per capita than in relatively higher income regions (i.e., 0.11 US$2002 per child in the AFRO, EMRO and SEARO regions, but only 0.007 $US2002 in the AMRO, EURO and WPRO regions). While not all high-income countries conduct AFP surveillance and more intense surveillance in recently polio-endemic countries explains part of the difference, we suspect this observation primarily results from the reality that lower income countries receive much more external funds for surveillance and that national-level contributions represent an important component of surveillance costs in countries of higher income.

Given the absence of data but acknowledging the potential importance of future environmental surveillance, we estimate a placeholder of its cost assuming a future global program with the same ability to detect polioviruses in every part of the world. We do not estimate the costs of a potential environmental surveillance targeted in high-risk areas given the lack of guidelines about the extent of such a program, although this may later emerge as the most cost-effective use of environmental surveillance.

Future surveillance costs

We assume no country-level costs for surveillance for a policy involving passive or environmental surveillance. If the policy involves AFP surveillance, we model the costs $AFP^i(t)$ in a country of income level i (i = *low*, *lower-middle*, *upper-middle*, or *high*) as follows:

$$AFP^i(t) = pop15^i(t) \times afpchild^i$$

where $pop15^i(t)$ = the population younger than 15 years of age in income level i, and
$afpchild^i$ = the annual cost of AFP surveillance per child younger than 15 years of age in income level i.

In addition, we model the fixed costs for running the global polio laboratory network. For convenience, we assume that these global costs remain independent of the number of countries that decide to continue AFP surveillance, although in reality the amount of countries conducting AFP surveillance clearly impacts the number of samples that the laboratory network analyzes. In the event of a global decision to establish systematic environmental surveillance, we assume that the laboratory network will carry out this type of surveillance. Thus, the fixed costs of the laboratory network increase by a constant factor, such that we can express the total annual global surveillance costs GSC_j (with j = *environmental surveillance*, or *no environmental surveillance*) as follows:

$$GSC_j = lab \times (1 + 1_j \times envfactor)$$

where lab = the fixed annual, global costs of running the laboratory network without a policy of systematic environmental surveillance,
$1_j = 0$ when j = *no environmental surveillance*, and $1_j = 1$ when j = *environmental surveillance*, and
$envfactor$ = the increase in the laboratory network costs with a policy of systematic environmental surveillance.

These formulae imply that we assume that surveillance costs only change over time in proportion to the change in the population younger than 15 years. In reality, the intensity of AFP surveillance may decrease after the achievement of wild poliovirus eradication, leading to a lower cost (but also to lower effectiveness). Furthermore, national surveillance systems may merge into integrated diseases surveillance (IDS)[62] systems resulting in a decrease in marginal costs for AFP surveillance. However, for purposes of this analysis we do not include these possible changes in the quality and implementation of future AFP surveillance.

Table 3 shows the inputs to the country-level AFP surveillance cost formula. We base our estimates of the costs of AFP surveillance per child on WHO financial databases containing information on the external resource requirements for the year 2002 in 61 different low-income countries (listing AFP surveillance and laboratory costs separately).[63] When applicable, we adjusted numbers according to official numbers published elsewhere.[52] In doing so, we attributed any differences between the listed total costs for laboratories and AFP surveillance in the latter source[52] and the sum of both components in the first data set[63] to AFP surveillance costs (i.e., not to laboratory costs). We estimated an average externally financed cost per child younger than 15 years of age in the 61 low-income countries of 0.0335 US$2002. The database also contains external resource requirements for other income levels, but given the much lower costs per child in those income levels (i.e., 0.0031 US$2002 on average in 24 lower-middle income countries and 0.0099 US$2002 on average in four upper-middle income countries), we conclude that (sub)national funds comprise a much greater proportion of AFP surveillance expenditures in those income levels. Even low-income countries may contribute directly (buildings, vehicles, fuel, etc.) or indirectly (opportunity cost, time of staff not dedicated to AFP surveillance, etc.) to their AFP surveillance, although no existing study provides a comprehensive analysis of AFP surveillance costs from a societal perspective for any country.

In the absence of data, we rely on our judgment to estimate that in low-income countries approximately 50% of the total AFP surveillance cost gets absorbed at the country-level, which leads to our best estimate of 0.067 US$2002 for the AFP surveillance cost per child in low-income countries (Table 3). For the other three income levels, we estimate the cost per child based on PPP factors (year 2002) between the income levels.[45] This results in estimates of $afpchild^{low} = 0.067$, $afpchild^{lower\text{-}middle} = 0.087$, $afpchild^{upper\text{-}middle} = 0.176$, and $afpchild^{high} = 0.306$ US$2002.

A recent survey among the 145 laboratories of the global polio laboratory network revealed that national contributions represent an important component of the total costs of running the laboratory network (approximately 50%, excluding the 7 global specialized laboratories)[64] which suggests much higher overall total costs than obtained from estimates based on external resource requirements alone.[60] The study estimates annual running costs of the laboratories of 22.5 million US$2002.[64] We assume that these remain constant over time and independent of the number of countries that continue AFP surveillance. However, we assume these costs increase if the laboratory network carries out environmental surveillance.

In theory and under optimal conditions, a 100-fold concentrated sample from sewage connected to up to 10,000 people could detect one infected individual.[59] This implies that the minimum number of samples required to detect a poliovirus point introduction through environmental surveillance greatly exceeds the annual incidence of AFP cases of about 1 per 100,000 children younger than 15 years of age.[58] With current technology, it appears unlikely that any environmental surveillance system could collect one sample per 10,000 people. Instead, we assume that an environmental surveillance system would collect approximately one sample

per million people every six months, or approximately 12,000 samples per year (i.e., 6 billion people × 2 samples / 1 million). The laboratory network aims analyzes approximately 85,000 samples annualy;[64] we estimate that the workload of the laboratory network would increase by 15% with an environmental surveillance program (*envfactor* = 0.15).

Other costs

Outbreak response

The total cost of any outbreak response depends on the occurrence of outbreaks after eradication, the time since (OPV) cessation and the country's response policies. Estimating the potential occurrence and size of outbreaks falls outside the scope of this paper, and we limit this discussion to the values of inputs required for the calculation of outbreak response costs. Polio outbreak responses generally consist of mass immunization campaigns in the form of NIDs,[65] sometimes targeting not only children but also adults,[66] and often including more costly mop-up campaigns in the focal area of the outbreak or in areas with low routine immunization coverage.[67] For a given response strategy r in income level i (i = *low*, *lower-middle*, *upper-middle*, or *high*), we suggest the following formula for the outbreak response costs ORC^i_r:

$$ORC^i_r = tg_r \times nr_r \times cov_r \times \left(vp^i_{OPV}(t)/(1 - w^i_{NID}) + nvcdose^i \times relcost \right)$$

where tg_r = the target population associated with response strategy r,
nr_r = the number of rounds associated with response strategy r,
cov_r = the proportion of the target group that gets vaccinated in each immunization round for response strategy r,
vp^i_{OPV} = the price of OPV in income level i,
w^i_{NID} = the wastage associated with OPV NIDs in income level i,
$nvcdose^i$ = the non-vaccine cost per OPV dose during NIDs in income level i, and
relcost = the relative cost of administering one dose of OPV during an outbreak response compared to regular SIAs.

While we assume that the price of OPV is the same as for routine immunization and regular SIAs, we factor in the increase in non-vaccine costs per dose due to mop-ups compared to regular SIAs (i.e., with the input *relcost*). We assume that besides vp^i_{OPV}, also w^i_{NID} and $nvcdose^i$ remain equal to the values of these inputs during regular NIDs. We model all other inputs in the formula as dependent on the selected response strategy, which we expect in reality will depend on any pre-existing national preferences, a global response plan, and the nature of the outbreak. We base our estimate of *relcost* on a comparison of the actual expenditures per child during mop-up campaigns and (S)NIDs in Nepal and Myanmar during 2000-2003[68], Cambodia during 1997-1998[48] and Turkey during 1998-1999.[48] These studies report a cost per child in those four countries on average approximately 1.9 times higher during mop-up campaigns than during regular (sub)NIDs. Assuming that an outbreak response campaign would typically reach 80% of the covered population through normal NID delivery and 20% through mop-up outreach activities, we estimate a relative cost per dose of 1.2 (i.e., 0.8 + 0.2 × 1.9) during a response compared to regular SIAs.

Accounting for further cost increases due to extra training and social mobilization in the event of a post-eradication outbreak, we estimate *relcost* = 1.5 (range 1-3). Without modeling this influence, we note that the cost of an outbreak response may be somewhat lower in countries that continued routine OPV immunization because of the immediate availability of vaccines and the presence of infrastructure and know-how for OPV immunization. Monovalent OPV (mOPV) is emerging as the preferred for outbreak response, because it would provide better single-dose

seroconverion than trivalent OPV[69, 70] and avoid the risk associated with re-introducing two extra live virus strains in the outbreak population.[71] The use of mOPV requires (re-)licensing the vaccine, which could take several years and lead to substantial costs, but with current efforts may occur prior to T_0.[11] Consequently, we view the costs related to licensure as costs prior to T_0 and assume equal prices for OPV before and OPV or mOPV after T_0.

Stockpile

The formula we suggested for outbreak response implicitly assumes that OPV remains available in sufficient quantities at the current price. If routine OPV use stops, however, the possibility and scope of an outbreak response with trivalent or monovalent OPV may depend on the existence of a global, national, or regional stockpile. While the WHO and individual countries initiated efforts to investigate issues considering the size, logistics, and contents of a polio vaccine stockpile, specific questions regarding size, contents, and financing currently remain unanswered. Consequently, we omit the costs of establishing and maintaining a stockpile from this analysis, but we emphasize the importance of analyses to estimate these costs since we expect them to require significant resources.

Immunization day before T_0

Studies recommend that cessation of OPV immunization only occur if coordinated globally, and they further recommend a coordinated cessation when population immunity around the world reaches the highest possible level to minimize the risk of vaccine-derived poliovirus outbreaks.[11, 21, 72, 73] While many questions remain concerning their feasibility, we assume that the WHO may coordinate a number of targeted SIAs aimed at raising the coverage to over 90% in all areas prior to T_0 (targeted immunization activities (TIAs)), or that in the extreme case an NID will target all children younger than 5 years of age in all low and middle-income countries (global immunization day (GID)). To estimate the cost of the TIAs or GID, we assume that any additional costs for coordination and logistics cancel out against cost reductions due to economies of scale, and we use the same formula and inputs as for country-level SIAs. Although these inputs assume coverage of less than 90% in low and lower-middle income countries, TIAs will probably still bring immunity above 90% in children younger than 5 due to existing immunity prior to the TIAs and secondary OPV spread. We assume the TIAs will target children younger than 5 years of age in areas totaling a population (i.e., of all ages) of 600 million in low-income countries and 100 million in lower-middle income countries.[74] This amounts to an estimated one-time cost of approximately 81 million US$2002 for the TIAs or 1.1 billion (US$2002) for the GID (0.7 billion US$2002 if we assume upper-middle income countries do not participate) (Table 6).

These one-time costs prior to OPV cessation do not factor into estimates of future costs that begin after T_0, but the decision to conduct supplemental immunization prior to OPV cessation might lead to both financial and risk implications carrying over beyond T_0 (e.g., if obligations lead to financial shortfalls for other areas and risk of larger outbreaks).

Containment

WHO estimated that activities relating to certification[75] of wild poliovirus eradication and containment of polioviruses in laboratories and IPV manufacturing sites require almost 25 million US$2002 in external funds for 2004-2008.[60] These estimates focus on the costs prior to the achievement of wild poliovirus certification and corresponding containment requirements,

which like the TIAs or GID costs remain out of scope after T_0.[75, 76] We assume that IPV manufacturing sites and those laboratories opting to continue to retain wild polioviruses would absorb any continuing operational costs of maintaining strict biosafety levels after T_0 and that these would represent relatively small costs given the relatively small number of likely facilities. Results of a survey of institutions and laboratories in the United States suggest that only a small proportion (180 of 29791 respondents) currently retain wild poliovirus-infectious materials.[77] Although future containment costs may represent a relatively small portion of the overall costs, not maintaining strict biosafety levels poses potentially very significant risks,[21] and therefore the decision and costs of containment represent critical risk management considerations. We assume small annual placeholder costs 150,000 US$2002 for maintenance of laboratory containment and another $150,000 for IPV production site containment globally (Table 6). However, in the event of continued OPV immunization, the stringent containment guidelines and corresponding costs become unnecessary. We emphasize that our assumption of these small costs after T_0 depends on aggressive containment prior to T_0 and that costs of maintaining containment, even if small, represent an important area for sustained commitment of resources to protect the multibillion dollar global investments made to eradicate polio.

Management of chronic excretors

Chronic OPV-virus excretors present a risk of outbreaks through reintroduction of vaccine-derived polioviruses after OPV cessation.[21] Although attempts to treat chronic excretors with antivirals failed to clear their poliovirus excretion,[78] more effective drugs may become available in the future. Regardless of availability of effective drugs, management of the risk from chronic excretors would involve costs of screening and education of such persons to limit the risk of reintroducing vaccine-derived polioviruses in the surrounding community. However, given the small number of identified chronic excretors and the lack of screening and education activities, viable treatment, and a comprehensive policy to date, we assume small annual costs of approximately 10,000 US$2002 per identified chronic excretor. We assume four identified chronic excretors surviving on average 5 years after the point of OPV cessation, based on current experience.[21]

Cost of paralytic polio cases

Estimates of the costs attributable for polio vary widely depending on the income level, included components and underlying assumptions. Miller et al. (1996) used an estimate of 1.4 million US$2002 derived from the average compensation awards to vaccine-associated paralytic polio cases in the US asserting that this reflected both the treatment costs and all non-health care related costs such as loss of productivity and other "intangible" costs.[26, Table 1] Bart el al. (1996) estimate "cost of treatment and rehabilitation" of 310 US$2002 in developing countries and 31,000 US$2002 in industrialized countries,[13, Table 1] and Musgrove (1988) estimated total treatment costs in Latin-America of approximately 11,000 US$2002 based on a Brazilian estimate of the acute costs and subsequent costs over a 10-year period[79] discounted at a 12% rate.[12] Given the lack of agreement both on the actual costs to include and the appropriate way to value paralytic polio cases across income levels, we exclude the costs of paralytic polio from this analysis pending further study.

Total costs

Figure 2 provides a summary of the total costs associated with the country-level policies of immunization and AFP surveillance. The figure demonstrates that IPV represents the most costly immunization strategy due both to the higher price of the vaccine and the higher non-vaccine costs associated with the use of an injectible vaccine. However, moving toward IPV in a combination vaccine diminishes the estimated costs by approximately 28-48% depending on the income level as a result of the reduced non-vaccine costs (i.e., since we assumed the incremental vaccine price would remain the same). Routine IPV immunization in high-income countries alone costs approximately as much as in all other income levels combined.

Although the non-vaccine costs are smaller during SIAs than during routine immunization (see Table 3), conducting SIAs once every three years remains more expensive than routine OPV immunization because more children get immunized in NIDs. AFP surveillance amounts to a global total cost of approximately 3 billion US$2002 over the 20-year time frame (with a 3% discount rate) if every country continues AFP surveillance at the pre-eradication intensity, a value lower than the routine immunization costs with either vaccine. Figure 2 does not include the global-level costs of the laboratories, maintenance of containment, management of chronic excretors, and a GID or TIAs prior to cessation, which we provided in Table 6. The figure also excludes the potentially very substantial costs related to a stockpile, which we believe future studies should address. Finally, these costs do not include resources earmarked for responding to the potential outbreaks that might occur, which we view as a necessity given the risks of a potential outbreak.[21] If the polio laboratory network maintains a global environmental surveillance system (in addition to supporting AFP surveillance), this results in costs of approximately 400 million US$2002 during the 20-year time frame and this is the largest component of the recurrent global costs (and substantially lower than any of the aggregated country-level costs for immunization or AFP surveillance). We estimate a one-time cost of approximately 0.7 to 1 billion US$2002 for a GID prior to OPV cessation and 81 million US$2002 for TIAs. For context, we emphasize that conducting a GID prior to cessation of OPV would cost approximately the same as 4 years of routine OPV immunization in low and middle-income countries. We expect that conducting an immunization push prior to OPV cessation may prove financially challenging given recent experience with funding gaps, and that part of the discussion about the GID or TIAs should focus on how these options compare over time in terms of their costs and benefits.

With our assumption that high-income countries continue routine IPV immunization under any scenario, the total discounted costs over the 20-year time frame and at all levels (i.e., global and national) range from approximately 6.5 billion US$2002 for the cheapest option (i.e., IPV in a combination vaccine in high-income countries, no routine elsewhere, and only passive surveillance) to 25 billion US$2002 for the most costly option (i.e., IPV in a single antigen vaccine in every country, AFP and environmental surveillance, maintenance of strict containment and management of chronic excretors, GID not included). However, the cheapest option does not include the potentially larger costs of responding to outbreaks. In contrast, the most expensive option of universal IPV becomes less expensive assuming alternative scenarios of the delivery (i.e., in a combination vaccine) and the price (e.g., a sharp decline in the first 3 years) of IPV (see Figure 3).

Figure 4 compares the costs of different available combinations of country-level policies for each income level for the first year of the time horizon T_0. For comparability, we focused on hypothetical countries of 100 million people in each income level, assuming the average

population breakdowns by age for each income level. Discontinuing polio immunization offers the least costly option for low and middle-income countries, with no country-level costs if they also discontinue AFP surveillance (not included in figure) and with costs of approximately 2 to 4.7 million US$2002 if they continue AFP surveillance (not including their contributions to the global polio laboratory network). Despite the slightly lower AFP cost per child younger than 15 years of age (see Table 3), low-income countries show slightly higher total AFP costs given their relatively younger populations compared to lower-middle income countries. Policies involving OPV without SIAs offer the next least costly options, regardless of whether AFP surveillance continues, followed closely by routine IPV immunization if delivered in combination vaccines (in upper-middle countries OPV with SIAs emerges as more costly than routine IPV in a combination vaccine). IPV delivered in a single antigen vaccine costs the most in each income level, whether or not combined with AFP surveillance. In high-income countries, we only estimated the costs of routine IPV immunization and AFP surveillance.[8] Although our insights from Figure 4 do not necessarily hold in every year of the time horizon due to changes in the population distribution, vaccine prices, and time-dependent factors that we did not consider, we expect that these estimates will provide a useful starting point for national cost analyses and quantitative discussions about costs.

DISCUSSION

We estimated the costs of polio risk management after eradication as a function of policies available to countries of different income levels and the aggregate global costs over a 20-year time horizon. The timing of actual policy changes will depend on events (e.g., time of eradication or certification, outbreaks, technological developments) and future analyses may need to focus on other time periods.

With routine IPV immunization assumed to continue in high-income countries, the decision to use IPV in a single antigen or combination vaccine drives the aggregate global costs. This influence results from the fact that we attributed only a fraction of vaccine administration costs to IPV if delivered in a combination vaccine. Moreover, we assumed that the incremental price of IPV in a combination vaccine would remain equal to the cost of IPV as a single antigen. With this approach, in low and middle-income countries routine immunization with IPV in combination vaccines becomes cheaper than continuing OPV supplemented with NIDs every three years and approximately twice as expensive as routine OPV without SIAs. While the best methods for attributing vaccine administration costs to antigens in a combination vaccine remain debatable, clearly substantial saving would arise from delivering IPV in a combination vaccine compared to a single antigen. Many high-income countries already offer IPV as part of combination vaccines.[30, 31] However, current combination vaccine use only acellular pertussis vaccine, while most developing countries using the whole-cell pertussis in their DTP vaccine. Developing countries considering a switch to IPV should investigate any possible hurdles (e.g., harmonization with vaccinations for other diseases, heat-stability, impact on coverage) for potentially using IPV combination vaccines in their routine immunization programs.

Comparison of these results with other studies on the costs for polio eradication or beyond remains challenging because of differing policy options, frameworks, time periods, and discount rates.[12-17] However, the totals in this paper generally appear on the high side compared to other studies. This results primarily from the projected growth in the global population until and beyond T_0 and our inclusion of nationally funded costs in all countries (with high-income countries representing an important proportion of the global totals for every policy).

We emphasize several limitations of the estimates presented in the analysis. We note that the future size of the world's population drives the total costs and that experience shows that these projections often prove somewhat inaccurate over time.[80]

While we showed the substantial impact of IPV prices potentially changing over time (Figure 3), we recognize that substantial uncertainty exists around these estimates. The literature about the expected change in price of newly introduced vaccines remains surprisingly sparse. Given the role of vaccination in the lives of children and the increasing cost pressures, we expect that future cost studies of vaccines should help characterize and model the projections of vaccine costs as a function of time, although these projections should also include some random perturbations. Given the importance of the price projections, we believe that analysts should consider additional scenarios that provide alternative possible price trajectories for consideration by decision makers. For example, resolving issues related to developing countries producing their own IPV in the future, including dealing with containment of wild polioviruses from IPV manufacturing sites and the possibility of limiting this risk by producing IPV from Sabin OPV strains, may further impact the future costs.[5]

We assumed that a coordinated decision to continue routine OPV immunization in the developing world would imply that the OPV price remains fixed. However, we do not know whether UNICEF would remain the main procurer of OPV or whether more developing countries would choose to produce their own polio vaccine, and given the difference between the price of domestically-produced and imported OPV[49] this could impact future OPV prices. Furthermore, the US experience with OPV reveals that its price fluctuated substantially and not always at the same rate as general price inflation.[81]

Our assumption that immunization coverage levels remain constant in the future also represents a simplification of the reality that developing countries might not be able to maintain current levels when external funding stops or the perceived risk of polio becomes very low after eradication. However, continued use of OPV would require high coverage to prevent outbreaks of vaccine-derived polioviruses,[21, 72] and a switch to IPV will probably only be effective in preventing any future outbreak if coverage stays as high as possible. Similarly, the intensity of AFP surveillance and the size of the global laboratory network may decrease after eradication, although early detection of outbreaks remains crucial for an efficient response.[71, 82] Therefore, any future polio risk management policy will involve substantial costs and require important commitments from all countries or donors. However, the prospects of combination IPV vaccines and integrated disease surveillance could potentially provide some relief to the cost burden for these policy options.

We could not fully cost out all components of each policy category, and we suggest that future studies should focus on these. Actual outbreak response costs obviously depend on the occurrence and characteristics of any future outbreaks, which fall beyond the scope of this paper. However, we expect that WHO will develop a response strategy that will require a reserve of resources, and we expect that once this plan and a specific plan related to a stockpile exist, analysts will develop appropriate cost estimates. We also faced significant challenges in estimating the travel and indirect costs to the child and/or caregiver of time associated with clinic visits for vaccination, although Miller et al. (1996) estimated 28.85 US$2002 for these costs per visit in the US.[26] If we estimate these costs based on PPP for the other income levels, we obtain first estimates of 16.60 US$2002 in upper-middle, 8.21 in lower-middle, and 6.32 in low-income countries, but the lack of good data for these costs suggests the need for additional studies if decision makers wish to include them. We also recognize that valuation issues that arise in

comparing the health costs expressed as cases of paralytic polio and financial costs for reducing the risks pose important questions for future economic studies, particularly when looking at the results for people in countries of different income levels.

We emphasize that more reliable assumptions about the costs of environmental surveillance require a strategy or plan for such a system and much better information on the costs associated with personnel, equipment, and logistics than currently exist. We include placeholder costs here to stimulate the necessary research to further investigate the costs and effectiveness of potential environmental surveillance opportunities.

We expect that the value of our cost estimates of different polio risk management strategies comes from our efforts to provide a starting point for discussions. We expect that these estimates may provide a means for decision makers to better consider the various options in conjunction with their implications, and we emphasize the need for complete economic evaluation of the policy options that integrate the costs with the risks. We anticipate that future national studies will further help communicate the implications of various choices, and we encourage future efforts to develop better estimates of national costs.

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Table 1: Vaccine prices per dose from selected sources.[1]

Source and context	Data year	IPV price in US$2002 (range if specified)	OPV price in US$2002 (range if specified)
Actual price quotes :			
Bart et al. (1996)[13]	1993		
Developing countries			0.10 (0.10-0.15)
Industrialized countries average			5.18
Miller et al. (1996)[26]	1995		
US private sector		13.63 (12.02-13.63)	12.02
US public sector		6.11 (2.68-6.11)	2.68
Zhang et al. (1998)[27]	1995		
China, domestically produced vaccine			0.012
China, imported vaccine			0.11
Tucker et al. (2001)[28]	1999		
Australia, single antigen			0.23
UNICEF price based on demand projections for 2003[29]			
Mostly developing countries			0.094
US[30]	2004		
US public sector, single antigen		9.63[2]	
US public sector, incremental price for IPV component in DTaP-Hep B-IPV vaccine		11.61[2]	
US private sector, single antigen		20.69[2]	
US private sector, incremental price for IPV component in DTaP-Hep B-IPV vaccine		26.95[2]	
Belgium[31]	2004		
Belgium, single antigen		6.15	
Belgium, incremental price for IPV component in DTaP-IPV vaccine		9.37	
Belgium, incremental price for IPV component in DT-IPV vaccine[3]		6.90	
Prospective estimates :			
Tucker et al. (2001)[28]	1999		
Australia, single antigen		12.70 (6.98-17.78)	
Australia, incremental cost of IPV in a combination vaccine		8.89 (5.08-12.70)	
Sangrujee et al. (2004)[16]	2002		
Low-income countries		2.00	0.10
Middle-income countries		5.00	0.10
High-income countries		10.00	
Liu et al. (2002)[17]	NS[4]		
Developing counties		1.00 (0.50-2.00)	0.10
Hall (2003)[32]	NS[4]		
World		0.75-3.00	

[1] Only includes vaccine prices, does not include any costs related to vaccine delivery.
[2] Includes $0.75 federal excise tax.
[3] DT vaccine not from same manufacturer as DT-IPV combination vaccine.
[4] Not specified, assume quoted prices are in US$2002.
DT = diphtheria and tetanus; DTaP = diphtheria, tetanus, and acellular pertussis; Hep B = hepatitis B; IPV = inactivated polio vaccine (enhanced-potency); NS = not specified; OPV = oral polio vaccine (trivalent)

Table 2: Non-vaccine cost estimates for routine immunization from selected publications.

Source and context	Data Year	Vaccine	Non-vaccine costs per dose (US$2002) (range if specified)	Included components
Creese (1984)[33]	1982			
Brazil		OPV	2.82	Staff time, transportation, supervision, supply, training, publicity, material costs
Bart et al. (1996)[13]	1993			
Developing countries		OPV	1.88 (1.88-3.73)	Staff and supervision salaries, buildings, vehicles, refrigeration, cold chain, fuel, spare parts
Industrialized countries		OPV	6.34	
Miller et al. (1996)[26]	1992			
US		OPV or IPV	21.84	Administration cost, indirect clinic visit cost (travel cost and time loss)[3]
Tucker et al. (2001)[28]	1999			
Australia		OPV or IPV	4.44	Administration cost
Kahn et al. (2003)[14]	2000			
Low-income countries		OPV	1.27[1]	Not specified, includes price of vaccine
Middle-income countries		OPV	2.74[1]	
Upper-middle-income countries		OPV	7.31[1]	
Sangrujee et al. (2004)[16]	2002			
Low-income countries		OPV	0.009	Labor cost, cold chain equipment, transport, cost of syringes (IPV)
Low-income countries		IPV	0.10	
Middle-income countries		OPV	0.044	
Middle-income countries		IPV	0.17	
High-income countries		OPV	-	
High-income countries		IPV	0.96	
Lui et al. (2002)[17]	NS[2]			
Low coverage countries		OPV	0.041	Injections (for IPV; includes sterilization and disposal), storage, transportation, vaccination visit
Low coverage countries		IPV	0.142	
Intermediate coverage countries		OPV	0.081	
Intermediate coverage countries		IPV	0.262	
High coverage countries		OPV	0.121	
High coverage countries		IPV	0.342	

[1] Includes price of vaccine.
[2] Not specified, we assumed quoted prices in US$2002.
[3] This study divided clinic visit costs by 3 to account for the fact that other vaccines administered during same visit.
IPV = inactivated polio vaccine (enhanced-potency); NS = not specified; OPV = oral polio vaccine (trivalent).

Table 3: Inputs for the estimation of future country-level costs.

Input [*and symbol in formulae (see text), if applicable*]	Low-income countries		Lower-middle income countries		Upper-middle income countries		High-income countries	
	Best estimate	Range	Best estimate	Range	Best estimate	Range	Best estimate	Range
Routine immunization:								
Average price of domestically produced OPV (US$2002)	0.012		0.012		NA		NA	
Price of imported OPV (US$2002)	0.10		0.10		NA		NA	
Proportion of OPV consumption produced domestically	0.1		0.1		NA		NA	
Average OPV price (US$2002) [$vp^i_{OPV}$]	0.091	0.012-0.100	0.091	0.012-0.100	0.100	0.012-1.000	NA	
Initial price per IPV dose (US$2002) [$vp^i_{IPV\ single}(T_0)=vp^i_{IPV\ combo}(T_0)$]	1.00	0.5-2.00	1.75	0.50-3.00	2.50	1.00-5.00	10	5.00-30.00
Proportion of birth cohort covered with 3 or more polio vaccine doses during routine immunization [$POL3^i$]	0.68	0.50-0.80	0.90	0.75-0.95	0.92	0.90-1.00	0.94	0.90-1.00
Average number of (routine) doses received per PIC [nd]	3		3		3		3	
Non-vaccine cost PIC with OPV (US$2002) [$nvcpic^i_{OPV}$]	2.08	0.50-4.00	2.08	0.50-4.00	5.46	1.00-10.00	NA	
Non-vaccine cost per PIC with single antigen IPV (US$2002) [$nvcpic^i_{IPV\ single}$]	3.25	1.00-10.00	3.25	1.00-10.00	8.53	5.00-20.00	48	10.00-100.00
Non-vaccine cost per PIC with IPV in combination vaccine (US$2002) [$nvcpic^i_{IPV\ combo}$]	0.71	0.50-2.46	0.71	0.50-2.46	1.86	1.00-10.00	10	5.00-48.00
Wastage for routine OPV immunization [w^i_{OPV}]	0.20	0.05-0.50	0.20	0.05-0.50	0.15	0.05-0.25	NA	
Wastage for routine IPV immunization [w^i_{IPV}]	0.10	0.05-0.50	0.10	0.05-0.50	0.05	0.01-0.25	0.05	0.01-0.25
SIAs:								
Average externally financed non-vaccine cost per dose from available data, 2002 (US$2002)	0.23		0.64		1.87		NA	
Correction factor for unaccounted components	2	1-3	2	1-3	2	1-3	NA	
Corrected non-vaccine cost per dose (US$2002) [$nvcdose^i_{NID}$]	0.46	0.23-0.50	1.28	0.64-2.00	3.74	1.87-4.00	NA	
Average number of NID rounds per year (i.e., NID-administered doses per child under age 5 per year) [nr]	0.67	0.40-2.00	0.67	0.40-2.00	0.67	0.40-2.00	NA	
NID coverage [cov^i_{NID}]	0.80	0.75-1.00	0.85	0.80-1.00	0.90	0.85-1.00	NA	
NID wastage [w^i_{NID}]	0.15	0.05-0.25	0.15	0.05-0.25	0.1	0.05-0.25	NA	
AFP surveillance:								
AFP cost per case per child < 15 years of age (US$2002) [$afpchild^i$]	0.067	0.03-0.10	0.087	0.03-0.12	0.176	0.10-0.20	0.306	0.03-0.50

AFP = acute flaccid paralysis; IPV = inactivated polio vaccine (enhanced-potency); OPV = oral polio vaccine (trivalent); NA = not applicable, i.e., input belongs to a policy option that we do not consider for given income level; NID = national immunization day; PIC = fully polio-immunized child; SIAs = supplemental immunization activities

Table 4: Non-vaccine cost estimates for supplemental immunization activities from selected sources.

Source and context	Vaccine	Data Year	Non-vaccine costs per dose (US$2002) (range if specified)	Included components
Country-specific cost studies:				
Creese (1984)[33]		1982		
Upper-middle income country (Brazil)	OPV		1.22	Staff time, transportation, supervision, supply, training, publicity, material costs
Yang et al. (1998)[27]		1995		
Lower-middle income country (China)	OPV		0.43 (0.36-0.52)	Personnel, logistics, training, publicity at local and national level, equipment, operations at national and international level
Levin et al. (2000)[48]				
Low-income country (Cambodia)	OPV	1997	0.25 (0.23-0.27)	Personnel, supplies, cold chain, transport, social mobilization, training, technical assistance (not included in Turkey analysis)
Lower-middle income country (Turkey)	OPV	1998	0.51 (0.48-0.88)	
Cost analyses for multiple countries:				
Bart et al. (1996)[13]		1993		
Developing countries	OPV		0.12 (0.12-0.98)	Staff and supervision salaries, buildings, vehicles, refrigeration, cold chain, fuel, spare parts
Industrialized countries	OPV		1.84	
Kahn et al. (2003)[14]		2000		
Low-income countries	OPV		0.26	Includes vaccine, other components not specified
Middle-income countries	OPV		0.99	
Upper-middle-income countries	OPV		2.56	
Lui et al. (2002)[17]		NS[1]		
Low coverage countries	OPV		0.081	Injections (for IPV; includes sterilization and disposal), storage, transportation, vaccination visit
Low coverage countries	IPV		0.182	
Intermediate coverage countries	OPV		0.161	
Intermediate coverage countries	IPV		0.422	
High coverage countries	OPV		0.241	
High coverage countries	IPV		0.582	
Sangrujee et al. (2004)[16]		2002		
Low-income countries	OPV		0.210	Labor cost, cold chain equipment , transport, NIDs operational costs (if applicable), cost of syringes (IPV)
Estimates extracted from WHO financial databases (unpublished):				
National budgets submitted to WHO[50]		2002		
14 African low-income countries	OPV		0.34 (0.11-0.65)	"NID operations"
WHO-estimated costs per dose for 2003[51]		2002		
20 African low-income countries	OPV		0.205 (0.03-0.86)	"NID operations" based on previous rounds, only external resource requirements

[1] Not specified, we assumed quoted prices in US$2002.

IPV = inactivated polio vaccine (enhanced-potency); OPV = oral polio vaccine (trivalent); NID = national immunization day; NS = not specified; WHO = World Health Organization

Table 5: Estimation of the total non-vaccine cost per dose administered during supplemental immunization activities based on Table 4, in US$2002.

Source	Low-income countries	Lower-middle income countries	Upper-middle income countries
Creese (1984)[33]			1.22
Yang et al. (1998)[27]		0.43	
Levin et al. (2000)[48]	0.25	0.51	
Bart et al. (1996)[13]	0.12[1]	0.12[1]	1.84[1]
Kahn et al. (2003)[14]	0.26	0.99[2]	2.56
Sangrujee et al. (2004)[16]	0.21		
National budgets submitted to WHO[50]	0.205		
WHO-estimated costs per dose for 2003[51]	0.34		
Averages	**0.23**	**0.64**	**1.87**
Correction factor for unaccounted or indirect costs	1.5	1.5	1.5
Best estimate for total non-vaccine cost per administered dose	**0.346**	**0.965**	**2.810**

[1] We assign the "developed countries" estimates from Bart et al. (1996) to low and lower-middle income levels, but "industrialized countries" estimate to the upper-middle income level.
[2] We assign the "middle-income" estimate from Kahn et al. (2003) to the lower-income level.
WHO = World Health Organization

Table 6: Inputs for the estimation of future global-level costs.

Input [*and symbol in formulae (see text), if applicable*]	Best estimate	Range
Cost of targeted immunization activities before OPV cessation (US$2002)	$81 million	$50 million-$150 million
Cost of a global immunization day before OPV cessation (US$2002)	$1.1 billion	$0.7 billion -$1.5 billion
Annual costs of the global polio laboratory network in absence of a systematic environmental program (US$2002) [*lab*]	$22.5 million	$15 million - $30 million
Increase in laboratory cost in presence of a systematic environmental surveillance program [*envfactor*]	0.15	0-0.5
Relative cost per dose during outbreak response compared to regular supplemental immunization activities [*relcost*]	1.5	1-3
Cost of maintaining laboratory and IPV production site containment per year (US$2002)	$300,000	0-$1million
Cost for management of chronic poliovirus excretors per year per identified chronic excretor (US$2002)	$10,000	0-$100,000
Cost per paralytic case (US$2002)	varies	$310 - $1.4 milion
Resulting total discounted costs over the 20-year time horizon	**Best estimate**	**Range**
Global laboratory network in absence of a systematic environmental program (US$2002)	$345 million	$230 million – $460 million
Global laboratory network presence of a systematic environmental program (US$2002)	$397 million	$345 million – $517 million
Maintenance of laboratory and IPV production site containment (US$2002)	$5 million	0 – $15 million
Management of chronic poliovirus excretors if OPV use stops at T_0 (US$2002)[1]	$190,000	0 - $1.9 million
Outbreak response	NA	NA
Stockpile	NA	NA

[1] We assume four identified chronic excretors excreting at on average up to 5 years after OPV cessation[21]

IPV = inactivated polio vaccine (enhanced-potency); NA = not applicable, component that we did not cost; OPV = oral polio vaccine (trivalent)

Figure 1: Base case and alternative scenarios for the inactivated polio vaccine (IPV) price as a function of time and income level.

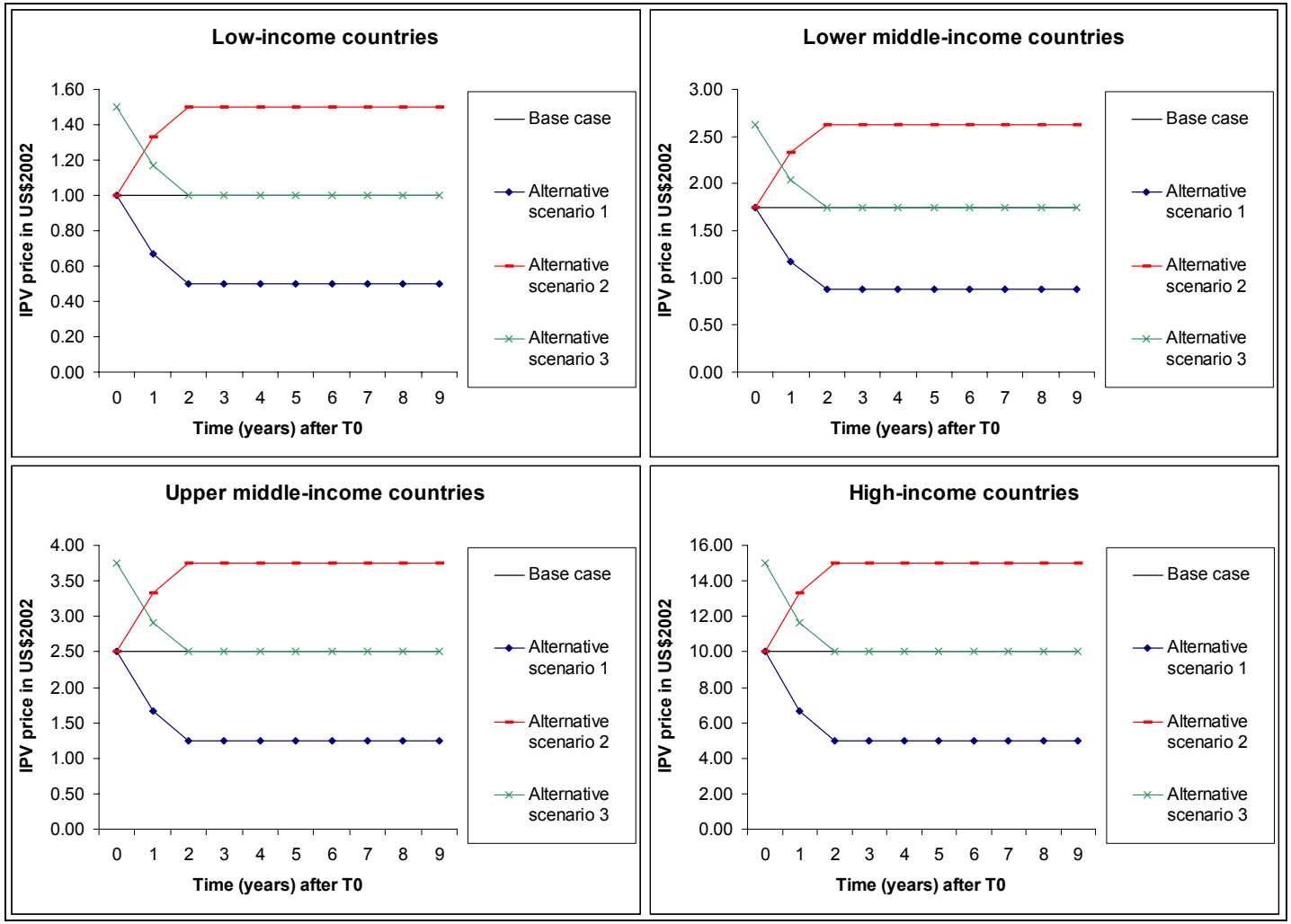
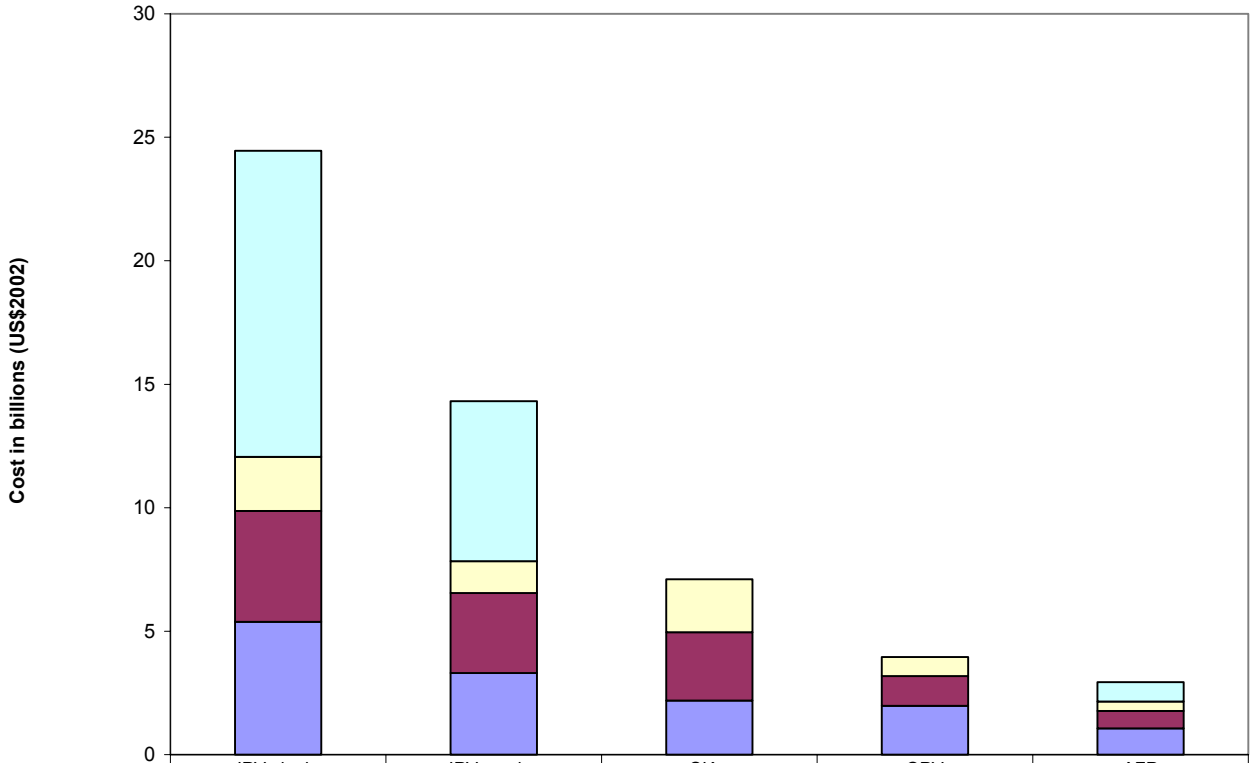


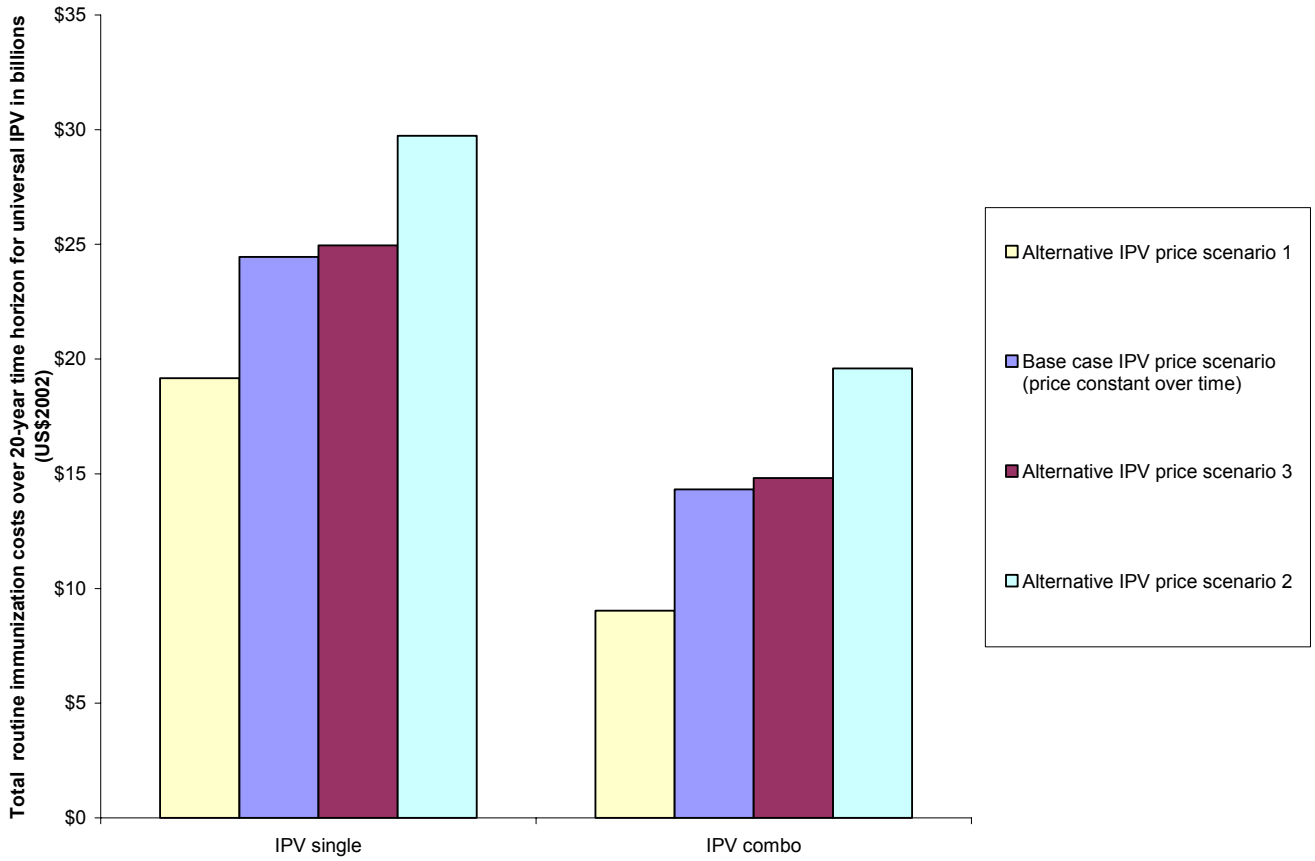
Figure 2: Total discounted costs the 20-year time horizon of major policy components for polio risk management after eradication.



	IPV single	IPV combo	SIAs	OPV	AFP
High-income countries*	12.4	6.5			0.8
Upper-middle income countries	2.2	1.3	2.1	0.8	0.4
Lower-middle income countries	4.5	3.2	2.8	1.2	0.7
Low-income countries	5.4	3.3	2.2	2.0	1.1

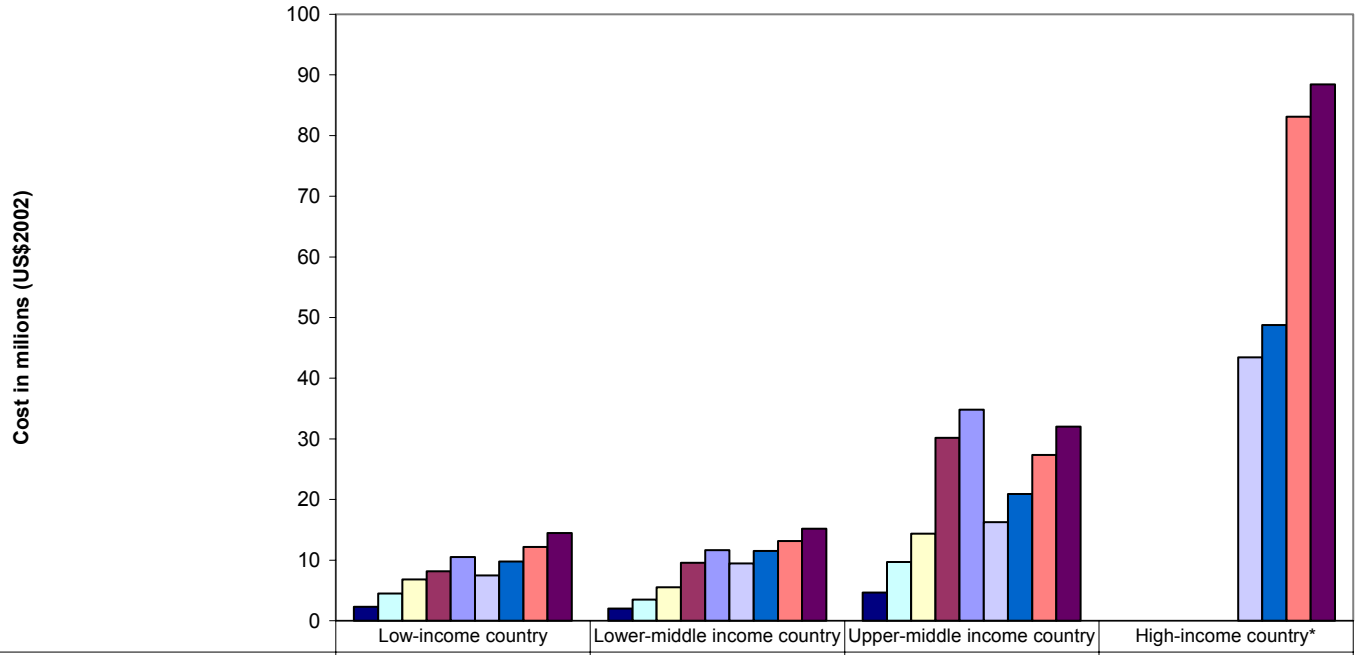
* We assume high-income countries will continue routine IPV immunization under any scenario and consequently we did not cost options involving OPV or no routine immunization for this income level.
AFP = acute flaccid paralysis surveillance; IPV combo = routine immunization with inactivated polio vaccine offered as part of a combination vaccine; IPV single = routine immunization with inactivated polio vaccine offered as a single antigen vaccine; OPV = routine immunization with trivalent oral polio vaccine; SIAs = supplemental immunization activities (with trivalent oral polio vaccine)

Figure 3: The total discounted costs of global inactivated polio vaccine (IPV) use over the 20-year time horizon for different scenarios for the vaccine price as a function of time (see Figure 1) and vaccine delivery in a single versus a combination vaccine.



IPV = inactivated polio vaccine (enhanced-potency); IPV combo = routine immunization with IPV offered as part of a combination vaccine; IPV single = routine immunization with IPV offered as a single antigen vaccine

Figure 4: Total costs during the first year of the time horizon (T_0) of different policy combinations for polio after eradication in hypothetical countries of 100 million people in each income level.



	Low-income country	Lower-middle income country	Upper-middle income country	High-income country*
No routine, No SIAs, AFP surveillance	2.3	2.0	4.7	
OPV, No SIAs, Passive surveillance	4.5	3.5	9.7	
OPV, No SIAs, AFP surveillance	6.8	5.5	14.3	
OPV, SIAs, Passive surveillance	8.2	9.6	30.1	
OPV, SIAs, AFP surveillance	10.5	11.6	34.8	
IPV combo, No SIAs, Passive surveillance	7.5	9.5	16.2	43.4
IPV combo, No SIAs, AFP surveillance	9.8	11.5	20.9	48.8
IPV single, No SIAs, Passive surveillance	12.2	13.1	27.4	83.1
IPV single, No SIAs, AFP surveillance	14.5	15.2	32.0	88.5

* We assume high-income countries will continue routine IPV immunization under any scenario and consequently we did not cost options involving OPV or no routine immunization for this income level.
AFP = acute flaccid paralysis; IPV combo = routine immunization with inactivated polio vaccine offered as part of a combination vaccine; IPV single = routine immunization with inactivated polio vaccine offered as a single antigen vaccine; OPV = routine immunization with trivalent oral polio vaccine; SIAs = supplemental immunization activities (with trivalent oral polio vaccine)

CHAPTER 4

Risks of Paralytic Disease due to Wild or Vaccine-derived Poliovirus after Eradication

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ABSTRACT

After the global eradication of wild polioviruses, the risk of paralytic poliomyelitis will still exist and require active management. Possible reintroductions of poliovirus that can spread rapidly in unprotected populations present challenges to policy makers. For example, at least one outbreak will likely occur due to circulation of a neurovirulent vaccine-derived poliovirus after discontinuation of oral poliovirus vaccine and also could possibly result from the escape of poliovirus from a laboratory or vaccine production facility or from an intentional act. In addition, continued vaccination with oral polio vaccines would result in the continued occurrence of vaccine-associated paralytic poliomyelitis. The likelihood and impacts of reintroductions in the form of poliomyelitis outbreaks depends on the policy decisions and on the size and characteristics of the vulnerable population, which change over time. A plan for managing these risks must begin with an attempt to characterize and quantify them as a function of time. This paper attempts to comprehensively characterize the risks, synthesize the existing data available for modeling them, and present quantitative risk estimates that can provide a starting point for informing policy decisions.

Keywords: Polio Eradication, Decision Analysis, Disease outbreak, Risk Analysis, Vaccine-associated Paralytic Poliomyelitis, Vaccine-derived Poliovirus, Bioterrorism, Laboratory Containment

INTRODUCTION

With the global eradication of wild polioviruses approaching,[1] policy makers must identify and evaluate available policies for management of the risk of poliomyelitis after interruption of wild poliovirus transmission.[2] Following debate about the immunization policy after eradication,[3-8] coordinated cessation of the use of trivalent oral poliovirus vaccine (OPV) for routine or supplemental immunization emerges as a necessary policy choice to accomplish the goal of eliminating paralysis from all wild or vaccine-derived polioviruses.[9, 10] Consequently, countries must decide among and implement options for surveillance, stockpiles, outbreak response, containment of poliovirus stocks in laboratories and IPV-manufacturing sites, and management of immunodeficient poliovirus excretors.[2, 11, 12] Any combination of these decisions carries future costs and risks; quantitative information can assist decision makers by informing them about the trade-offs among strategies. Several studies exist on the economic benefits and costs of wild poliovirus eradication,[13, 14] but none to date thoroughly explore quantitatively the risks, costs, and benefits of the future poliomyelitis risk management options. In developing a decision analytic model for poliomyelitis risk management after eradication, analysts must identify the policy options,[2] estimate their costs[15] and associated risks, and characterize outbreak consequences using a dynamic transmission model.[16] By integrating all these components into a quantitative model, analysts can fully evaluate the trade-offs among various options in health and economic terms.

Aylward and Cochi (2004) presented a framework for characterizing the risks of poliomyelitis after eradication using two categories for "risks related to the continued use of OPV and risks associated with the unsafe handling of wild polioviruses."[11, p. 42] The first category included the likely occurrence of outbreaks due to vaccine-derived polioviruses (VDPVs)[17] and sporadic cases of vaccine-associated paralytic poliomyelitis (VAPP). OPV viruses replicating for a period of time can revert to neurovirulent and transmissible VDPVs through accumulated mutations in the genome. This can occur as a result of continued person-to-person transmission that can ultimately lead to an outbreak of paralytic cases (cVDPVs). In addition, VDPVs could emerge as a result of prolonged intestinal replication of viruses initially obtained through an OPV infection among individuals with severe immunodeficiencies (iVDPVs). The second risk category includes unintentional release of wild poliovirus from an IPV-manufacturing facility or a laboratory, and intentional release of wild polioviruses (i.e., bioterrorism). Unsafe handling of OPV viruses or VDPVs could also potentially lead to outbreaks in the future. We assume that the re-emergence of virus from the environment or from a population in which wild polioviruses continued to circulate undetected represent remote possibilities after certification of eradication in all six World Health Organization (WHO) regions[18] and we assume negligible risks for these.[19, 20]

While Aylward and Cochi (2004) identify most of these risks and summarize the frequency and burden of disease associated with each, they recognize that these risks depend strongly of the policies implemented after eradication.[11] We aim to quantitatively assess the probability of VAPP cases and of poliomyelitis outbreaks as a function of population size, time, future poliomyelitis risk management policies, and income level. We do not address the consequences or burden of disease related to outbreaks, which requires the use of a dynamic disease model,[16] but we discuss the expected burden of VAPP cases in different populations.

Following discussions about the risks of cVDPVs, the policy makers at the WHO recognized that minimizing the burden of paralytic polio requires coordinated global cessation of OPV vaccination as soon as possible after assurance of the interruption of wild poliovirus

transmission but not longer than necessary to avoid the risks associated with OPV use.[10] While the exact year still remains uncertain, we define T_0 as the time when the world will implement its poliomyelitis risk management policies for the post-eradication era, and consider an analytical time horizon stretching up to 20 years after T_0. This time horizon enables consideration of the uncertain but important long-term trends, without exceeding the limits of reasonable extrapolations over time. We emphasize that our starting point assumes successful eradication of wild poliovirus. The next section explains the metrics and data we used to assess each risk. We then present the evidence and provide our best quantitative estimates for each risk facing policy makers. We move from the relatively more certain risks (e.g., VAPP from routine OPV use) to the less certain risks (e.g., bioterrorism), and provide a discussion of our uncertainty for each risk. Finally, we discuss the potential use of these results in a decision analytic modeling tool to help inform policy makers.

METHODS

Stratification by income level and future policies

We develop risk functions representing the probabilities of outbreaks and VAPP cases for each country for each of the 20 years of the time horizon. To accomplish this, we stratify the world into four types of countries according to the 2002 World Bank income levels (i.e., low (LOW), lower-middle (LMI), upper-middle (UMI) or high (HIGH)).[21] While imperfect, stratification by income level provides a means to characterize factors that influence the risks, for example, different levels of routine immunization coverage, vaccine immunogenicity, and sanitation, which correlate with wealth. For convenience, we assume that this stratification does not change over time.

We use the term *scenario* to refer to a given set of relevant policies for a country in a specified income level based on prior research.[2] For example, we might discuss an upper middle-income country of 100 million people that uses IPV for routine immunization, does not carry out supplemental immunization activities (SIAs), and maintains a strict policy for enforcing laboratory and IPV-manufacturing site containment. In this sense, these characterizations represent typical scenarios of countries that may experience significantly different risks resulting in different outbreak consequences.

For purposes of this paper, we focus on a typical national population of 100 million people. In this hypothetical context, dividing the 2001 global population into countries of this size results in approximately 25 low-income, 21 lower-middle income, 5 upper-middle income, and 9 high-income countries of 100 million people.[21, 22]

Risk Metrics

We evaluate the risks using several risk metrics. We address the probability of recipient and contact VAPP in individuals and extrapolate this to the population level. In contrast, we focus on the probability of outbreaks in populations without addressing the individual risk of paralytic poliomyelitis due to outbreaks.

We define an outbreak as the occurrence of at least 1 confirmed case of paralytic poliomyelitis due to wild or circulating vaccine-derived poliovirus (although we do not consider iVDPVs as outbreaks unless they spread and cause paralysis beyond the immunodeficient patient). Thus, in estimating outbreak probabilities we do not consider virus re-introductions that "die out" as outbreaks (i.e., unsustained chains of transmission that do not result in paralytic

cases potentially detected by surveillance). However, this definition includes isolated cases (with no epidemiological link to other virus isolates or detected cases).

We model outbreaks as random events, with the number of outbreaks in a year following a Poisson distribution with 1 parameter, λ, that represents the rate of occurrence per year per 100 million people.[23] For a relatively small λ (e.g., less than 0.2), the Poisson distribution approximates the probability of 1 event in a year (since the probability of 1 event is Poisson(1) = $\lambda e^{-\lambda} \approx \lambda$ for small λ). We characterize outbreak probabilities per 100 million people recognizing the additivity of the rates (i.e., assuming that we can divide the population into a number of equally sized subpopulations, with outbreak events that follow independent and identical Poisson distributions). For example, if 3 outbreaks occurred in low-income countries (approximated as 25 countries each with populations of 100 million) over the last 6 years, this would translate into an average estimated rate of occurrence in low-income settings of $3/(6\times25) = 0.02$ per year for each population of 100 million people, or similarly 0.002 outbreaks per year for each population of 10 million people, etc.

We base our quantitative risk estimates on available data from the peer-reviewed literature, conference presentations, or institutional data, and extrapolate when possible and as needed. In the event of OPV cessation, however, we face significant challenges in extrapolating from historical data because of the unprecedented susceptibility that will exist in the population after eradication due to the absence of exposure to live polioviruses. With uncertainty unavoidable, we use any available qualitative information about the risks, expected trends, and influences over time to delineate the quantitative estimates.

THE RISK OF VACCINE-ASSOCIATED PARALYTIC POLIOMYELITIS

Factors influencing the risk of VAPP

OPV contains live, attenuated poliovirus strains (i.e., *Sabin* strains) selected for their low neurovirulence.[24] However, soon after the introduction of OPV it became apparent that in rare instances infection with an OPV virus can lead to VAPP, a form of poliomyelitis clinically indistinguishable from that caused by wild poliovirus. With massive use of OPV for routine or supplementary immunization, ample opportunity exists for infection with the OPV virus both due to administration of the vaccine (i.e., primary infection) and exposure of contacts of vaccine recipients (i.e., infection with a Sabin-like virus, which for convenience we henceforth refer to as secondary OPV infection). We refer to VAPP cases that occur in vaccinees as *recipient VAPP* and to those cases associated with secondary (and tertiary, etc.) infections as *contact VAPP*. Table 1 summarizes individual risk factors for contracting VAPP including the lack of prior immunity, genetic pre-susceptibility (i.e., primary immunodeficiencies),[25] infection with type 3 OPV (as opposed to the other 2 serotypes)[26-29] and intramuscular injections.[30, 31] We denote monovalent oral poliovirus vaccine as mOPV to distinguish it from OPV and we include a number at the end to indicate the serotype when appropriate (e.g., mOPV1). The rapid rate of genetic mutation among polioviruses means that the viruses that OPV recipients excrete can evolve and acquire higher neurovirulence than the original vaccine virus. Therefore, secondary OPV infection may present a higher risk than primary OPV infection (i.e., vaccination) in fully susceptible individuals.

At the population level, the risk in terms of expected annual number of VAPP cases due to routine immunization depends primarily on two factors: the amount of OPV used and the density of susceptibles. In a stable population with a low, constant density of susceptibles, the amount of OPV administered yearly to the birth cohort remains the main factor influencing the

incidence of VAPP. In the context of routine OPV use with high coverage, industrialized countries reported relatively consistent rates of paralytic poliomyelitis of about 0.3 to 0.7 (recipient plus contact) VAPP cases per million distributed or administered doses.[27, 29, 32-36] These studies also reported consistent rates of first-dose recipient VAPP cases ranging from 0.7 to 1.5 cases per million first doses.

However, the literature suggests that the population risk for VAPP does not follow a linear relationship in the number of doses. India administered 733 million OPV doses in 1999 to about 125 million children aged less than five years, representing an average of over 5 doses per child.[37] Despite a high overall incidence of approximately 0.18 VAPP cases per million people that year, this corresponded to a very low rate of 0.2 cases per million administered doses. For comparison, the US experienced an overall incidence between 1980 and 1995 of only 0.032 VAPP cases per million people annually (i.e., nearly a factor of 6 lower), but this corresponded to a 2-fold higher rate of approximately 0.4 cases per million distributed doses.[34] This suggests that the per-dose risk may decrease as the number of doses per child becomes very high, because already immune children receive many of the administered doses.[38, 39] At the same time, the accumulation of many susceptibles in India prior to the intensified vaccination efforts in 1999 combined with a large proportion likely remaining susceptible due to poor seroconversion rates[40] and the more efficient secondary OPV spread in India would explain both the high rate of approximately 2 contact VAPP cases per recipient VAPP case and the high overall incidence of VAPP that occurred in 1999. Supporting this hypothesis, the overall VAPP incidence in India dropped significantly as a result of better population immunity to 129 in 2000 and 109 in 2001.[41]

The lower section of Table 1 lists a number of factors that influence the population risk for VAPP in the event of an outbreak response involving OPV.[26, 40]

Quantification of the risk of VAPP

We express the risk of VAPP in terms of the rates of paralytic poliomyelitis per primary OPV infection and per secondary OPV infection, so that the expected number of VAPP cases (V) as a function of time and the scenario equals:

$$V = r_1 \times I_1 + r_2 \times I_2$$

where r_1 = the rate of paralytic poliomyelitis per primary OPV infection in fully susceptibles,
r_2 = the rate of paralytic poliomyelitis per secondary OPV infection in fully susceptibles,
I_1 = the number of primary OPV infections in fully susceptibles in a year or during an immunization response as a function of time and the scenario, and
I_2 = the number of secondary OPV infections in fully susceptibles in a year or during an immunization response as a function of time and the scenario.

We assume that the rates of paralytic poliomyelitis per OPV infection depend only on the vaccine (i.e., trivalent or monovalent), and not on the setting, the type of vaccine delivery (routine, mass campaigns) or the immunity status of the population. We aggregate over the individual risk factors except prior immunity, which we account for in estimating the number of primary and secondary OPV infections in fully susceptibles. The disadvantage of this approach

is the difficulty in estimating the number of susceptibles that typically get infected with OPV. The advantage derives from the direct cause-effect relationship between OPV infections and the total number of VAPP cases, and the utility of this method for both routine and outbreak response immunization.

Assuming VAPP rates independent of the setting, we based our estimates on US data because of the large size of the data set, the completeness and consistency of these data, and our access to them. A total of 89 recipient and 58 contact VAPP cases (including cases in immunodeficient persons) occurred in the USA during 1980-1997,[27, 42, 43] for an average size of the annual birth cohort of nearly 4 million.[44] Three major US surveys provide coverage estimates among 2 year old children for this time period, although they include incomplete data.[45] We assume that the results of the US Immunization Survey of children born through 1983 underestimated the true coverage by 15%, based on comments in Simpson et al (2001).[45] We do not adjust data for the National Health Interview Survey of children born 1989-91 and the National Immunization Survey of children born after 1991.[45, 46] Deriving estimates for missing years from any available retrospective surveys among preschoolers[47, 48] and interpolating between remaining years, we obtain an average coverage (weighed by birth cohort sizes) for children born 1980-1997 of approximately 75% (i.e., coverage by age 2 with 3 or more OPV doses). We further assume a primary seroconversion rate of 95% for 3 OPV doses (averaging over serotype-specific rates)[24] and that on average 95% of each birth cohort eventually seroconverts (with all 3 serotypes) due to primary or secondary OPV infections (i.e., the effective take rate). Using these numbers, Table 2 shows the breakdown by primary and secondary infections, and the VAPP rates that follow. This results in rates of 1.9 recipient VAPP cases per million OPV infections and 3.7 contact VAPP cases per million secondary OPV infections.

The effective take rate estimate (of 95%) impacts only the contact VAPP rate. Although the true effective take rate for various immunization programs remains uncertain, given generally high seroprevalence in children by age five[46, 49] its range most likely does not exceed 80% to 100% for US cohorts born since 1980. Using these bounds yields a range for the contact VAPP rate of 3.1 to 10.3 per million secondary OPV infections. However, this implies a very limited range of 2.1 to 2.6 total VAPP cases per total number of OPV infections in susceptibles (i.e., aggregating recipient and contact VAPP). The average vaccination coverage drives the ratio of primarily to secondarily infected individuals and therefore the difference in risk estimates for recipient and contact VAPP per infection. For example, if we vary the average coverage between 65% (i.e., the average without correcting for underestimation) and 90% (i.e., the coverage in the 1990s), we obtain contact VAPP rates of 2.6 and 9.2 cases per million secondary OPV infections, respectively (with other inputs kept at their base case values).

Only 16 of the 58 contact VAPP patients observed between 1980 and 1997 were born during that time period and onset of contact VAPP occurred at an average age of approximately 25 years.[42, 43] This approach implicitly assumes that the same number of contact VAPP cases reported between 1980-1997 would eventually occur in the cohort born between 1980-1997 given the same level of routine OPV vaccination. However, the US switched to a sequential IPV-OPV schedule in 1997 and to an all-IPV schedule in 2000 (and consequently members of this birth cohort would no longer experience potential cases of contact VAPP) and increased vaccination coverage reported for 1980-1997 correlated inversely with the proportion of contact VAPP cases in that birth cohort.[27, 42, 43]

For outbreak response after OPV cessation, mOPV is emerging as the preferred vaccine

given its more efficient seroconversion compared to trivalent OPV[40, 50] and given that trivalent OPV would unnecessarily reintroduce poliovirus serotypes not related to the outbreak.[12] Therefore, we must consider the VAPP risk associated with potential mOPV use for outbreak response. While we can rely on extensive data about VAPP from trivalent OPV use, limited documented experience exists with VAPP cases from widespread mOPV use. Only four large population-based studies in the US and Hungary provide some limited basis for quantitative estimates for VAPP associated with mOPV.[50] Dömök (1984) describes the only data set in the context of widespread mOPV use for largely susceptible birth cohorts,[26] but the type 3 mOPV strain used at the time probably does not reflect the properties of the currently used strains. Given the limitations in the available data, we assume similar risks as we obtained for trivalent OPV and we assume wide uncertainty ranges reflecting the experience in Hungary (i.e., 1.9 recipient VAPP cases per million primary mOPV infections, range 0.7-8.9, and 3.7 contact VAPP cases per million secondary mOPV infections, range 0-6.6) based on Dömök (1984)[26, Table 2] and an assumed 75% effective take rate for children in Hungary). The base case estimates reflect the average risk of the three serotypes, while the ranges reflect the variability across serotypes. However, the true serotype-dependent risk remains highly uncertain until further experience with new mOPV vaccines.

Table 3 shows inputs and rates for the VAPP risk as a function of several scenarios. The overall VAPP rate per million OPV infections in susceptibles due to routine immunization shows little variation. In terms of the risk per million in a birth cohort, the estimates range from 1.83 to 2.43 cases per million for middle-income countries conducting no SIAs and low-income countries conducting no SIAs, respectively. Recent estimates of the global burden of VAPP assumed a range of 2 to 4 cases per million in a birth cohort.[24, 39] The lower end of this range reflected the US experience, while the upper end reflected the VAPP incidence in India in 2001 divided by the size of the birth cohort. In India in 1999, the cohort risk of VAPP appeared even higher at a rate of 7 per million birth cohort.[37] However, this higher rate primarily resulted from a "catch-up" phenomenon due to the push for wild poliovirus eradication in India in 1999. With continuation of stable routine OPV and SIAs we expect that the number of VAPP cases per million in a birth cohort would probably approach an incidence closer to 2 per million in the birth cohort.

Note that both in the calculation of the observed risk of VAPP (Tables 2 and 3) and in the estimation of the future risk of VAPP (Table 4), we neglected the influence of maternal antibodies. The fact that newborns may benefit from some level of antibodies, which decays at a half life of about 28 days,[51] implies that some proportion of seroconversions, especially those associated with doses given at early age, do not represent OPV infections in *fully* susceptibles. Consequently, we probably overestimate the number of OPV infections in fully susceptibles, resulting in lower VAPP rates (i.e., r_1 and r_2). However, if we assume that the extent of overestimation in the calculation of VAPP rates in the past equals that in the prospective estimation of the number of secondary infections (i.e., I_1 and I_2), the effects of neglecting maternal antibodies cancel out when multiplying the VAPP rates by the numbers of OPV infections. In the event of a massive outbreak response with OPV, this approach might underestimate the number of VAPP cases because only a very small proportion of first OPV infections would then occur in infants still protected through maternal antibodies.

THE RISK OF OUTBREAKS DUE TO VACCINE-DERIVED POLIOVIRUSES

As with wild polioviruses, infection with the live, OPV virus leads to excretion of a slightly modified virus. If the virus can accumulate sufficient mutations through continued replication in a single, immunodeficient long-term excretor or through continued person-to-person transmission, then it can revert back to a virulent and transmissible form that may cause outbreaks similar to wild poliovirus.[17] The virologic definition of *vaccine-derived polioviruses* (VDPVs) includes those strains with between 1 and 15% divergence from the original vaccine strain in the VP1 region (by convention, *Sabin-like* viruses diverge less than 1% and wild-type polioviruses are more than 15% different from the vaccine strain).[52] Several types of VDPVs exist and they warrant different treatment with respect to quantifying the risk of VDPV outbreaks after OPV cessation. In this paper we define three mutually exclusive types of VDPV events:

- Circulating VDPV (cVDPV) event: isolation of VDPVs from at least 2 cases (epidemiologically linked) of paralytic poliomyelitis or acute flaccid paralysis (AFP),
- Immunodeficient VDPV (iVDPV) event: isolation of a VDPV from an immunodeficient person excreting at least 6 months after infection with the vaccine virus, and
- Ambiguous VDPV (aVDPV) event: isolation of VDPVs from a single immunocompetent AFP or paralytic poliomyelitis patient with or without additional isolates from contacts, or from healthy individuals or the environment in absence of paralytic poliomyelitis cases. (We emphasize that by definition we consider the occurrence of at least 1 confirmed case of paralytic poliomyelitis as an outbreak, although we note that not all analyses might use this same definition).

We discuss the first two risks in separate subsections recognizing that the occurrence of iVDPV events depends on distinctly different factors than the occurrence of cVDPV events and we assign each aVDPV event to one of these two categories depending on the nature of the event.

The probability of cVDPV outbreaks

Inventory of confirmed and suspected cVDPV events

Table 4 separately lists documented episodes of confirmed cVDPVs and suspected cVDPVs that remain classified as aVDPVs given the presence of only a single case.[53-60] We further categorize the data into events before and after 1999, recognizing that the choice of the time period substantially impacts estimates of outbreak frequencies (derived by dividing the number of outbreaks by the time period). The observation that the last wild-type isolate of the detected VDPV serotype occurred at least 3 years prior to the event, except for the outbreaks in Peru and possibly in Romania in 1980, suggests that the eradication of a serotype may substantially increase the risk of cVDPVs. For this reason, we believe that estimates of prospective risks of cVDPVs should focus on events that occurred between 1999 and 2004, which represents a 6-year period characterized by historically high global OPV use, complete elimination of all type 2 wild polioviruses, and elimination of type 3 and type 1 wild polioviruses in most parts of the world.

Investigators analyzed viruses obtained from four recent cVDPV outbreaks with at least two paralytic cases (Hispaniola, Philippines, Madagascar, China) and four recent aVDPVs isolated from acute flaccid paralysis (AFP) cases (Kazakhstan, Romania, Nigeria, Pakistan). Reflecting the uncertainty about the appropriate interpretation of the aVDPVs, we consider two cases: one case based on the four confirmed cVDPV outbreaks only and a second case based on all cVDPV and aVDPV events after 1999, as shown at the bottom of Table 4. Note that we

consider the Dominican Republic outbreak as a part of the Haitian outbreak (i.e., as a single Hispaniola outbreak) since it began with an imported virus from the Haitian outbreak.[56] We classified events as occurring on a background of SIAs if any SIAs occurred in the two years preceding the outbreak. In addition to these cVDPV and aVDPV events, Table 5 lists aVDPVs that we did not include in Table 4 or our risk estimates given weak evidence for circulation or their emergence from settings unrepresentative of the current situation (e.g., the event in Poland appears to have involved widespread circulation but did not involve an OPV strain currently in use).[54, 58, 61-65]

Thus, our risk estimates rely on the evidence of 4 confirmed cVDPVs or alternatively 8 combined cVDPVs and aVDPVs in 6 years with a background of routine OPV immunization including 1 confirmed cVDPV or alternatively 4 combined cVDPVs and aVDPVs in 6 years in countries carrying out some form of SIAs as shown at the bottom of Table 4.

Dependence on time and scenarios

With continued use of OPV, decreased population immunity increasingly appears to represent a key risk factor for the emergence and spread of cVDPVs.[17] Therefore, we anticipate that in the context of routine OPV vaccination, regular SIAs decrease the risk while cessation of SIAs increases the rate of occurrence compared to the risk in OPV-using countries that conduct SIAs. Furthermore, for either SIA policy, population immunity probably correlates with income because of decreased OPV effectiveness[24] and generally lower routine immunization coverage in low-income settings.[22] In addition, we assume poor hygiene, tropical climate, and crowding all correlate with low income, and favor the spread of polioviruses and the emergence of cVDPVs. If OPV use continues, the possible decreasing OPV coverage would lead to an increase in cVDPV risk as the time since eradication increases.

If the world stops OPV use completely, population immunity levels will decrease with the addition of unvaccinated and unexposed birth cohorts. However, the cessation of OPV use in those scenarios ends the routine introduction of large amounts of potential VDPVs into the population through vaccination. Few experiences exist with cessation of OPV to estimate the ability of OPV viruses to persist in such a situation. Since 1962 in Cuba and until the early 1990s in several Eastern European countries, vaccination occurred exclusively with OPV during mass immunization campaigns, with no vaccine available between campaigns and virtual absence of wild polioviruses during most of these time periods.[30, 66] Several studies investigated the persistence of polioviruses in between campaigns in Cuba and found no evidence of OPV virus persistence for longer than a few months,[67-69] and no detected cVDPV events occurred in the months between the OPV campaigns. However, researchers isolated an in Romania in 1980 aVDPV (Table 4). Furthermore, the aVDPV in Belarus (Table 5) following cessation of OPV during 1963-1966 in a local population of about 160,000[17, 65] suggests some possibility that VDPVs can emerge after stopping OPV use when neighboring populations continue using OPV.

IPV vaccination provides less efficiency in preventing poliovirus excretion than OPV and offers no benefits from secondary immunizations.[70-72] Consequently, the population immunity protection against infections decreases with time with implementation of a policy of switching from OPV to IPV. As with the cessation of polio vaccinations altogether, this increases the likelihood that OPV viruses can circulate and become cVDPVs, but at the same time OPV cessation drastically limits the prevalence of OPV viruses.

Recent experience with the transition of countries from OPV to IPV provides some

insights. New Zealand made a rapid switch from routine OPV to IPV immunization in 2002. A study searching for OPV viruses in several surveillance systems (pediatric, enterovirus, and environmental) found no VDPVs and a rapid decline in prevalence of Sabin-like viruses in the months following the switch to IPV (with a few isolates up to 11 months after the switch probably representing OPV virus importations rather than continued circulation).[73] A type 3 outbreak involving viruses derived from an experimental OPV strain (i.e., USOL-D-bac, not used anymore) occurred in Poland in 1968 on a background of low, type 3 (non enhanced potency, low potency vaccine) IPV-immunity.[17, 64] The very weak evidence in the case of the Polish experience, which occurred with much lower quality vaccines than currently used, suggests that even in a temperate climate and upper-middle income setting, VDPVs could emerge, circulate, and cause paralytic poliomyelitis in the context of imperfect (non enhanced potency) IPV-induced protection[17] and that a switch to IPV (with low coverage) does not exclude the possibility of cVDPVs. Uncertainty still exists concerning the ability of modern IPV vaccines to reduce transmission of polioviruses in developing countries due to the lack of experience with IPV in those settings. Most importantly, the experiences in Belarus, Poland, and New Zealand underscore the risk of failing to coordinate the cessation of OPV globally.

For any policy, the population immunity level at T_0 impacts the probability of cVDPV outbreaks in subsequent years. Based on the experience in countries that already eradicated polio, it appears realistic to assume that countries may stop conducting SIAs and/or maintaining high routine immunization coverage at least 3 years prior to T_0. We refer to this as the realistic population immunity (RPI) scenario. Alternatively, if countries continue SIAs until T_0 or carry out a coordinated pulse to bring coverage in all areas up to more than 90%, this would provide maximum population immunity at T_0, and we refer to this as the maximum population immunity (MPI) scenario.

Quantification of the probability of outbreaks due to cVDPVs

Table 6 (top) shows the average annual frequency of cVDPV outbreaks per 100 million people in low or lower-middle income settings both with and without SIAs during 1999-2004 based on the outbreaks counted in Table 4.

Two competing trends drive this risk after OPV cessation: (1) a rapid decline in the prevalence of vaccine-derived viruses, which implies a decreased outbreak risk, and (2) a decrease in population immunity as newborn children remain unvaccinated, which implies an increased outbreak risk. Conditioning on the prevalence leads to the following expression for the probability of a cVDPV outbreak:

$$\begin{aligned} P(\textit{cVDPV outbreak}) &= P(\textit{prevalence} \geq 1 \ \textit{virus}) \times P(\textit{outbreak} | \textit{prevalence} \geq 1 \ \textit{virus}) + \\ &\quad P(\textit{prevalence} = 0 \ \textit{viruses}) \times P(\textit{outbreak} | \textit{prevalence} = 0 \ \textit{viruses}) \\ &= P(\textit{prevalence} \geq 1 \ \textit{virus}) \times P(\textit{outbreak} | \textit{prevalence} \geq 1 \ \textit{virus}) \end{aligned}$$

The first term on the right hand side of the equation declines over time after OPV cessation. Three data sets from Cuba where OPV cessation occurs twice a year consistently show sharp declines in virus prevalence with different virus detection methods (i.e., serology, stool samples of children, environmental sampling).[67, 69] Figure 1 shows the limited serology data and the best-fit exponential decay curve for unvaccinated infants reflecting secondary exposure to circulating OPV viruses following a National Immunization Day (NID). The stool samples and environmental sampling data also show rapid decay.[67, 69] Although the prevalence of OPV viruses does not equal the probability that prevalence of virus exceeds 1, we assume that both decline at a similarly rapid rate.

The second term on the right hand side of the equation depends on many factors, including the transmissibility of polioviruses and immunity to infections in the population. While random virus mutations and person-to-person spread ultimately determine whether a virus leads to an outbreak, population immunity thresholds (dependent on the transmissibility of the virus) probably play an important role in the potential for outbreaks given the prevalence of a virus.[74] If we knew exactly the population immunity profile and transmissibility of the virus, we could more confidently predict that either the probability of an outbreak given the prevalence of at least one virus approaches 1 (population immunity below threshold) or that the probability approaches 0 (population immunity above threshold). However, we remain uncertain about the true transmissibility of OPV viruses as they evolve towards VDPVs and the effective immunity that polio vaccines provide against infections. In addition, important variability exists both in the immunity and the transmissibility even within income strata (e.g., contact patterns in populations, serotypes, hygiene, climate and seasons). Consequently, although clearly the conditional probability of an outbreak given the prevalence of at least one virus will increase with time after OPV cessation, the time at which immunity decreases to below the threshold in a given population remains challenging to predict.

We make the simplifying assumption that this conditional probability increases at a much slower rate than the exponential decay of the virus prevalence, which implies that the first term on the right hand side dominates. Given this assumption, we approximate the resulting decline in the overall risk by an exponential decay, distinct from the virus prevalence decay, with a decay parameter k, where k represents the aggregate effect of the two competing trends. Consequently, the following generic formula represents our characterization of the Poisson rate of occurrence of cVDPV outbreaks in low and middle-income countries, with the inputs shown in the lower section of Table 7:

$$\lambda_{\text{cVDPV}} = \{\lambda_{\text{without SIAs}}+(\lambda_{\text{with SIAs}}-\lambda_{\text{without SIAs}})\times 1_{\text{MPI}}\}\times \pi_{\text{income}}\times \text{Exp}[k\times(1-1_{\text{OPV}})\times y]$$

where
- $\lambda_{\text{with SIAs}}$ = the initial average annual frequency of cVDPV outbreaks per 100 million people on a background OPV with SIAs in low and lower-middle income countries,
- $\lambda_{\text{without SIAs}}$ = the initial average annual frequency of cVDPV outbreaks per 100 million people on a background without SIAs in low and lower-middle income countries,
- π_{income} = the relative initial frequency of cVDPV outbreaks compared to low and lower-middle income countries,
- k = the constant of the exponential decay of the rate of occurrence (equals -Ln(0.5)/*half-life* and depends on the scenarios),
- 1_{MPI} = 1 with maximum population immunity at T_0 or 0 otherwise,
- 1_{OPV} = 1 for policies involving OPV and 0 otherwise, and
- y = the year after T_0.

To capture the impact of the population immunity at T_0, we assume for the RPI scenario that the initial Poisson rate equals the average frequency of cVDPV outbreaks on a background of OPV without SIAs, while for the MPI scenario we assume that it equals the average frequency of cVDPV outbreaks on a background of OPV with SIAs. For a policy of continued OPV without SIAs, but with maximum population immunity at T_0, we linearly increase the Poisson rate to the $\lambda_{\text{without SIAs}}$ level over N years, where N=3 at the base case:

$$\lambda_{\text{cVDPV}} = \begin{cases} [\lambda_{\text{with SIAs}} + (\lambda_{\text{without SIAs}} - \lambda_{\text{with SIAs}}) \times y / N] \times \pi_{\text{income}}, & \text{if } y \le N \\ \lambda_{\text{without SIAs}} \times \pi_{\text{income}}, & \text{if } y > N \end{cases}$$

where N = number of years to reach $\lambda_{\text{without SIAs}}$ level after stopping SIAs.

We assume that the decay of the cVDPV risk in IPV-using countries occurs twice as fast as in countries that stopped polio vaccinations altogether. We assume that high-income countries switched to IPV 10 years before T_0 and consequently they face negligible, constant risk of cVDPVs (i.e., Poisson rate of 1 per million per year), with only cVDPV importations from any OPV-using countries or escape of OPV-derived viruses from laboratories possibly leading to cVDPV outbreaks.

Figures 2 and 3 show the cVDPV outbreak rates over time for each policy and income level based on only the confirmed cVDPVs and on the combined cVDPVs and aVDPVs during 1999-2004 as listed in Table 4, respectively. The inclusion of the aVDPVs as potential signals of cVDPV risk leads to an increase in the values of $\lambda_{\text{without SIAs}}$ and $\lambda_{\text{with SIAs}}$, but the shapes of the functions remain equal for both cases (note the different scales used in the figures.) If OPV were to continue, the rate of occurrence remains constant over time and equal for both income levels, with probably a higher risk in the absence of SIAs than with continued SIAs. If OPV immunization ceases, the rate starts at the average yearly number of outbreaks per 100 million people on an OPV background with or without SIAs, depending on the population immunity at T_0 (RPI or MPI) and then declines quickly to less than 0.0001 outbreaks per year per 100 million people within 5 years in all income levels. The decline occurs most rapidly with a switch to IPV in upper-middle income countries (corresponding to the shortest half life) and most slowly with cessation of all polio vaccinations in low-income countries (longest half life). The number of documented cVDPV and aVDPV events during 1999-2004 does not differ much for low and lower-middle income countries (Table 4). Consequently, $\lambda_{\text{without SIAs}}$ and $\lambda_{\text{with SIAs}}$ reflect the initial rates in either of the two lowest income levels. Thus, $\pi_{\text{income}} = 1$ for both low and lower-middle income countries and therefore the figures for those two income levels differ only in the speed of decay after OPV cessation. In contrast, we assume $\pi_{\text{income}} = 0.1$ for upper-middle income countries implying a 10-fold lower initial risk compared to low and lower-middle income countries.

This simple approach does not incorporate several important factors that influence the risk of cVDPV outbreaks. First, the conditions in Cuba that motivate our assumption that the rapidly declining prevalence of OPV viruses dominates the risk reflect a lower-middle income country with very good population immunity and sanitation. Extrapolation of these results to settings of lower hygiene and/or population immunity requires caution.[68, 75] The observed decline in detection of OPV viruses corresponds to a situation of OPV cessation immediately after a mass immunization campaign to boost population immunity. From a global perspective, a comparable, optimal level of population immunity would occur only if all currently OPV-using countries discontinue routine OPV use after a final globally synchronized immunization day just prior to cessation. No experience exists with countries that stop OPV use in an environment of sub-optimal population immunity and poor hygiene, and the decline in virus prevalence in those settings may occur much more slowly than in Cuba.

Second, coordinated cessation represents a crucial factor. If some countries discontinue OPV while other countries (especially neighbors) continue to use OPV, the former provide an ideal opportunity for the emergence of cVDPVs. Evidence of frequent OPV virus importation in non-OPV-using countries exists now, with researchers in high-income countries regularly isolating OPV viruses through various surveillance systems.[73, 76] We assume for purposes of our risk estimates that cessation occurs in a coordinated fashion. In the event of uncoordinated

cessation, countries that stop OPV may effectively face an increased risk instead of experiencing a decreased risk.

Finally, responding to poliomyelitis outbreaks with mOPV or trivalent OPV after cessation of routine OPV vaccination and SIAs represents an important opportunity for emergence of cVDPVs since any area not covered by a response would face a risk of importing vaccine strains used in response to the outbreak. While this risk decreases as a function of the intensity of contact with the outbreak population, reduced population immunity (after OPV cessation) implies that OPV strains used in the response could, with some probability, reestablish circulation and create cVDPVs, although we currently lack evidence to quantify this risk.

The probability of iVDPV-related outbreaks

Inventory of confirmed and suspected iVDPVs

Two recent investigations of the likelihood of long-term excretion in individuals with primary immunodeficiencies (PIDs) found no long-term excretors among 384 persons with PIDs (344 with IgG deficiencies, 40 with IgA deficiencies) in Italy,[77] the US, Brazil, Mexico, and the UK.[78] Both studies concluded that long-term excretion appears rare, and Halsey et al. (2004) reported a 95% confidence interval upper bound of 1.0% for the probability of observing 0 iVDPV excretors among 306 persons with IgG deficiencies.[78] With the prevalence of individuals with PIDs who could potentially excrete long-term roughly estimated at 1:100,000 in high and upper-middle income countries,[78] this translates into an upper bound for the prevalence of iVDPV excretors in those countries of 140 (i.e., 1.4 billion people × 1/100,000 × 0.01). Estimating the number of PIDs in developing countries remains a challenge,[78, 79] but we expect much smaller numbers (despite larger and younger populations in developing countries) because of the shorter survival of individuals with PIDs. Although HIV currently represents the most prevalent form of immunodeficiency, particularly in developing countries, no known iVDPV excretors exist among HIV-infected persons and the risk of prolonged excretion appears low.[80]

Table 7 lists iVDPVs detected to date.[24, 53, 58, 59, 80-94] Our definition of an outbreak as at least 1 case of paralytic poliomyelitis suggests that we should count as an outbreak any iVDPV viruses that spread to the community and cause at least 1 paralytic case. In this context, iVDPV excretors who developed paralytic poliomyelitis themselves do not represent outbreaks given their original infection with Sabin-like viruses (i.e., not with a VDPV virus). To date, investigators detected or investigated no spread beyond the immunodeficient patients in Table 7,[95] and consequently while the evidence provides some information about the prevalence of iVDPV excretors, it offers no information about the likelihood of outbreaks associated with iVDPVs.

A limited number of iVDPV excretors continued to shed virus for well over 5 years while most excretors stopped excreting or died within at most four years of the associated OPV infection. In the context of OPV cessation, the former category carries the greatest risk as they could reseed VDPVs in a population with much reduced population immunity. However, this type of excretor appears to survive only in high- and possibly upper-middle income countries. The latter category occurs also in countries of lower income, but would only represent a threat during the OPV cessation transition period while population immunity remains fairly high. Based on the distinction of extended excretion potential, rather than an immunological argument, we define for our analysis the following two types of iVDPV excretors:

- Prolonged excretors: individuals excreting VDPVs at least 6 months but no longer than 5 years after the associated OPV infection
- Chronic excretors: individuals excreting VDPVs at least 5 years after the associated OPV infection

During 43 years of widespread OPV use (1962-2004), investigators detected 4 chronic excretors, 13 prolonged excretors (including 3 with uncharacterized viruses), and 2 prolonged excretors with the potential to become chronic excretors (Table 7). We also include in our analysis 3 virus isolates from the environment that strongly suggest the presence of a chronic excretor. In addition, we list 4 iVDPVs with more than 1% VP1 divergence from the original OPV strain associated with immunodeficient patients who excreted for less than 6 months, but we exclude these from further analysis given their short durations of excretion. In estimating the duration of iVDPV excretion, we exclude the first 6 months of excretion, because we consider viruses excreted during that period as similar to OPV viruses that immunocompetent persons excrete after OPV infections. Thus, for vaccinated iVDPV excretors, we assume that the total duration of excretion equals the time from the associated OPV infection until the last positive sample minus 6 months, unless evidence suggests a different duration of excretion. For unvaccinated iVDPV excretors and environmental iVDPV isolates, we estimate the duration of excretion from the divergence of the virus to the original OPV strain and assume a rate of 1% (range 0.9-1.3) nucleotide divergence in the VP1 region per year.[96] This amounts to an average duration of excretion of approximately 12 years for chronic excretors and 1.8 years for prolonged excretors.

The sum of all duration estimates in Table 7 suggests 111 person-years of iVDPVs excretion (i.e., not including the first 6 months of virus excretion). If the probability of an iVDPV outbreak in any year where an iVDPV excretor exists follows a Bernoulli distribution with parameter p,[23] then the upper bound of the 95% confidence interval for p for observing 0 successes in 111 samples equals 0.027, based on the Binomial(111, p) distribution.[97] Thus, a reasonable estimate of the average probability of an iVDPV outbreak during a year in the presence of an iVDPV excretor in the context of an OPV background and a developed country should not exceed the upper bound, although this conditional probability may differ for lower income settings.

Dependence on time and scenarios

While the individual risk of becoming an iVDPV excretor proved extremely low, even in the presence of massive, global OPV use, the population risk of iVDPV-related outbreaks may change after T_0 for several reasons. Among the available immunization policies, OPV routine immunization leads to the highest prevalence of iVDPV excretors, but high population immunity may reduce the impact and occurrence of iVDPV-related outbreaks and continue to do so if OPV use continues. With cessation of OPV use, we anticipate that the prevalence of iVDPVs will approach 0 within several years, depending on the duration of excretion and the survival of iVDPV excretors, which appears lowest in low-income settings.[79] However, OPV cessation will limit the ability of the surrounding community to stop transmission of viruses excreted by an iVDPV excretor. Therefore, the risk of iVDPV-related outbreaks in those instances may initially increase over time. Nevertheless, in high-income countries that switched from OPV to IPV, no documented cases of paralytic poliomyelitis in the general population occurred in association with iVDPVs. We emphasize that all of the known chronic excretors occurred in developed countries (i.e., 4 in high-income countries, with an additional 3 possible iVDPV excretors

detected through environmental surveillance in upper-middle or high-income countries), and it remains unclear whether the increased risk due to a higher transmissibility of polioviruses in low-hygiene settings outweighs the decreased risk due to a shorter survival of immunodeficient people in those settings.

A theoretical, deterministic condition prescribes that the initial *net reproductive number* (R_n, defined as the average number of secondary infections that an infectious person causes) must exceed 1 for a single virus introduction to cause an outbreak (i.e., if each new infection leads to only <1 new infections on average the outbreak will die out, but if each leads to >1 new infections on average the outbreak can take off). Given the proportion of susceptibles (s) in a population and the *basic reproductive number* (R_0, defined as the average number of secondary infections that an initial infection causes in a entirely susceptible population), the net reproductive number satisfies the equation $R_n=R_0/s$.[74] If we assume that R_0 behaves as a random variable, then we can estimate the theoretical probability of an outbreak per secondary iVDPV infection as a function of s as follows:

P(outbreak in income level i|1 virus introduction) = 1- $P_i(R_0 \leq 1/s)$

where P_i = the income-level specific probability distribution for R_0. Unfortunately, this probability depends heavily on the choice of the probability distribution. For example, if the median value of R_0 falls far from the threshold of $1/s$ (e.g., a median R_0 of 9 or less in a population where s = 10%), the spread in the probability distribution of R_0 dominates the resulting conditional outbreak probability. Estimating risk ratios with different values of s based on this theoretical threshold remains challenging given substantial variability and uncertainty in R_0.

With a median $R_0 > 10$ and $s > 10\%$, values not uncommon for wild polioviruses in low-income settings,[98, 99] the outbreak probability exceeds 0.5 regardless of the variance of R_0. The lack of observed iVDPV-related outbreaks despite the theoretically high probability in those settings may reflect the absence of iVDPV excretors due to the low survival rate of people with PIDs in developing countries. In addition, we remain uncertain about the R_0 for iVDPVs. Consequently, it remains difficult to find a functional relationship between population immunity and the conditional probability of iVDPV-related outbreaks given the presence of an iVDPV excretor.

Risk management strategies, such as identification and education of immunodeficient excretors and/or immunization of their contacts, may further reduce the risk of iVDPV-related outbreaks by reducing the number of secondary infections from an iVDPV excretor and increasing the immunity barrier provided by the immediate surroundings. Although attempts to use existing antivirals for one known chronic excretor failed,[83] new technology involving treatment of iVDPVs with an antiviral may become available at some point, which could reduce the viral output of iVDPV excretors and thus the risk of iVDPV excretors causing an outbreak. However, this would require substantial investment in the development of such an antiviral, and given that antivirals can only reduce excretion for identified excretors we remain uncertain about its overall effectiveness and whether society will make this investment.

Quantification of probability of outbreaks due to iVDPVs

In this subsection, we estimate the annual Poisson rate of occurrence of outbreaks due to iVDPVs per 100 million people. The very small rate under any scenario approximates the probability of an outbreak due to an iVDPV in a year per 100 million people and it equals the probability of the presence of (at least) one iVDPV excretor times the conditional probability of

an outbreak in one year given the presence of an iVDPV excretor. We assume that the prevalence equals the probability of at least one iVDPV excretor (mathematically justified given the very low prevalence of iVDPV excretors per 100 million people). We base our estimates of the prevalence of prolonged and chronic excretors on the data in Table 7. Given that the lack of any positive sewage sample following the single isolate from sewage in Estonia,[85] this virus likely originated from a visitor, presumably from a high-income country. While uncertainty remains about the origin, we classify this event as evidence of an otherwise unidentified high-income chronic iVDPV excretor. We estimate the prevalence as the product of the incidence of first OPV infections, which we define as the annual number of successful vaccinations and secondary immunizations of fully susceptible persons, the rates of iVDPV excretors per first infection and the mean duration of excretion beyond the first 6 months after the last OPV infection. With steady state-routine OPV immunization, the prevalence $Prev_{iVDPV}$ per 100 million people as a function of income level equals:

$Prev_{\text{iVDPV}} = b \times (d_{\text{prolonged}} \times r_{\text{prolonged}} + d_{\text{chronic}} \times r_{\text{chronic}})$

where b = the income-level-dependent average birth rate (≈ birth cohort as a proportion of total population),
$r_{\text{prolonged}}$ = the rate of prolonged iVDPVs excretors as a function of income level,
$d_{\text{prolonged}}$ = the mean duration of excretion of prolonged excretors beyond the first 6 months after the associated OPV infection, in years and as a function of income level,
r_{chronic} = the rate of chronic iVDPVs excretors as a function of income level, and
d_{chronic} = the mean duration of excretion of chronic excretors beyond the first 6 months after the associated OPV infection, in years and as a function of income level.

These formulae assume that in the presence of routine OPV immunization and absence of wild poliovirus transmission the entire birth cohort eventually acquires an OPV infection due to vaccination or secondary OPV spread, regardless of income level or immunization coverage. In reality, less than 100% may seroconvert, especially in low-income countries that stop SIAs. Therefore, this formula may slightly overestimate the prevalence of iVDPV excretors in some countries. However, we assume that in the end this cancels out against the reduced probability of outbreaks that result from better population immunity from a higher effective take rate. This implies equal probabilities of iVDPV outbreaks for all OPV-using countries, regardless of SIA policy.

Table 8 displays our best estimates of the inputs in the above formula. We obtain the value of the rates of iVDPV excretors ($r_{\text{prolonged}}$ and r_{chronic}) by dividing the number of documented iVDPV excretors by the total number of OPV recipients or people immunized secondarily prior to receiving IPV or contracting a wild poliovirus infection during approximately 40 years of widespread OPV use. For high and upper-middle income countries we roughly estimate this at 450 and 250 million people, respectively, representing half of the current population in those countries.[21, 22] For low and lower-middle income countries, we estimate this at 1.5 billion people, corresponding to the current number of people aged less than 15 years, given that widespread OPV use started approximately 15 years ago in these countries. Thus, using the numbers of iVDPVs from Table 7, we estimate $r_{\text{prolonged}} = 12/4.5 \sim 2.7$ and $r_{\text{chronic}} = 6/4.5 \sim 1.3$ excretors per 100 million first OPV infections in high-income countries, $r_{\text{prolonged}} = r_{\text{chronic}} = 1/2.5 \sim 0.4$ in upper-middle income countries and $r_{\text{prolonged}} = 2/15 \sim 0.1$ and $r_{\text{chronic}} = 0$ in low and lower-middle income countries. In the absence of documented prolonged excretors in

low-income countries, we artificially set their average duration of excretion at 0.5 years to reflect the shorter survival of persons with PIDs in those countries.

The prevalence formula results in estimates for $Prev_{iVDPV}$ of 0.002, 0.004, 0.190, and 0.236 per 100 million people for low, lower-middle, upper-middle, and high income countries, respectively, using average birth rates in 2001 (which inversely correlate with income; the difference between upper-middle and high-income countries is a results from the higher birth rates in upper-middle income countries in 2001).[21, 22] Multiplying by the total populations (year 2001) in each income level in multiples of 100 million, this translates into aggregate *status quo* prevalence of iVDPV excretors of 0.05, 0.09, 0.95, and 2.18 for low, lower-middle, upper-middle, and high-income countries, respectively.

In a scenario involving OPV cessation, we assume the prevalence follows an exponential decay at a rate of 1 over the average duration of excretion per year (i.e., *initial rate* × Exp(-y/d), where y = the year after cessation and d = the average duration of excretion).

Due to the lack of any observed outbreaks caused by an iVDPV, the very low prevalence of iVDPV excretors, and the limitations in using theoretical thresholds, we estimate the very small annual probability of iVDPV outbreaks given the presence of an iVDPV excretor during the *status quo* ($P_{outbreak|iVDPV}$; 0.001 on average, but multiplication by the relative risk for the income level implies a maximum risk of 0.008 in low-income countries with continued OPV) in the context of limited information. We assume that iVDPV excretors effectively immunize their close contacts prior to excreting highly-diverged viruses, and this substantially reduces the risk that iVDPV excretors initiate outbreaks. Furthermore, we assume that iVDPV excretors typically lack pharyngeal excretion and survive only in relatively good hygiene settings with limited fecal-oral spread, and consequently the conditional probability of outbreaks given iVDPV excretion remains lower than this probability for wild virus introductions (see below). Table 8 also provides estimates for the relative risk 20 years after T_0 compared to T_0, and we use simple linear interpolation to express this probability as a function of time although we recognize the limited evidence and significant uncertainties. In the event of OPV cessation, we assume a relative risk after 20 years compared to T_0 such that the probability of an outbreak given iVDPV excretion equals 0.08 after 20 years in low-income countries stopping polio vaccinations altogether (Table 8).

To obtain the time-dependent Poisson rates we multiply the prevalence of iVDPV excretors by the annual probability of an outbreak given a single iVDPV excretor such that the annual rate of occurrence of iVDPV-related outbreaks (λ_{iVDPV}) per 100 million people in low, lower-middle, and upper-middle income countries equals:

$$\lambda_{iVDPV} = [(rr_{20} - 1)\times y/20 + 1]\times P_{outbreak|iVDPV}\times rr_{p|income}\times b\times\{r_{prolonged}\times d_{prolonged}\times \text{Exp}[-y\times(1-1_{OPV})/d_{prolonged}] + r_{chronic}\times d_{chronic}\times\text{Exp}[-y\times(1-1_{OPV})/d_{chronic}]\}$$

where,
- 1_{OPV} = 1 for policies involving routine OPV use and 0 otherwise,
- $P_{outbreak|iVDPV}$ = the baseline yearly probability of an outbreak given the presence of a single excretor,
- $rr_{p|income}$ = the relative risk of $P_{outbreak|iVDPV}$ for a given income level compared to the baseline probability,
- rr_{20} = the relative risk 20 years after T_0 as a function of the routine immunization policy (i.e., OPV, IPV, or stop), and
- y = the year after T_0.

Consistent with our assumption that high-income countries switched to IPV 10 years prior to T_0 (on average), the formula for the rate of occurrence of iVDPV outbreaks in high-income countries equals:

$$\lambda_{iVDPV} = \begin{cases} [(rr_{20}-1)\times(y+10)/20+1]\times P_{outbreak|iVDPV}\times rr_{p|income}\times b\times\{r_{prolonged}\times d_{prolonged}\times \\ \text{Exp}[-(y+10)/d_{prolonged}]+r_{chronic}\times d_{chronic}\times\text{Exp}[-(y+10)/d_{chronic}]\}, & \text{if } y\leq 10 \\ rr_{20}\times P_{outbreak|iVDPV}\times rr_{p|income}\times b\times\{r_{prolonged}\times d_{prolonged}\times \\ \text{Exp}[-(y+10)/d_{prolonged}]+r_{chronic}\times d_{chronic}\times\text{Exp}[-(y+10)/d_{chronic}]\}, & \text{if } y>10 \end{cases}$$

Figure 4 shows the breakdown of the outbreak rates by prolonged and chronic excretors by income level. The total rates (i.e., λ_{iVDPV}) equal the sum of the curves for prolonged on chronic excretors of the respective scenarios. Due to the lack of chronic excretors in low and lower-middle income countries, we expect very low Poisson rates despite the increasing conditional probability of an outbreak given an iVDPV as time since OPV cessation elapses. However, the existence of chronic excretors in upper-middle income countries suggests that these countries face the highest risk of iVDPV-related outbreaks, although if they switch to IPV this risk would decrease more rapidly. The longest average duration of excretion may occur in high-income countries. However these countries experience the lowest conditional probability of an outbreak given an excretor, due to good sanitation (low R_0) and population immunity, and lower prevalence of iVDPV excretors than upper-middle income countries, due to the cessation of OPV use dating back 10 years prior to T_0 (which reduced the introduction of new iVDPV excretors into the population).

We emphasize that our base case analysis includes 3 possible chronic iVDPV excretors detected through environmental surveillance and no other evidence exists for the possibility of chronic excretors in upper-middle income countries. The interpretation of these environmental iVDPVs drives the risk in these countries. A current investigation in Slovakia may succeed in finding the individual associated with the detected virus, but further research concerning these cases remains very important to fully understanding their implications.

Uncertainty about the true number of iVDPVs

While our base case analysis accounts only for those iVDPV excretors detected to date, important uncertainty exists regarding the true number of iVDPV excretors. In this subsection, we address the uncertainty about the number iVDPV excretors (without distinguishing chronic and prolonged excretors) and present an estimate for the true number of iVDPVs based on very limited prior knowledge using Bayes' theorem.[100] As future research regarding iVDPVs becomes available, this approach allows updating the estimates to reflect the reduced uncertainty. Table 7 reveals that individuals with PIDs both with and without paralysis can become iVDPV excretors. Systematic clinical surveillance (i.e., AFP or passive poliomyelitis surveillance) can detect iVDPV excretors who developed paralysis through analysis of viruses and follow-up of paralytic patients with PIDs. Although clinical surveillance probably does not detect paralytic iVDPV excretors with 100% sensitivity, the primary uncertainty remains the true number of iVDPV excretors without paralysis. Limited screening of persons with PIDs exists to detect any iVDPV excretors without paralysis, and consequently we do not know how many people with PIDs commonly get investigated for long-term poliovirus excretion.

We use Bayesian updating[100] to combine our uncertainty about the investigated number of persons with PIDs and the results of prior studies that provided a denominator (i.e., 384 persons with IgG deficiencies)[77, 78] to obtain a distribution for the true number of iVDPV excretors. We focus on upper-middle and high-income countries because of the greater survival

of PIDs in those countries. We define θ as the probability that a person with a PID currently excretes an iVDPV. We rely on estimates of $M = 4$ iVDPV excretors without paralysis that we know currently excrete (Table 7; includes environmental isolates) and estimates of the prevalence of individuals with PIDs (excluding IgA deficiencies) of roughly 1 per 100,000 in developed countries,[78] or 14,000 in upper-middle and high-income countries, to get the prior distribution for θ. Thus, we know that the number of investigated persons with PIDs must lie between 4 and 14,000, and lacking further knowledge we assume equal likelihood for values within that range (i.e., prior distribution for θ = Uniform(k_1,k_2), with k_1=M/14,000 and k_2=1). We use a Binomial(n, θ) distribution to represent the number of iVDPVs (y) in a sample of size n given θ. Using Bayes theorem, we derive the following posterior distribution for θ given the observation of y=0 iVDPVs among n persons with PIDs:

$$P(\theta|y=0,n) = (1-\theta)^n \times (n+1)/[(1-k_1)^{n+1}-(1-k_2)^{n+1}]$$

Using the observation of 0 iVDPV excretors among 384 persons with PIDs, we estimate a mean of this distribution of 0.0029. This translates into an estimate for the prevalence of 40 iVDPV excretors without paralysis with a 95th percentile of 112.

THE RISK OF OUTBREAKS DUE TO WILD POLIOVIRUSES

The risk of outbreaks due to wild polioviruses represents the most uncertain risk category. However, we know wild polioviruses could reemerge through several pathways and that this risk may dominate as the risks associated with OPV use disappear, and therefore we cannot ignore this risk. While we provide our current best estimates for these risks, the reader must recognize that they rely on very limited or no data, often involve judgment and that characterizing the risks and uncertainty better requires further research or could benefit from formal expert judgment elicitation. We consider 2 types of events that could lead to wild poliovirus outbreaks after T_0:

- An unintentional breach in containment of wild poliovirus stocks in a laboratory or in an IPV-manufacturing facility, and
- An intentional release of wild poliovirus through an act of bioterrorism.

Unintentional breach in containment of poliovirus stocks

Containment breaches in the past

Limited reports suggest that reintroduction of wild poliovirus from an unintentional breach in containment poses the risk of greatest concern for reemerging wild poliovirus after eradication.[4, 19, 101, 102] While direct transmission from a laboratory to the environment remains theoretically possible (e.g., through sewage), high levels of population immunity probably concealed any such historical laboratory escapes, which make it difficult to assess the historic frequency of these events.[102] Escapes via infection of laboratory workers provide some evidence about a breach in containment for this pathway. The WHO reports 12 known cases of poliomyelitis between 1941 and 1976 associated with virus use in laboratories infecting laboratory workers, which occurred predominantly in the pre-vaccine era and included 2 cases that led to death.[102] In addition, researchers isolated a wild poliovirus in two separate events in the Netherlands; one strain from the son of a worker in an IPV manufacturing facility accidentally exposed to a prototype virus strain, and one from a child exposed to another reference strain from an unknown origin.[103] These events demonstrate the potential for unintentional virus release into a population through asymptomatic infection of laboratory workers.[4] More recently, investigators isolated viruses closely related to a laboratory reference

strain of type 2 wild poliovirus (MEF-1) in India,[104] including from 3 AFP cases in 2000, 5 in 2002, and 2 in 2003 (years that followed the global elimination of the naturally occurring type 2 wild polioviruses). Finally, the fact that the last case of smallpox occurred after a laboratory release of virus in the UK underscores the importance of managing this risk after eradication of a disease.[102]

Dependence on the scenario and time

The probability of an outbreak due to a wild poliovirus containment breach depends on the amount of virus stocks (i.e., the number IPV production sites or laboratories that continue to keep wild polioviruses after T_0), the probability of virus release from such places, and the likelihood that a release actually leads to an outbreak. WHO published a global action plan for laboratory containment aimed at reducing the first two risks.[102] An extensive, country-based survey now underway will identify laboratories that contain either wild poliovirus infectious materials or potential wild poliovirus infectious materials. One year after the last documented isolation of wild poliovirus, these laboratories must either: (1) render materials non-infectious or destroy them, (2) transfer materials to laboratories with sufficient biosafety standards, or (3) implement sufficient biosafety standards. Successful containment efforts in a post-OPV era minimize the amount of (potentially) poliovirus infectious materials, the exposure of laboratory workers or the community to laboratory polioviruses, and the susceptibility of laboratory workers to poliovirus infection (through OPV or IPV vaccination).[105]

Although implementation of containment guidelines substantially reduces the risks of unintentional release of poliovirus, countries that do not maintain high-quality biosafety after T_0 will experience a relatively higher risk of an outbreak. Thus, a country's decision to enforce long-term laboratory containment substantially reduces the risk of an unintentional wild poliovirus release.

We expect that developed countries will continue to maintain the highest numbers of laboratories containing (potentially) wild poliovirus infectious materials but maintain the most rigorous containment. While these countries currently also produce the entire global IPV supply,[106] low or middle-income countries may elect to produce their own IPV for economic reasons if they switch to IPV. The greater likelihood of outbreaks in these countries, given the generally higher transmissibility of polioviruses and uncertainty about the protection from IPV against infections, suggests an increased risk. This risk motivates some discussion on the feasibility of making IPV from Sabin strains rather than wild virus strains.[6]

The likelihood that a release of wild virus leads to an outbreak correlates inversely with R_0 and the population immunity where the release occurs. As discussed above, population immunity depends on the vaccination policy, with increasing time since stopping OPV use and lower income level both implying lower population immunity.

Intentional Release

With the anthrax attacks in the US in the fall of 2001 demonstrating the reality of bioterrorism and leading to significant concerns about the potential use of smallpox as a bioweapon, clearly any discussion of future risks must consider the possibility of intentional releases of poliovirus. Some proponents of aggressive biodefense lean toward the assumption that society should act as if intentional reintroduction of an eradicated disease will occur with certainty (i.e., with probability 1, although no time period specified), while others argue that the risks remain so remote that they approach 0. In reality, the best estimate of the risk lies

somewhere in between, and the uncertainty around the best estimate also represents a narrower range.

In the context of this analysis, we consider the possibility and probability of intentional reintroduction to characterize the risk of an outbreak. If a reintroduction occurs but dies out, then this would not necessarily represent a significant event from a burden of disease perspective, although it could represent a significant event from a national defense perspective. If an intentional release leads to widespread dissemination of poliovirus, then this could lead to extensive undetected circulation resulting in multiple outbreaks necessitating a massive vaccination response. We recognize that the mechanism of intentional introduction could significantly influence the consequences, and we suggest that sensitivity analyses should consider multiple scenarios.

Although the level of concern about bioterrorism appears greater in high-income countries, an intentional release of poliovirus in a country that stopped vaccination may logically lead to a larger impact than the same release in a country that continues either OPV or IPV because of the greater probability of causing paralytic cases. The trend of this risk over time remains very uncertain, driven by important cultural and political factors. Similar to the other risks involving a release of virus, the conditional probability of an outbreak given a release increases as population immunity decreases (i.e., with increased time since the end of vaccination). Given uncertainty and lack of data about this risk, we rely on judgment and focus on presenting bounding estimates of the risks and on characterizing their potential dependence on the vaccination policy, such that they increase as population immunity decreases in countries that stop vaccination.

Quantification of wild poliovirus outbreak risks

As with the risk of iVDPV-related outbreaks, we estimate the Poisson rates for wild poliovirus outbreaks as the product of the probability of a virus release and the probability of an outbreak given a single release. Although we recognized many dependencies of the frequency of wild poliovirus outbreaks, we focused on the most significant influences on our already very uncertain base case estimates. Table 9 displays the inputs we use to estimate the risk function for wild poliovirus outbreaks. The risk function follows from adding the 3 possible types of releases (laboratory, IPV production site, or intentional) and multiplying by the appropriate income level dependent conditional probability of an outbreak given a release. We assume that the conditional probability functions remain linear over time, similar to those we used for iVDPV-related outbreaks.

We estimate the frequency of virus releases from a laboratory at 1 per 1,000 years per 100 million people in high and upper-middle income countries. However, we assume a 5-fold increase in risk for countries that do not enforce containment guidelines. Given the likelihood of a much lower prevalence of laboratories containing polioviruses in low and lower-middle income countries, we estimate a 10-fold lower frequency of releases of 1 per 10,000 years per 100 million people in those countries. In aggregate (using average world population 2009-2028 by income level), this amounts to approximately 0.5 releases globally over 20 years (given enforced containment), with approximately 3-fold higher frequency in the two highest income levels.

Given the current use of wild polioviruses in IPV production, we assume much higher risks for release from an IPV manufacturing site (i.e., for countries that domestically produce IPV). We assume that high and upper-middle income countries will probably produce IPV domestically if their routine immunization policy involves IPV, and we estimate a 10-fold higher risk of virus release from IPV production sites than from laboratories, or 1 release per 100 years

per 100 million people (given enforced containment). In contrast, we assume that low and lower-middle income countries probably will not produce their own IPV, and consequently we assume a frequency of only 1 release per 1,000 years per 100 million people (this assumes that a small, but nonzero chance exists that these countries might produce OPV domestically). For universal IPV use, this translates into approximately 4 IPV production site releases globally over the entire 20-year period, assuming a linear relationship between the frequency of releases and the magnitude of the IPV-covered population. If a country does not use IPV for routine immunization, we assume a very low frequency (i.e., 10^{-6}) of releases, perhaps attributed to the remote possibility of maintained IPV production capacity for outbreak response. We suggest future sensitivity analyses explore a range of effectiveness of containment for IPV production sites and for laboratories.

We estimate the frequency of attempts at intentional releases for all countries as equal to virus escapes from laboratories (with enforced containment) in developing countries if the policy involves OPV cessation. If not, we estimate a 10-fold lower frequency, based on an assumption of less attractiveness of polioviruses as a bioweapon. Given the absence of historical data and the inherent uncertainty in predicting the future geopolitical situation, we emphasize the need to vary this frequency over a wide range (see Table 9).

We multiply the frequency of releases by a conditional probability of an outbreak given a release of at most 0.05 (in low-income countries), and as a result the Poisson rates reflecting the wild poliovirus outbreak risks all remain very small. Figure 5 shows the outbreak rates over time for each scenario. The aggregated rates lead to a global expected number of wild poliovirus outbreaks from any source during 20 years after T_0 between approximately 0.02 (continued OPV without SIAs) and 1.1 (switch to IPV without enforcing containment). Although small compared to the initial VDPV risks, in the event of OPV cessation wild poliovirus outbreaks may represent the most important risk in the longer term. The risk of an intentional release remains the most difficult to model.

DISCUSSION

This analysis provides the first comprehensive quantitative synthesis of the existing data related to the risks of poliomyelitis after wild poliovirus eradication. These estimates provide a starting point for analyses of the trade-offs between the risks, costs, and benefits of different policy choices. We anticipate that this effort will stimulate discussions and iterations of the estimates, and we hope that future studies will further develop these initial estimates and update them as conditions change and knowledge evolves. We emphasize that our approach relies on using simple functions to represent complicated concepts that in reality depend on many factors and that these assumptions may suffice for some analyses, even if they prove insufficient for others.

We recognize that many uncertainties exist about the future of poliomyelitis and poliomyelitis risk management and we believe that global, national, and regional policy makers face significant challenges. Most importantly, they must decide how to coordinate the transition to future immunization policies. These planned discussions should occur soon to allow sufficient opportunity for planning and implementation. Our estimates of the cVDPV outbreak risk soon after OPV cessation dominate in most scenarios, even with our assumption of coordinated cessation. If coordination efforts fail, we expect that the cessation of polio vaccinations would unnecessarily increase the risk. On the other hand, failure to stop OPV vaccinations virtually guarantees increasing numbers of cVDPV outbreaks as SIA activities wane. We further find it

imperative that decision makers continue to plan and begin implementation of processes to develop a vaccine stockpile and to prepare for the likely possibility of an outbreak after OPV cessation. Clearly, future studies should recognize the existence of potential risks and assess costs related to developing, maintaining, and using a polio vaccine stockpile. We emphasize that responding to an outbreak with either OPV or mOPV also represents a potential for generating vaccine-derived polioviruses, and policy makers must factor this into the discussions and decisions as they evaluate and develop the much-needed post-eradication response plan(s). Although discussing the magnitude of outbreaks lies beyond the scope of this paper, we emphasize that a late response implies an important risk of large numbers of paralytic poliomyelitis cases.[12, 16, 107] Obviously, the number of expected cases in the event of an outbreak differs depending on the policies and income level and increases as time since cessation elapses.

Given the reality of the risks discussed in this paper, we emphasize that efforts to minimize and manage the risks must not promise zero risk or create an expectation that no outbreaks can occur after eradication. Instead, the world must prepare for the post-eradication transition and commit to sustained eradication and containment, which may require redefining the goal after interruption of wild poliovirus transmission as continued absence of sustained circulation of polioviruses (including VDPVs). In this context, any outbreak that occurs, particularly during the process of OPV cessation, does not undermine or undo the achievement of global eradication, and this analysis suggests that policy makers should assume some nonzero chance of at least one outbreak during the transition period and prepare for it.

This paper does not deal with other potentially important risks, including the financial risks that may impair the ability to actually implement a preferred policy option, in particular the costly option of vaccinating with IPV indefinitely.[108] Clearly countries must continue to weigh the risks of VAPP and VDPVs associated with the use of OPV, and the costs associated with any options they choose.

We highlight several limitations of our analysis by emphasizing that some of our key assumptions significantly oversimplify the complex reality. For example, our characterization of risk per 100 million people represents a simplification of the real world in which viruses spread from one population to another with no recognition of boundaries. This means that an outbreak in one population represents an increased risk of an outbreak in all other populations, although we did not explicitly characterize exportation or the dependencies that arise. Stratification by income level represents an important simplification of the true variability among countries. For example, while the validity of our assumption that high-income countries will have switched to IPV 10 years prior to T_0 appears valid on average, the aVDPV event in Taiwan demonstrates the possibility that some high-income countries may continue using OPV up to T_0 and consequently face a higher risk of iVDPVs than countries that switched to IPV earlier.

Also, our framework that models policies over a 20-year time horizon may not represent the preference of countries and may not cover the possible future options that may emerge (e.g., the use of antivirals to reduce iVDPV risks). We may also fail to adequately cover all of the potential mixed strategies that may truly emerge after T_0 (e.g., use of IPV only until the risks of VDPV outbreaks decrease to a point where stopping IPV vaccination does not lead to a significant risk). Moreover, we anticipate iteration on these risk estimates as events continue to evolve and further research results become available. For example, a recent discovery of a indigenous type 3 wild poliovirus in Sudan that re-emerged after its apparent eradication from this subregion[109] suggests a risk of continued undetected circulation in the context of

suboptimal surveillance coverage. Similarly, ongoing and future investigations of possible iVDPVs detected through environmental surveillance or the prevalence of asymptomatic iVDPV excretors could influence related risk estimates (and characterization of the uncertainty). Understanding the existing uncertainties helps to identify priority topics for research. A further limitation of our estimation of the risks associated with continuation of OPV in most countries lies in the assumption that coverage remains at the current levels. In reality, resource-scarce countries probably cannot maintain their current coverage beyond the point of global eradication, and pre-eradication experience demonstrates that coverage drops in polio-free countries without external financial support. Therefore, the constant outbreak risk estimates for countries continuing OPV may represent a best-case scenario.

In the context of using the risk estimates presented here in a decision analytic model, analysts should appreciate the uncertainty in each risk.[110] Although we provided ranges for many inputs, these do not represent specific confidence intervals or uncertainty distributions. We provide them as alternative assumptions that give some indication of potentially high and low possible values. Improved quantification of the uncertainty in each risk might require further iteration and possibly warrants expert elicitations.[111] We suggest that the sensitivity of detection for iVDPVs, the implications of the environmental iVDPV isolates, the uncertain potential of IPV to prevent outbreaks in low-hygiene settings, and the design of outbreak response strategies and a vaccine stockpile represent areas for future research. Nevertheless, in the context of the risk framework presented by Aylward and Cochi,[11] we believe that this paper offers a significant step further down the path of quantification and consequently toward improved and more informed decision making.

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Table 1: Factors influencing the risk of VAPP at an individual level and during an outbreak response after OPV cessation.

Individual risk factors	**Effect**
Lack of prior immunity from maternal antibodies, previous wild or OPV virus infection, or previous IPV vaccination. Age at first OPV dose and birth order may impact risk (with older siblings benefiting from increased maternal antibody titres due to recent secondary OPV exposure of their mothers from vaccination of the first sibling).	Prior immunity eliminates risk of VAPP
Genetic pre-susceptibility, such as primary immunodeficiencies involving B-cell system abnormalities (e.g., agammaglobulinemia or hypogammglobulinemia).[25] No evidence exists that HIV presents a risk factor.[4] No other currently identifiable genetic predisposition factors exist.	Persons with primary immunodeficiencies face several 1000-fold higher risk
Frequent intramuscular injections recently after OPV vaccination (provocation poliomyelitis).[30, 31]	Increased risk of VAPP
Type 3 OPV virus infection. Recipient or contact VAPP is most frequently associated with type 3 infections both for (trivalent) OPV and mOPV.[27, 50] Contact VAPP with OPV type 1 occurs very rarely in industrialized countries, but more frequently in developing countries.[27-29]	Highest risk with type 3, then type 2, then type 1
Primary OPV infection (i.e., vaccination) vs. secondary OPV infection	Secondary OPV infection may represent somewhat higher risk (although little evidence supports this)
Factors influencing population risk during an outbreak response involving OPV	**Effect**
Lack of prior population immunity	Potential for large number of VAPP cases in post-cessation response
Vaccine used in response	Same serotype-variability as for individual risk
Amount of OPV used, with more use of OPV leading to more OPV infections, but coverage and timing influence the proportion of secondary vs. primary infections and therefore probably the number of VAPP cases.	Functional relationship unclear
Setting-specific seroconversion rates of the vaccine. Higher seroconversion rates imply a higher proportion of primary OPV infections and therefore probably a lower number of contact VAPP cases (seroconversion rates appear generally lower in developing countries.)[40]	High seroconversion rates reduce risk of contact VAPP

HIV = human immunodeficiency virus; IPV = inactivated polio vaccine; mOPV = monovalent oral poliovirus vaccine; OPV = (trivalent) oral poliovirus vaccine; VAPP = vaccine-associated paralytic poliomyelitis

Table 2: OPV VAPP rates estimated using reported cases[36, 42, 43], adjusted vaccination coverage (see text)[45, 47, 48], seroconversion rates[24] and population data[44] from the US between 1980 and 1997.

Symbol [and formula if derived]	Input	Value	Notes
T	Take rate for 3 OPV doses	0.95	Approximate average of serotype-specific seroconversion rates
E	Effective take rate, i.e., proportion of each birth cohort eventually seroconverting due to OPV infection	0.95	Judgment
B	Average size of US birth cohort 1980-97 (in millions)	3.87	
C	Average coverage with 3 or more OPV doses by age 2	0.75	See text
I1 [I1=T*B*C]	Number of primary OPV infections (i.e., first infections in OPV recipients) in each birth cohort (in millions)	2.76	Count successful trivalent OPV vaccination as 1 infection although in reality it amounts to 3 infections. This cancels out later because we also count VAPP cases due to all 3 serotypes
I2 [I2=E*B-I1]	Eventual number of secondary OPV infections in each birth cohort (in millions)	0.91	
Y	Number of years between 1980 and 1997	18	
rV	Reported recipient VAPP cases (including recipient iVAPP), US 1980-97	89	Includes recipient iVAPP cases
cV	Reported contact VAPP cases (including contact iVAPP), US 1980-97	58	Includes contact iVAPP cases
cr	Completeness of reporting	0.96	Derives from comparing number of reported cases during 1980-91 (as of 2004, references 42 and 43) with number of cases expected for this period after correcting for underreporting (reference 36)
ArV [ArV=rV/(cr*Y)]	Average yearly number of recipient VAPP cases, US 1980-97 (including recipient iVAPP)	5.17	
AcV [AcV=cV/(cr*Y)]	Average yearly number of contact VAPP cases, US 1980-97 (including contact iVAPP)	3.37	
r1 [r1=ArV/I1]	**Recipient VAPP cases per million primary OPV infections in fully susceptibles**	**1.87**	**Lower bound 1.56 (if C=0.90) and upper bound 2.17 (if C=0.65)**
r2 [r2=AcV/I2]	**Contact VAPP cases per million secondary OPV infections in fully susceptibles**	**3.71**	**Lower bound 2.28 (if E=1.0 and C=0.65) and and upper bound 10.3 (if C=0.75 and E=0.8)**
RR [RR=r2/r1]	Relative risk *contact VAPP* vs. *recipient VAPP*	1.98	
tVI [tVI=(rV+cV)/(Y*E*B)]	Rate of total VAPP cases per million total (primary and secondary) OPV infections	2.33	

iVAPP = immunodeficient VAPP; OPV = (trivalent) oral poliovirus vaccine; VAPP = vaccine-associated paralytic poliomyelitis

Table 3: Inputs and estimates for prospective calculation of VAPP risk.

Symbol [and formula if derived]	Variable/input	Income level and OPV immunization policy						
		LOW		LMI		UMI		USA 1980-97
		no SIAs	SIAs	no SIAs	SIAs	no SIAs	SIAs	no SIAs
C	Coverage with at least 3 OPV doses	0.68	0.80	0.9	0.85	0.92	0.90	0.75
e	Primary take rate for 3 OPV doses (% seroconverting)	0.71	0.71	0.85	0.85	0.85	0.85	0.95
E	Effective take rate for birth cohorts	0.75	0.99	0.85	0.99	0.92	0.99	0.95
r [r=(C*e*r1+(E-C*e)*r2)/E]	Rate of (recipient + contact) VAPP cases per million (primary + secondary) OPV infections	2.53	2.66	2.06	2.37	2.15	2.29	2.33
rbc [rbc=r*E]	Rate of VAPP cases per million birth cohort	1.90	2.63	1.75	2.34	1.98	2.27	2.21
	Inputs relating to VAPP due to outbreak response	**LOW**		**LMI**		**UMI**		**HIGH**
e1	Primary take rate for 1 OPV dose (trivalent)	0.45		0.65		0.65		0.78
em1	Primary take rate for 1 monovalent OPV dose (averaging over serotypes)	0.8		0.8		0.8		0.96
psec	Proportion of susceptibles secondarily infected per mass immunization round	0.60		0.37		0.30		0.2

r1 = rate of recipient VAPP cases per 100 million primary (trivalent) OPV infections (see Table 2); r2 = rate of contact VAPP cases per 100 million secondary (trivalent) OPV infections (see Table 2)

HIGH = high-income country; LMI = lower-middle income country; LOW = low-income country; OPV = (trivalent) oral poliovirus vaccine; SIAs = supplemental immunization activities; UMI = upper-middle income country; VAPP = vaccine-associated paralytic poliomyelitis

Table 4: Characterization of cVDPV and aVDPV events.

Time Period	Country	Serotype	Number of isolates (% divergence)[1]	Paralytic cases	Last wild case or isolate (excluding importations)	Last SIAs before event	Scenario	Source
Documented cVDPV outbreaks (1999-2004):								
2004	China (Guizhou)	1	4 (1.0-1.2)	2	<1985 (WPV2)	SNIDs ongoing	LMI, OPV, SIAs	(53)
2002	Madagascar	2	6 (2.5-3.0)	4	1997	Between 1997 and 1999	LOW, OPV, no SIAs	(54)
2001	Philippines	1	4 (3.1-3.5)	3	1993	1997[2]	LMI, OPV, no SIAs	(55)
2000-2001	Haiti	1	10 (~2.6)	8	1989	< 1996	LOW, OPV, no SIAs	(56)
2000-2001	Dominican Republic[3]	1	21 (~1.9)	13	1985	1996	LMI, OPV, no SIAs	(56)
Documented cVDPV outbreaks prior to 1999 (i.e., not included in further analysis):								
1988-1993	Egypt	2	30 (4.0-7.0)	30	1979 (WPV2)	Probably none	LMI, OPV, no SIAs	(57)
Documented aVDPVs with possible circulation (1999-2004):								
2002-2003	Kazakhstan	2	2 (2.3)	1	< 1985 (WPV2)	1999	LMI, OPV, no SIAs	(53)
2002	Romania	1	8 (1.1-1.3)	1	< 1996	SNIDs ongoing	LMI, OPV, SIAs	(58)
2002	Nigeria	2	1 (2.4)	1	1998 (WPV2)	Ongoing	LOW, OPV, SIAs	(58)
2000	Pakistan	2	1 (2.3)	1	1997 (WPV2)	Ongoing	LOW, OPV, SIAs	(59)
Documented aVDPVs with possible circulation prior to 1999 (i.e., not included in further analysis):								
1983	Peru	2	1 (5.8)	1	WPV2 circulation ongoing	Probably none	LMI, OPV, no SIAs	(59)
1980	Romania	1	1 (1.2)	1	Limited WPV1 transmission ongoing	Ongoing	LMI, OPV, SIAs	(60)

Total number of events[4]	**cVDPV outbreaks**	**cVDPV outbreaks and aVDPV events**
Total	5	10
Total 1999-2004 (all on OPV background)	4	8
On *OPV with SIAs* background	1	4
On *OPV without SIAs* background	3	4

[1] Percent divergence refers to the number of nucleotide changes in the VP1 region compared to the parent OPV strain.
[2] However, several provinces not involved in the outbreak conducted SNIDs in 1998 and 1999.
[3] Outbreak involved a strain imported from the Haiti outbreak.
[4] Excluding the cVDPV event in the Dominican Republic since this outbreak involved a strain imported from the Haiti outbreak.
aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; LMI = lower-middle income country; LOW = low-income country; OPV = (trivalent) oral poliovirus vaccine; SIAs = supplemental immunization activities; SNIDs = sub-national immunization days; VP1 = viral protein 1; WPV1, WPV2 = wild poliovirus type 1, 2, respectively

Table 5: aVDPV events not included in the risk estimates[1]

Year	Country	Income level	Serotype	Number of isolates (% divergence)[2]	Paralytic cases	Notes	Sources
2004	Syria	LMI	2	1 (1.1)	1	In context of high national OPV coverage	Unpublished
2004	Laos	LOW	2	3 (1.1)	1	In context of local gaps in OPV coverage	Unpublished
2003	Mongolia	LOW	1	1 (1.3)	0	In context of high national OPV coverage	(58)
2002	Taiwan	HIGH	1 and 2	2 (1.1-1.3)	1	Type 1 (1.1% divergence) isolated from an AFP case, type 2 (1.3% divergence) from a contact	Unpublished
2002	Zimbabwe/ Ireland	LOW/ HIGH	1	17 (1.1-1.5)	0	All viruses isolated in Ireland over a 4-month period from a healthy child born from and HIV-positive mother and vaccinated in Zimbabwe	(61)
2001	Syria	LMI	2	3 (1.3-1.5)	1-3	In context of high national OPV coverage; total number of cases uncertain	Unpublished
2001	Madagascar	LOW	2	1 (1.0)	1	Unrelated to Madagascar cVDPV outbreak but also in context of very low OPV coverage	(54)
1999	Russia	LMI	1	1 (2.6)	1	Isolate from an orphanage	(62)
1999	Russia	LMI	3	1 (1.8)	0	Isolate from an orphanage	(63)
1968	Poland	UMI	3	8 (NR)	464	Outbreak virus related to USOL-D-Bac strain; background of poor IPV-induced immunity; percent divergence from Sabin strain not reported and not applicable because the starting point was a USOL-D-Bac strain	(64)
1965	Belarus	LMI	2	9 (1.1)	0	In context local OPV cessation; only the most divergent among the 9 isolates showed more than 1% VP1 divergence	(65)

[1] Further VDPVs with little over 1% VP1 divergence and weak evidence for significant spread have been detected through AFP or other surveillance in recent years.(53, 58, 112)

[2] Percent divergence refers to the number of nucleotide changes in the VP1 region compared to the parent OPV strain.

AFP = acute flaccid paralysis; aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; HIGH = high-income country; IPV = inactivated polio vaccine; LMI = lower-middle income country; LOW = low-income country; NR = not reported; OPV = (trivalent) oral poliovirus vaccine; SIAs = supplemental immunization activities; SNIDs = sub-national immunization days; UMI = upper-middle income country; VP1 = viral protein 1

Table 6: Inputs to the cVDPV outbreak risk estimation, based on frequency of events during 1999-2004 (see Table 4), country-specific policies of OPV vaccination during this period and 2001 population data.[22]

`	Variable/input	cVDPVs	cVDPVs and aVDPVs		Note
Calculation of initial risk on OPV background					
Y	Number of years considered	6	6		1
Nsia	Number of outbreaks on OPV with SIAs background 1999-2004, LOW or LMI	1	4		
Nnosia	Number of outbreaks on OPV without SIAs background 1999-2004, LOW or LMI	3	4		
P	Population in OPV-using countries 1999-2004 (in 100 millions), LOW or LMI	46	46		2
F	Fraction of OPV-using population in countries conducting SIAs	0.75	0.75		3
Lsia [Lsia=Nsia/(Y*P*F)]	Average annual frequency of outbreaks on background of OPV with SIAs per 100 million people at risk, LOW or LMI	0.005	0.019		
Lnosia [Lnosia= Nnosia/(Y*P*(1-F))]	Average annual frequency of outbreaks on background of OPV without SIAs per 100 million people at risk, LOW or LMI	0.043	0.058		
Other inputs (all by assumption/judgment)		**Base case**	**Min**	**Max**	**Note**
RRumi	Relative risk *UMI* vs. *LOW or LMI*	0.1	0.05	0.2	
Hlowstop	Half life (LOW, stop) in years	0.5	0.25	1	
Hlmistop	Half life (LMI, stop) in years	0.4	0.25	1	
Humistop	Half life (UMI, stop) in years	0.2	0.1	0.5	
Hlowipv [Hlowipv=Hlowstop/2]	Half life (LOW, IPV) in years	0.25	0.1	0.5	
Hlmiipv [Hlmiipv=Hlmistop/2]	Half life (LMI, IPV) in years	0.2	0.1	0.5	
Humiipv [Humiipv=Humistop/2]	Half life (UMI, IPV) in years	0.1	0.05	0.25	
Kopv	Decay constant (any income level, any OPV continuation policy)	0	0	0	4
Lhigh	Risk in HIGH	0.000001	0	0	5
Y	Number of years to reach *OPV without SIAs* level after stopping SIAs	3	1	5	6

[1] 1999-2004 by assumption.
[2] Assume all low and lower-middle income countries used OPV during 1999-2004.
[3] Equals sum of population of countries doing SIAs in each year of 1999-2003 divided by world population minus high-income countries times five years.
[4] This assumption implies that the risk is constant over time if OPV use continues.
[5] Reflects a small risk of any cVDPV importations or escapes of OPV-derived viruses from a laboratory.
[6] This input determines how fast the rate for OPV-using countries stopping SIAs increases to the *OPV without SIAs* level if population immunity is optimal at T_0 (i.e., assuming SIAs continue until T_0or an coordinated immunization push is held at T_0). We assume the increase is linear.
aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; HIGH = high-income country; IPV = inactivated polio vaccine; LMI = lower-middle income country; LOW = low-income country; SIAs = supplemental immunization activities; OPV = (trivalent) oral poliovirus vaccine; UMI = upper-middle income country

Figure 1: Reduction in seroprevalence of unvaccinated infants born between national immunization days (NIDs) in Cuba.[69, Table 3] Given the lack of maternal antibodies at age of sample collection (i.e., prior to next NID) and absence of routine immunization between NID rounds, seropositivity indicates prior (secondary) exposure to circulating oral polio vaccine viruses. The fit corresponds to an exponential decay with a half-life of approximately 0.45 months. The same data set showed a faster decay for the other 2 serotypes.[69, Table 3]

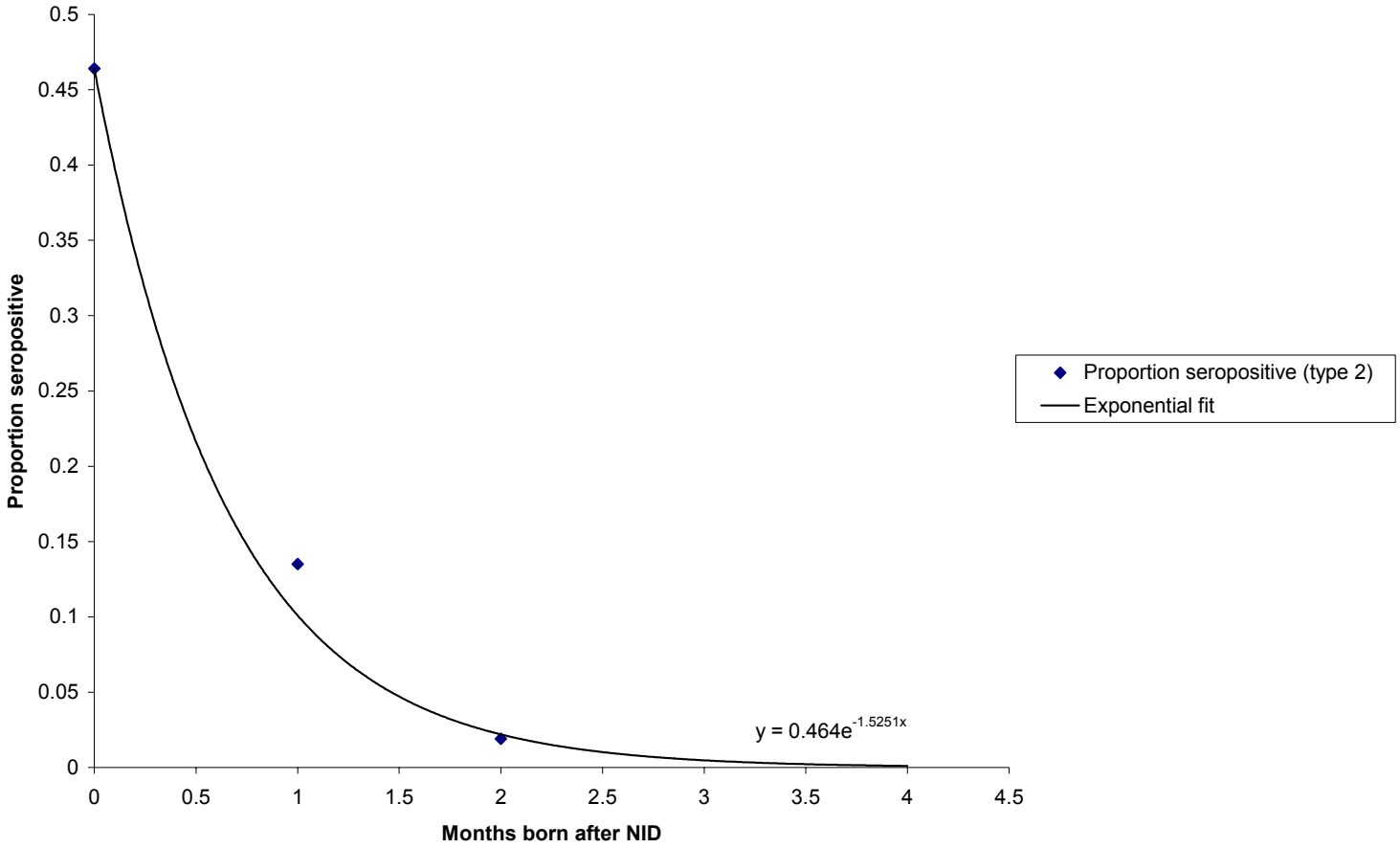


Figure 2: Yearly (Poisson) rate of occurrence of cVDPV outbreaks per 100 million people, by income level based on only the 4 cVDPV outbreaks from Table 4. The scales on the y-axis are not all equal. (cVDPV = circulating vaccine-derived poliovirus; IPV = inactivated polio vaccine; MPI = maximum population immunity at T_0; OPV = (trivalent) oral poliovirus vaccine; RPI = realistic population immunity at T_0; SIAs = supplemental immunization activities).

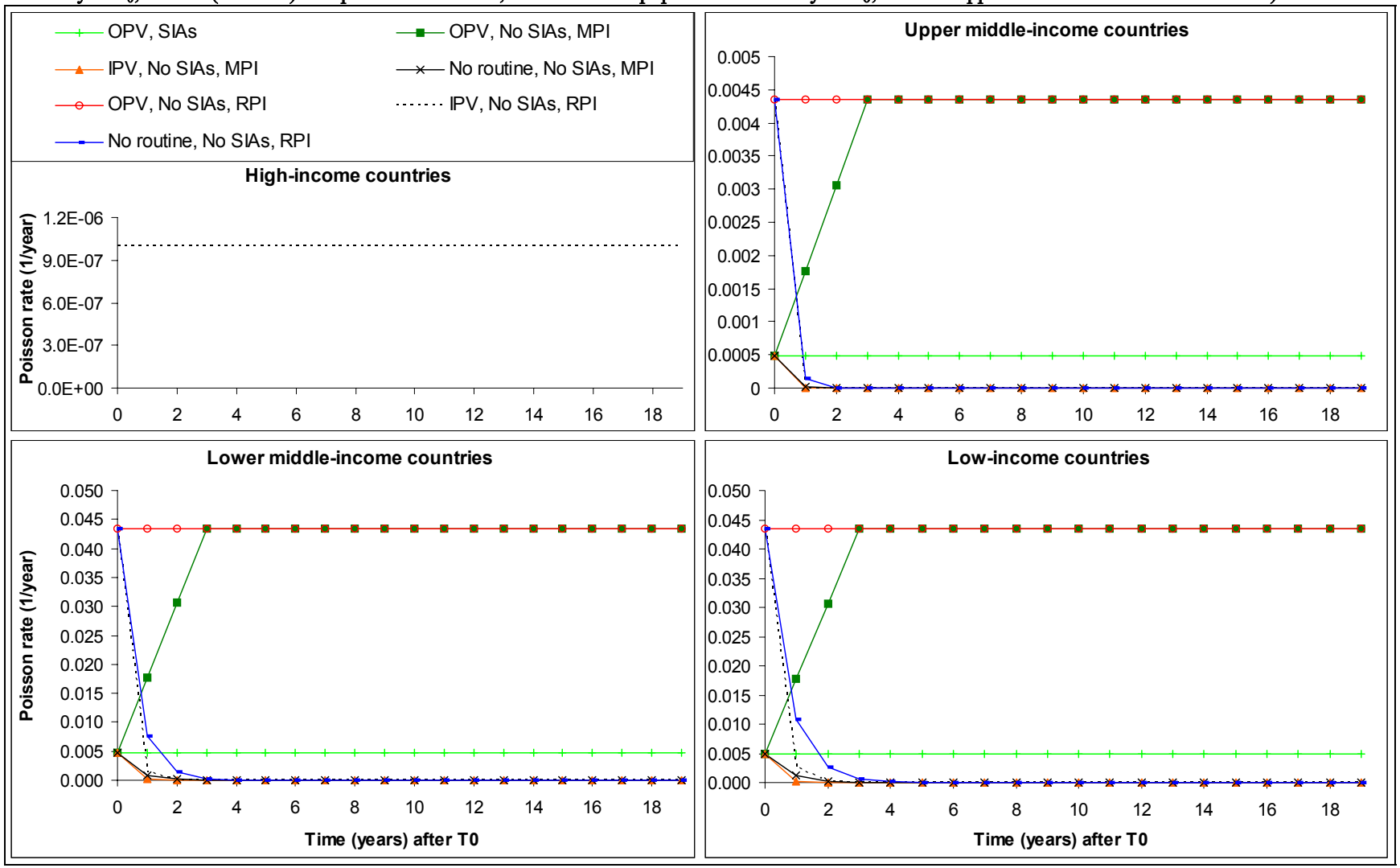


Figure 3: Yearly (Poisson) rate of occurrence of cVDPV outbreaks per 100 million people, by income level based on the 8 cVDPV and aVDPV events from Tables 4. The scales on the y-axis are not all equal. (aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; IPV = inactivated polio vaccine; MPI = maximum population immunity at T_0; OPV = (trivalent) oral poliovirus vaccine; RPI = realistic population immunity at T_0; SIAs = supplemental immunization activities).

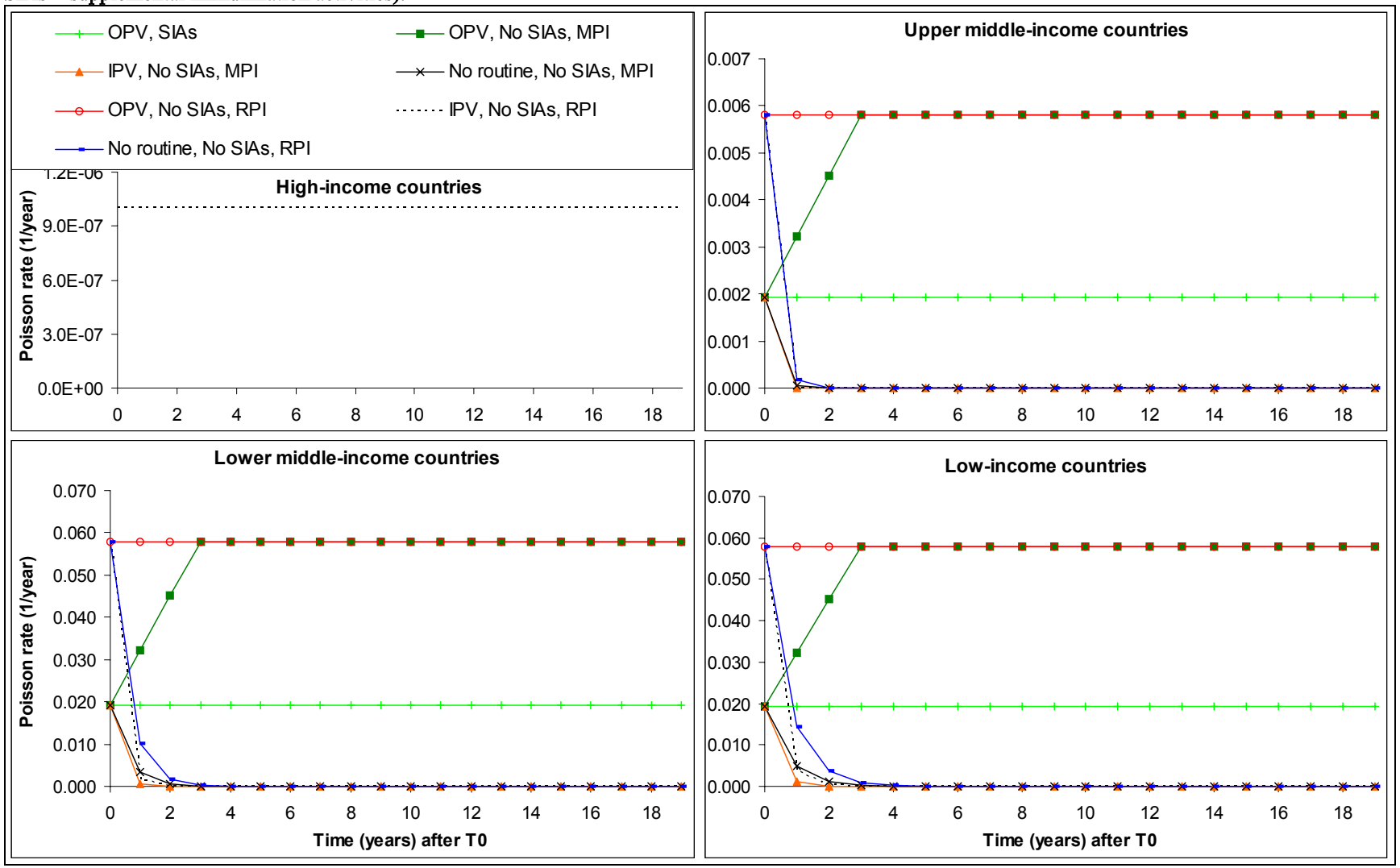


Table 7: Documented iVDPV excretors.

Year of onset of paralysis or first sample collection[1]	Country	Income level	Immune deficiency	Paralysis (Yes/No)	Serotype	Age (years) at onset of paralysis or first sample collection	Interval between associated OPV dose and last positive sample (years) (as of 1/1/04)	Maximum VP1 divergence (%)[2]	Estimated duration of iVDPV excretion (years)[3]	Excreting in 2004? (Yes/No)	Outcome	Sources
Chronic iVDPV excretors (excreting more than 5 years after the associated OPV infection/dose)												
1981	USA	HIGH	CVID	Yes	1	17	7.6	10.0	7.1	No	Died	(81)
1986	USA	HIGH	CVID	No	1 and 2[4]	11	9.6	11.8	9.1[5]	Unknown	Alive	(24, 59)
1990	Germany	HIGH	CVID	Yes	1	7	NA[6]	8.3	7.8	No	Alive	(82)
1995	UK	HIGH	CVID	No	2	25	22	12.9	21.5[5]	Yes	Alive	(83)
Suspected iVDPVs detected through environmental sampling												
1998	Israel	HIGH	NA	NA	2	NA	NA	13.8	13.3[5]	Yes	NA	(53, 84)
2002	Estonia	UMI[7]	NA	NA	3	NA	NA	13.3	12.8	No[8]	NA	(85)
2003	Slovakia	UMI	NA	NA	2	NA	NA	13.4	12.9[5]	Yes	NA	(58)
Prolonged iVDPV excretors (excreting between 6 months and 5 years after the associated OPV infection/dose)												
1962	UK	HIGH	Hypogamma	No	1	3	2.7	Unknown	2.2	No	Died	(86, 87)
1962	UK	HIGH	Hypogamma	No	3	20	1.8	2.3	1.3	No	Died	(88, 89)
1977	Japan	HIGH	XLA	Yes	2	3	3.4	Unknown	2.9	No	Died	(90, 91)
1980	USA	HIGH	Agamma	Yes	2	1.7	1[9]	Unknown	0.5	No	Died	(80)
1987	UK	HIGH	CVID	No	2	34	NA[10]	4.1	3.6	No	Alive	(92)
1990	USA	HIGH	SCID	Yes	2	1.3	0.8	1.9	0.3	No	Died	(80)
1995	Iran	LMI	Ab def.	Yes	2	1.5	Unvaccinated	2.2	1.0[11]	No	Died	(24)
1995	USA	HIGH	SCID	Yes	2	0.3	3.7	2.1	3.2	No	Died	(80)
1998	Argentina	UMI	XLA	Yes	1	3	Unvaccinated	2.8	2.3	No	Alive	(93)
2000	Germany	HIGH	Ab def.	Yes	1	24	2	3.5	1.5[12]	Yes	Alive	(24)
2001	Taiwan	HIGH	CVID	Yes	1	8	3	3.5	2.5	No	Alive	(94)
2002	UK	HIGH	CVID	No	2	15	Unknown	3.3	2.8[12]	Yes	Alive	Unpublished
2002	UK	HIGH	ICF syndrome	No	2	1.5	Unknown	2.5	2.0	No	Alive	Unpublished
2002	Kuwait	HIGH	MHC II def.	No	2	2	0.9	2.0	0.4	No	Died	Unpublished
2003	Peru	LMI	Agamma	Yes	2	0.8	0.8	1.2	0.3	No	Alive	(53)
Immunodeficient persons excreting diverged viruses, but no longer than 6 months after the associated OPV infection (excluded from further analysis)												
1986	USA	HIGH	XLA	Yes	2	0.9	0.4	2.0	NA[12]	No	Alive	(80)
1989	USA	HIGH	Agamma	Yes	1	0.6	0.3	1.1	NA[12]	Unknown	Unknown	(80)
1991	USA	HIGH	CVID	Yes	2	0.7	0.4	1.4	NA[12]	No	Alive	(80)
2003	Thailand	LMI	Hypogamma	Yes	2	1.5	0.3	2.2	NA[12]	No	Unknown	(53)

[1] Indicates year of onset of paralysis for paralytic cases and year of first sample collection for iVDPV excretors without paralysis.
[2] Percent divergence refers to the number of nucleotide changes in the VP1 region compared to the parent OPV strain.
[3] When available, duration estimate equals interval between the associated OPV dose and last positive sample minus the first 6 months (during which we assume excretion of Sabin-like viruses similar to viruses that immunocompetent individuals excrete after OPV infection). Otherwise, we estimate this assuming a molecular clock with a rate of 1% nucleotide divergence per year.
[4] Investigators isolated a type 1 iVDPV with 5.4% VP1 divergence in 1986 and two subpopulations of type 2 iVDPVs with 10.9% and 11.8% VP1 divergence in 1992, respectively. No recent virus detection occurred, but no evidence exists of absence of excretion.
[5] Duration may increase in future as excretion continues.
[6] Patient received 3 OPV doses between 9.5 and 11.5 years prior to the last positive specimen, but uncertainty exists regarding the associated infection (i.e., first, second or last OPV dose or secondary infection). We estimate the duration from the VP1 divergence.
[7] Although the virus detection occurred in an upper-middle income country, no further detections occurred. We assume the excretor represents an otherwise unidentified chronic excretor who visited from a high-income country. In further analysis, we classify the excretor as a high-income excretor.
[8] Environmental surveillance failed to detect the virus in 2003 and 2004.
[9] Not including a neural isolate obtained at autopsy approximately 4.3 year after last OPV dose.
[10] Last OPV dose not relevant since patient most likely was a contact VAPP case.
[11] Duration estimated as the age at onset of paralysis minus 6 months.
[12] May become a chronic excretor in the future if excretion continues.
[13] Duration of excretion not estimated since no excretion observed beyond the first six months.
Ab def. = antibody deficiency; Agamma = agammaglobulinemia; CVID = common variable immunodeficiency disorder; IPV = inactivated polio vaccine; HIGH = high-income country; Hypogamma = hypogammaglobulinemia; ICF = Immunodeficiency-Centromeric instability-Facial anomalies; iVDPV = immunodeficient vaccine-derived poliovirus; LMI = lower-middle income country; MHC II def. = major histocompatibilty complex class II molecule deficiency; NA = not applicable; OPV = oral poliovirus vaccine (any formulation); SCID = severe combined immunodeficiency disorder; SIAs = supplemental immunization activities; UMI = upper-middle income country; XLA = X-linked agammaglobulinemia

Table 8: Inputs for estimation of iVDPV-related outbreak risks based on documented iVDPVs (table 7) and population data.[22, 113]

Input	Base case	Min	Max	Notes
Documented chronic iVDPV excretors*, HIGH	6	6	6	These numbers in fact represent underestimates due to imperfect surveillance sensitivity for iVDPV detection; ranges in last 2 rows reflect the uncertainty
Documented chronic iVDPV excretors, UMI	1	1	1	
Documented chronic iVDPV excretors, LOW and LMI	0	0	0	
Documented prolonged iVDPV excretors**, HIGH	12	12	12	
Documented prolonged iVDPV excretors, UMI	1	1	1	
Documented prolonged iVDPV excretors, LOW and LMI	2	2	2	
Number of first OPV infections, 1962-2004 (x100M), HIGH	4.5	4.5	4.5	Assume this equals half of current population
Number of first OPV infections, 1962-2004 (x100M), UMI	2.5	2	2	Assume this equals half of current population
Number of first OPV infections, 1962-2004 (x100M), LOW and LMI	15	15	15	Assume this equals half of current population younger than 15 years
Incidence of chronic iVDPV excretors per 100 million first OPV infections, HIGH	1.3	1.3	1.3	
Incidence of chronic iVDPV excretors per 100 million first OPV infections, UMI	0.4	0.5	0.5	
Incidence of chronic iVDPV excretors per 100 million first OPV infections, LOW and LMI	0.0	0.0	0.0	
Incidence of prolonged iVDPVs excretors per 100 million first OPV infections, HIGH	2.7	2.7	2.7	
Incidence of prolonged iVDPVs excretors per 100 million first OPV infections, UMI	0.4	0.5	0.5	
Incidence of prolonged iVDPVs excretors per 100 million first OPV infections, LOW and LMI	0.1	0.1	0.1	
Mean duration of excretion for chronic excretors (after the first 6 months), all countries	12.0	10.0	18.0	Average of all chronic iVDPV excretors; upper end assumes duration of 25 years for currently excreting chronic excretors
Mean duration of excretion for prolonged excretors (after the first 6 months), HIGH, UMI, and LMI (years)	1.8	1.0	2.0	Average of all prolonged excretors
Mean duration of excretion for prolonged excretors (after the first 6 months), LOW (years)	0.5	0.1	1.5	Judgment
Average birth rate, HIGH	0.011	0.011	0.011	Average over projected birth rates for 2009-2028
Average birth rate, UMI	0.016	0.016	0.016	Average over projected birth rates for 2009-2028
Average birth rate, LMI	0.014	0.014	0.014	Average over projected birth rates for 2009-2028
Average birth rate, LOW	0.024	0.024	0.024	Average over projected birth rates for 2009-2028
P(outbreak|excretor) per year, status quo average	0.001	0	0.03	Judgment, range corresponds approximately to the upper end of the 95%CI for 0 observed outbreaks given historical prevalence of iVDPVs
Relative risk P(outbreak|excretor) on OPV background, *HIGH* vs. *status quo average*	1.0	1.0	1.0	Judgment
Relative risk P(outbreak|excretor) on OPV background, *UMI* vs. *status quo average*	1.5	1.0	3.0	Judgment
Relative risk P(outbreak|excretor) on OPV background, *LMI* vs. *status quo average*	5.0	3.0	7.0	Judgment
Relative risk P(outbreak|excretor) on OPV background, *LOW* vs. *status quo average*	8.0	5.0	10.0	Judgment
Relative risk P(outbreak|excretor) on OPV background, year 20 vs. year T0	1.0	1.0	1.5	Judgment
Relative risk P(outbreak|excretor) on IPV background, year 20 vs. year T0	5.0	1.0	10.0	Judgment
Relative risk P(outbreak|excretor) 20 years after cessation (i.e., of OPV and IPV), LOW, LMI, and UMI (not applicable for HIGH given continued IPV use)	10.0	5.0	abs. risk 1	Judgment base case yields P(outbreak|excretor) 20 years after T0 of 0.08, 0.05 and 0.015 in LOW, LMI and UMI, respectively

* We define chronic excretors as those individuals excreting iVDPVs more than 5 years after associated OPV infections.

** We define prolonged excretors as those individuals excreting iVDPVs no more than 5 years but no less than 6 months after associated OPV infection.

CI = confidence interval; IPV = inactivated polio vaccine; HIGH = high-income country; iVDPV = immunodeficient vaccine-derived poliovirus; LMI = lower-middle income country; LOW = low-income country; OPV = oral poliovirus vaccine (any formulation); UMI = upper-middle income country

Figure 4: Yearly (Poisson) rate of occurrence of outbreak due to iVDPVs per 100 million people. For the OPV scenario we assume equal rates with or without supplemental immunization activities. The scales on the y-axis are not all equal (IPV = inactivated polio vaccine; iVDPV = immunodeficient vaccine-derived poliovirus; OPV = (trivalent) oral poliovirus vaccine).

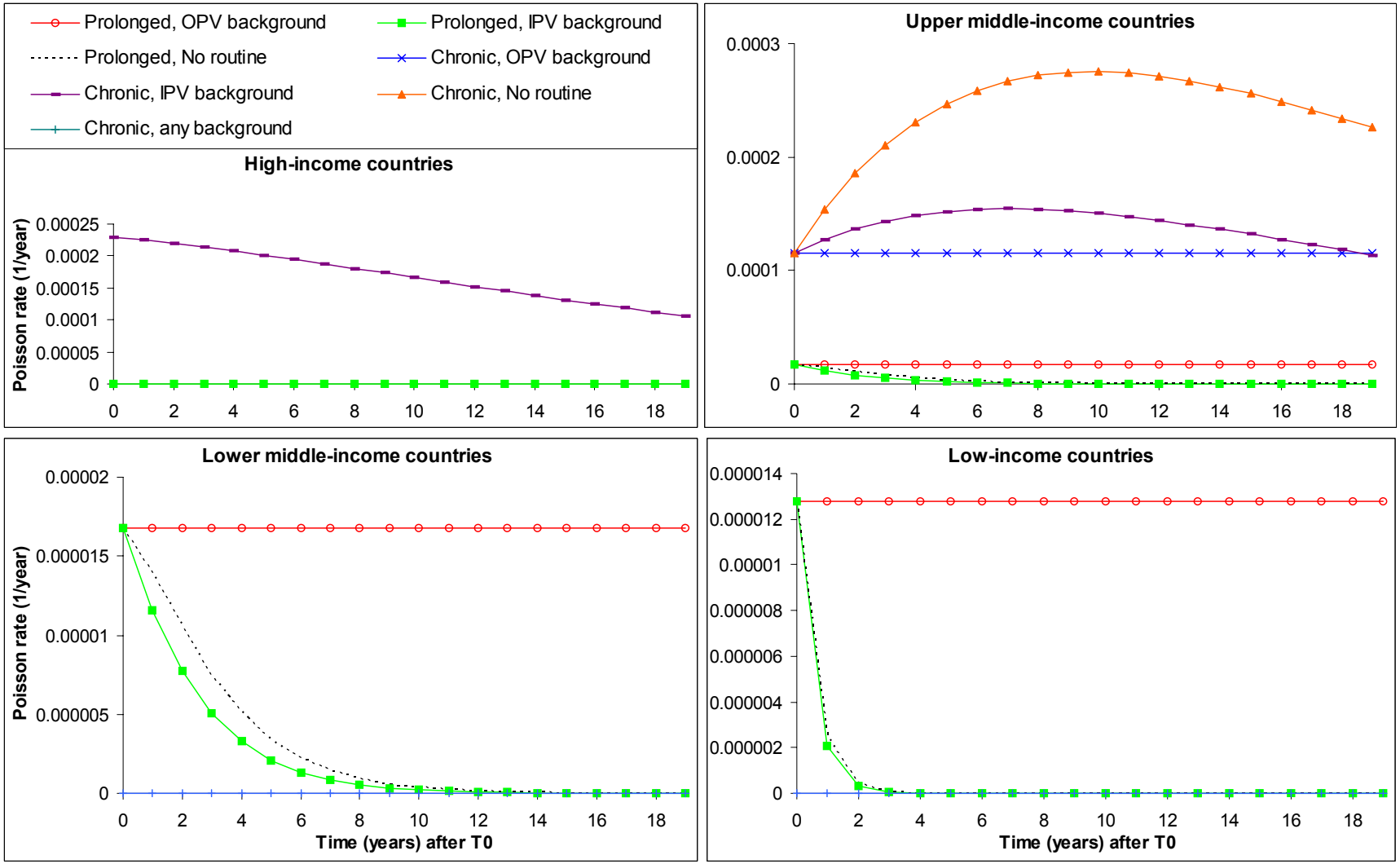
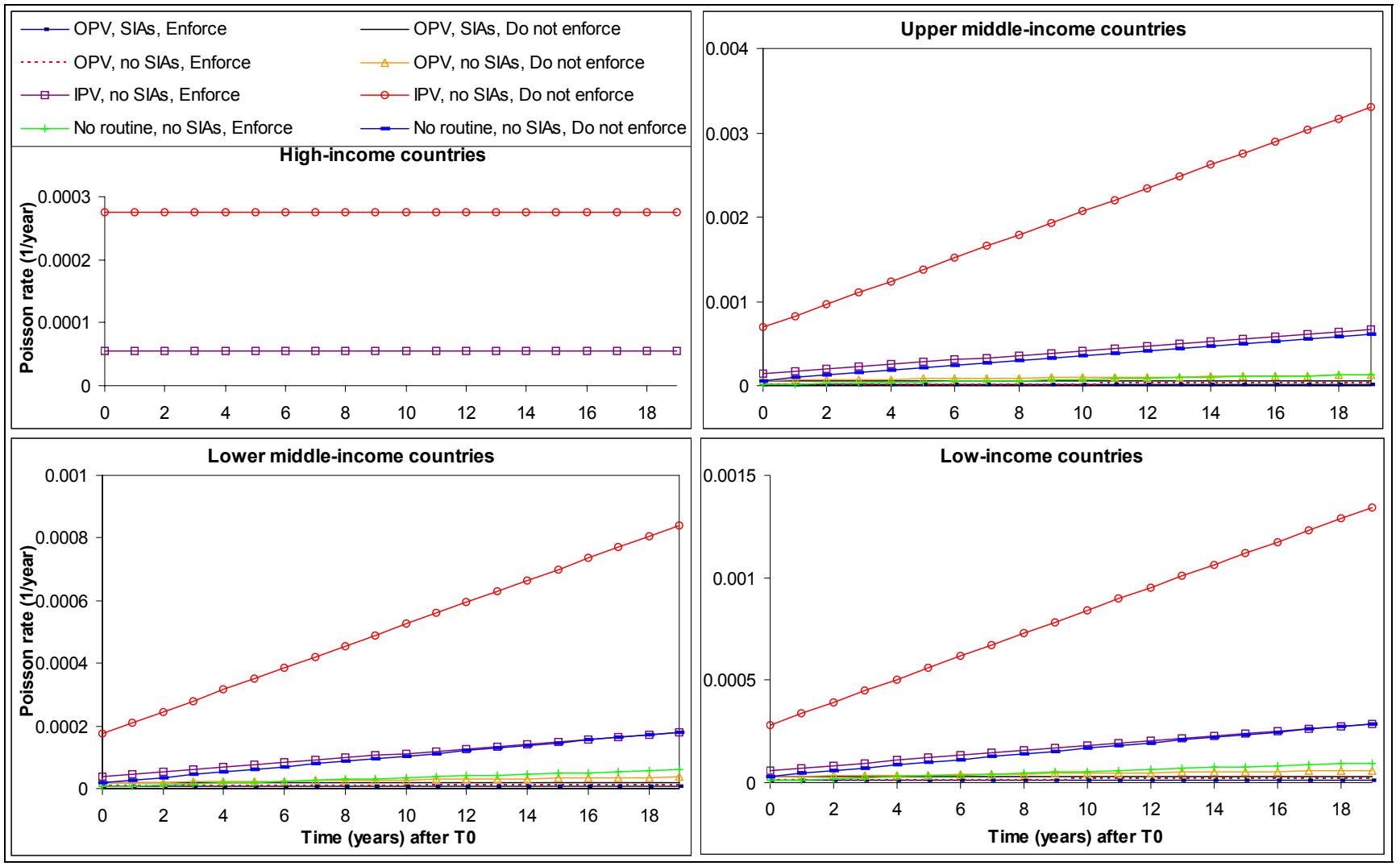


Table 9: Inputs used for the estimation of the risk functions for wild poliovirus outbreaks.

Input	Base case	Min	Max	Notes
Number of releases per year due to breach in laboratory containment per 100 million people, HIGH and UMI	0.001	0	0.01	Judgment
Number of releases per year due to breach in laboratory containment per 100 million people, LOW and LMI	0.0001	0	0.001	Judgment
Number of releases per year due to escape from IPV manufacturing facilities per 100 million people if policy involves IPV, HIGH, UMI	0.01	0	0.05	Judgment; assumes HIGH and UMI countries would produce IPV domestically.
Number of releases per year due to escape from IPV manufacturing facility per 100 million people if policy involves IPV, LOW, LMI	0.001	0	0.02	Lower risk than in HIGH and UMI due to lower likelihood of domestic IPV production in LOW and LMI countries, but "Max" scenario equivalent to domestic IPV production with 2-fold risk
Number of releases per year due to escape from IPV manufacturing facility if immunization policy involves no IPV	0.000001	0	1E-04	Low risk from maintained IPV production capacity for outbreak response
Number of intentional releases per year per 100 million people, OPV cessation, any income level	0.001	0	0.05	Vary e.g. as follows: 0; 10^(-6);10^(-5); 10^(-4); 10^(-3); 10^(-2) and 0.05 (upper bound corresponds to 1 attempt during the 40 years)
Number of intentional releases per year per 100 million people, IPV or OPV routine, any income level	0.0001	0	0.01	Vary e.g. as follows: 0; 10^(-6);10^(-5); 10^(-4); 10^(-3) and 10^(-2) (upper bound reflects a somewhat lower upper end than under a policy of cessation)
Relative risk if containment not enforced, any income level	5	0	10	Judgment
P(outbreak|release), LOW in year T0	0.05	0.001	0.2	Judgment
Relative risk P(outbreak|release), LMI vs. LOW in year T0	0.625	0.5	1	Judgment
Relative risk P(outbreak|release), UMI vs. LOW in year T0	0.25	0.1	1	Judgment
Relative risk P(outbreak|release), OPV with SIAs, year 20 vs. year T0	1	0.8	1.2	Judgment
Relative risk P(outbreak|release), OPV without SIAs, year 20 vs. year T0	2	1	3	Judgment
Relative risk P(outbreak|release) year 20 vs. year T0 with IPV in LOW, LMI and UMI	5	1	10	Judgment
Relative risk P(outbreak|release) 20 years after T0 with cessation (i.e. of OPV and IPV) in LOW, LMI and UMI	10	0.1	abs. risk 1	Judgment; base case yields P(outbreak|release) 20 years after T0 of 0.5, 0.31 and 0.13 in LOW, LMI and UMI, respectively
Relative risk P(outbreak|release) IPV, HIGH, any year vs. LOW in year T0	0.1	0	0.25	Judgment

HIGH = high-income country; IPV = inactivated polio vaccine (any formulation); LMI = lower-middle income country; LOW = low-income country; SIAs = supplemental immunization activities; OPV = (trivalent) oral poliovirus vaccine; UMI = upper-middle income country

Figure 5: Yearly (Poisson) rate of occurrence of wild polio outbreaks per 100 million people as a function of time and scenario. Enforce refers to the policy decision to enforce biosafety levels. Scales on the y-axis are not all equal. (IPV = inactivated polio vaccine; OPV = trivalent oral poliovirus vaccine; SIAs = supplemental immunization activities).



CHAPTER 5

A Dynamic Model of Poliomyelitis Outbreaks: Learning from the Past to Help Inform the Future

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ABSTRACT

Policy makers now face important questions regarding the tradeoffs among different strategies to manage polio risks after they succeed with polio eradication. To estimate the potential consequences of reintroductions of polioviruses and the resulting outbreaks, we developed a dynamic disease transmission model that can simulate many aspects of outbreaks for different post-eradication conditions. We identify the issues related to prospective modeling of future outbreaks using such a model, including the reality that predicting the conditions and the associated model inputs accurately prior to future outbreaks remains challenging. We explore the model's behavior in the context of three recent outbreaks that resulted from importation of poliovirus into previously polio-free countries and find that the model reproduces reported data on the incidence of cases. We expect that this model can provide important insights into the dynamics of future potential polio outbreaks and in this way serve as a useful tool for risk assessment.

Keywords: Dynamic Model, Polio Eradication, Decision Analysis, Disease Outbreak

The efforts following the 1988 World Health Assembly resolution to eradicate polio worldwide (1) reduced the number of wild polio-endemic countries from 125 in 1988 to six in 2003 (2). With the formal certification of global polio eradication approaching (3), global, regional, and national decision makers face important choices among strategies for managing future polio risks, including whether to continue vaccination with any of the available vaccines (4). Apart from the relatively predictable occurrence of vaccine-associated paralytic polio (VAPP) with the continued use of oral polio vaccine (OPV), polio cases could occur due to the unintentional reintroduction of wild polioviruses into a population from a laboratory or an inactivated polio vaccine (IPV) manufacturing site (5), the emergence of circulating vaccine-derived polioviruses (cVDPVs) with neurovirulence and transmission characteristics similar to wild viruses (6), or bioterrorism. The reasonably well-characterized current frequency and disease burden will "change substantially in the post-certification era, depending on future policy decisions" (reference 7, p. 42).

Several factors will influence the course of post-certification outbreaks (8). However, the absence of existing comprehensive dynamic models for polio outbreaks limits the ability of researchers and policy makers to quantitatively understand the interactions that influence the magnitude of outbreaks and the impacts of different strategies. While prospective modeling tools typically deal with the lack of information about the actual future conditions by relying on average conditions, model users must recognize that deviations from assumed conditions can lead to substantially different outcomes.

This paper describes and evaluates a mathematical model specifically designed to simulate the spread of polioviruses during an outbreak in a pre-defined population. We focus on controlled outbreaks and do not study the possibility of re-established endemic transmission. This transmission model estimates the incidence of polio cases over time during an outbreak but does not address the probability of outbreaks. The model uses a large number of inputs that reflect properties of the virus, vaccines, outbreak population and immunity, and immunization response, which give the model flexibility to simulate outbreaks in different plausible future situations. We describe the model and results of simulations of three actual outbreaks in populations previously free of wild poliovirus to demonstrate the model's behavior and identify key inputs that substantially influence the size of outbreaks. We discuss the prospective use of this model as a tool for estimating the burden of disease due to potential future polio outbreaks in the context of a larger effort to quantify the risks, costs, and benefits of future polio risk management policies.

MATERIALS AND METHODS

Background on polioviruses and vaccines

Typically, infection with a poliovirus causes no clinical symptoms, but in approximately 1 in 200 susceptible humans paralysis occurs (9-13). As the only known natural reservoir, humans transmit polioviruses mainly via the fecal-oral route in developing countries with poor hygiene and sanitation, and also via the oral-oral route, which may dominate in developed countries (14). Infection induces an immune response that leads to serotype-specific protection, with a low degree of cross-immunity (14). However, reinfection may occur and result in boosted immunity and a period of limited virus shedding. Two widely used vaccines provide effective protection against disease. Most industrialized countries currently use the enhanced-potency inactivated polio vaccine (15) (we write eIPV to refer specifically to enhanced-potency IPV currently in use and IPV to refer to any inactivated polio vaccine). The trivalent oral polio

vaccine continues as the vaccine of choice of the Polio Eradication Initiative (12) (we use tOPV to refer to trivalent OPV specifically, mOPV to refer to monovalent OPV specifically, and OPV to refer to any form of oral polio vaccine). When administered in the proper schedule (three or more doses required, dependent on setting) both vaccines provide lasting individual protection against disease, while OPV appears more efficient at preventing infection by providing better mucosal immunity in the intestinal tract (16, 17). The use of live OPV offers the additional benefit of secondary immunization of contacts of vaccine recipients. However, primary seroconversion (take) rates of eIPV appear higher than those of tOPV in many settings (18, 19).

Outbreaks of paralytic polio occur in both wild polio-endemic areas and previously polio-free areas (i.e., importation outbreaks that result from an initiating infection acquired elsewhere) (20). Most conceivable future outbreaks would resemble current importation outbreaks, since they would represent a reintroduction of wild virus into a previously wild polio-free population or a single initiating infection with a VDPV.

Poliovirus importations only lead to an outbreak if the virus can establish effective person-to-person transmission and infect enough individuals to cause paralytic cases. In the initial stage, if carriers infect less than one new susceptible individual on average during their infectious period the outbreak will die out, but if this number (the *net reproductive number*) exceeds one then the outbreak can continue and expand. Dynamic infection/disease transmission models factor in the dependence between the rate of acquiring infections and the susceptible and infectious proportions of a population.

The model

We build on generic transmission models (21-23) and existing deterministic (13, 24-27) and stochastic (28-30) poliovirus transmission models to develop our polio outbreak model, a deterministic, compartmental model that assumes continuously divisible populations in every compartment (a technical appendix available on request provides complete details). Each compartment represents the number of individuals in one of 25 age groups with a given infection state as a function of time (i.e., susceptible, latent, infectious, removed/recovered). Mathematically, the model consists of a set of non-linear ordinary differential equations (31), where the non-linear term reflects the dependence of the force of infection on the number of infectious persons. A deterministic model assumes that transitions between compartments occur at the average rate. In reality, biological variability implies that each person has different transfer rates and an actual outbreak represents just one realization of a stochastic process that could result in a wide range of outbreaks. We assume homogeneous mixing within (sub)populations, implying that an infected individual instantly mingles within the entire (sub)population.

With incomplete protection from infection, we denote previously infected or successfully vaccinated persons as *partially infectibles* as opposed to *fully susceptibles* to distinguish them from those never exposed to live or killed polioviruses. We distinguish recently live poliovirus (i.e., OPV, VDPV or wild) infected (group 1), historically live poliovirus infected (group 2), and only IPV-vaccinated (group 3) partially infectibles. We consider only those that acquired an infection during the outbreak (the *removeds*) as fully protected from re-infection with the outbreak virus; they no longer participate in transmission during the outbreak after completing their infectious period. We assume no individuals begin as *uninfectible* prior to the outbreak, although we assume that all partially infectibles and removeds remain fully immune to *disease* (i.e., they can become infected and participate in transmission but do not become paralyzed).

We solve the equations numerically in Mathematica™ (Wolfram Research, Incorporated, Champaign, IL) for the time period that extends from the day of virus introduction through the subsequent 2 years when the incidence approaches zero due to the increased population immunity resulting from natural infection and the mass immunization response, or due to a seasonal trough in R_0. We performed one-way analyses based on ranges for the model inputs as well as a limited number of multi-way sensitivity analyses on key inputs.

Model inputs

We base estimates for the model inputs on peer-reviewed studies, available unpublished data, or on our own best judgments given the absence of other information. If more than one data set exists for an input, we use the most applicable estimates based on our assessment of the weight of the evidence. The inputs in table 1 represent polio-specific characteristics that do not depend on the attributes of the outbreak, although they may depend on the serotype (in which case the table presents a serotype-average estimate). The basic reproductive number, R_0, (the average number of secondary infections caused by one infection introduced into an entirely susceptible population) represents a theoretical summary measure of transmissibility. We base our estimates of R_0 on other studies that calculated R_0 from pre-vaccine era data (20, 32) and we use an oscillating function to reflect seasonal variations in transmissibility (11). The estimates differ by population because of variations in contact rates and the survival of polioviruses in different settings.

We define the relative susceptibility of partially infectibles of group i as the probability that a partially infectible person of group i acquires infection divided by the probability that a fully susceptible person acquires an infection in an identical situation. We similarly define the relative infectiousness as the relative ability to transmit an infection.

Based on data availability and other attributes, we chose three outbreaks with different attributes, including two wild poliovirus importation outbreaks (Albania and the Netherlands) and one cVDPV outbreak (Dominican Republic), that occurred in developed (the Netherlands) and developing (Dominican Republic and Albania) countries, using OPV (Albania and Dominican Republic) and IPV (the Netherlands), and involving serotypes 1 (Albania and Dominican Republic) and 3 (the Netherlands).

Tables 2 lists model inputs for the Albanian outbreak and the assumed initial population immunity profiles. The large, well-documented outbreak in Albania in 1996 (138 paralytic cases) involved almost the entire country (33). All virus isolates belonged to one lineage (34) strongly indicating a single virus introduction led to the outbreak. Lacking conclusive information about the date of the virus introduction, we assumed it occurred approximately two months before the first paralytic case. The fact that the index patient showed onset of paralysis within two weeks of a preventive National Immunization Day (NID) in April and May 1996 targeted only at young children (34) supports our belief that the introduction happened before this NID.

The importation of a type 1 cVDPV from Haiti in the spring of 2000 resulted in the first reported case in the Dominican Republic outbreak on 12 July 2000 (35-40). Authorities reported a total of 13 confirmed and 13 polio-compatible cases, with the last confirmed case showing paralysis onset on 25 January 2001. Reported cases occurred only in children under age 15, all scattered in low-coverage communities of five provinces along the North-South axis of the country demonstrating substantial heterogeneity in immunity in the population. To capture the clear confinement of the outbreak, we defined the outbreak population as a homogeneous group

consisting of the five provinces in which the reported cases occurred. We made the key assumption that VDPVs with the capacity of causing outbreaks possess the same transmissibility and neurovirulence characteristics as wild polioviruses, consistent with laboratory studies (35, 41, 42). We assumed that the introduction occurred during May 2000 based on extrapolation of the observed genetic changes in the VP1 region among the outbreak isolates back to a common origin and assuming a constant mutation rate.

Finally, we modeled the large polio outbreak that occurred in the Netherlands in 1992-3 affecting almost exclusively members of specific religious communities (43-47). The Netherlands relies exclusively on IPV for routine immunization and consistently reaches around 97 percent coverage (43); however a substantial proportion of members of orthodox reformed churches refuses vaccination, leading to very low coverage in those subpopulations. The wild poliovirus type 3 outbreak in 1992-3 resulted in 71 cases (61 with paralysis, including two deaths) between 17 September 1992 and 19 February 1993 (43). Cases distributed approximately evenly among age groups up to age 40, with three patients older than 40. As the approximately 300,000 members of religious communities in the Netherlands live in a "sociogeographically closely-knit network" (44, p. 208), we modeled the Dutch population as two subpopulations with distinct population immunity profiles. To estimate the transmission rates we assumed 99 percent of potentially infectious contacts for any member of the subpopulation of 300,000 occurred within this subpopulation and 1 percent involved members of the other subpopulation.

RESULTS

Simulation of the three recent outbreaks

Figure 1 shows the actual reported incidence of paralytic polio and the results of the simulation of the Albanian outbreak with all inputs at their base case values. Assuming that the virus introduction occurred in mid-February and that the virus survived the spring NID, we find very good correspondence of the model with the reported incidence during most stages of the outbreak. The simulated incidence reaches its maximum during the same week as the peak of reported cases, with 12 simulated versus 15 reported cases. The simulation predicts a cumulative incidence up to the week before the response that matches the 113 actual reported cases, but slightly overestimates the incidence after the response (31 cases vs. 25 reported).

Both the geographic distribution and number of polio cases due to cVDPVs in the Dominican Republic appear much more limited than during the Albanian outbreak (although inadequate surveillance in the Dominican Republic prior to detection of the outbreak suggests the possible missed polio cases). The small number of cases and uncertainty about the true magnitude of the outbreak limit our ability to accurately define the outbreak population. The simulation results (shown in the technical appendix) contain some notable differences compared to the reported numbers of confirmed and polio-compatible cases with (i.e., 31 of 46 cases occurred after the first NID in the model, but only 5 of 26 reported cases occurred after the first NID). Furthermore, the model predicts a much smaller incidence in the first weeks than reported. The virus introduction potentially occurred at the other end of the plausible range for this input (i.e., approximately 6 weeks earlier), but when we assume an earlier virus introduction the model incidence dramatically overestimates the reported numbers. Alternatively, a somewhat lower R0 and/or rate of paralytic cases per infection for the strain of vaccine-derived viruses in this outbreak compared to wild polioviruses could explain the difference. Finally, the random path of the virus through this highly heterogeneous population (i.e., first in a small

number of very low-coverage communities where it caused the majority of cases, and then in the general population) ultimately must have determined the observed kinetics of this small outbreak. Given the lack of detailed population immunity data, our average-based model produced a mediocre representation.

In the Dutch outbreak, we again find heterogeneity in the population as an important consideration. However, in this case we could more adequately model the religious communities as a subpopulation because the outbreak involved them specifically and good data exist about their size and vaccination status. As in the reported numbers, cases in the religious subpopulation dominate the simulated model incidence, while the high levels of population immunity and low contact rate between the two subpopulations prevent any substantial outbreak in the general population. Unlike the simulations of the two other outbreaks, this model appears to simulate the observed incidence very well in the early stages. The timing of the peak corresponds well to the peak in reported incidence and the 59 model-predicted polio cases up to week 60 (last reported case) compares well with 71 reported cases.

Sensitivity Analysis

Using total number of outbreak cases as the outcome measure, we performed one-way sensitivity analyses on inputs for each of the modeled outbreaks based on the ranges in tables 1 and 2 for the Albanian and similar ranges for the other two outbreaks (tables in technical appendix). The sensitivity analyses identified several uncertain key inputs, including the duration of infectiousness, the relative infectiousness and relative susceptibility of the most prevalent type of partially infectibles, R_0, and the time between virus introduction and response. Furthermore, the date of introduction and peak day of seasonal transmission both interact importantly with each other, R_0 and its amplitude, and in some instances we observed non-monotonic behavior of the model output as a function of these inputs.

Prospective model

In developing a modeling tool for characterizing potential future outbreaks, we recognize the inherent uncertainty in outcome projections given limited information and the reality that in fact many possible futures exist. However, we believe based on insights from our extensive synthesis of the literature and experience from modeling three historical outbreaks that poliovirus transmission models provide helpful tools in studying potential outbreaks after eradication. We offer a generic prospective model that we believe might help assess the relative impact of various factors, including the prior vaccination policy (including no vaccination), coverage, and the timeliness and intensity of the outbreak response. Given that different baseline conditions exist, we believe that prospective modeling should stratify countries according to income level (an imperfect but effective surrogate for critical factors that influence key model inputs). Tables 1 and 3 provide the "average" inputs that we believe represent the best starting points for modeling potential future outbreaks.

Table 3 omits suggested typical inputs for the date of virus introduction relative to the seasonal peak since these remain unknown prospectively. We anticipate difficulties in estimating the time between virus introduction and outbreak detection because the date of virus introduction in past outbreaks often remains unknown and the time until detection depends on many conditions (13). Our approach estimates the time at detection from the prospective outbreak model itself by using detection triggers (e.g., the occurrence of a certain number of

clinical cases) that represent different surveillance systems (table 3). We assume that routine immunization coverage remains stable from the present up to the time of the outbreak, independent of the vaccine used. We also implicitly assume unlimited access to vaccine for response, presumably either from on-going production or from a stockpile. With specific guidelines for the strategy to respond to polio outbreaks after eradication still developing, table 3 includes two demonstrative response strategies. Response 1 involves three NID rounds beginning 45 days after detection and response 2 involves two rounds beginning 70 days after detection.

Figure 2 provides an example of a potential future outbreak based on the prospective model for a hypothetical low-income country with 100 million inhabitants in the fifth year after cessation of polio vaccinations for response 2 with either mOPV or tOPV as the vaccine used for immunization response.

DISCUSSION

We developed a dynamic disease transmission model aimed at simulating the spread of poliovirus infections after a virus reintroduction into a wild polio-free population. Given that any outbreak represents only one of many possible realizations of a stochastic process, we cannot expect an average-based model to perfectly reproduce the exact same numbers as reported, although it we should expect it to reasonably match the kinetics of an outbreak. In this sense, the Albanian and Dutch outbreak models produced close matches of the reported epidemiological data with plausible model input values, but inadequate data about heterogeneity in the Dominican Republic population made modeling that outbreak more difficult. Based on review and synthesis of the literature and our experience from modeling these outbreaks, we identified and estimated inputs for a prospective model for polio outbreaks. We hope the prospective model will serve as a useful tool in exploring future policies related to polio risk management (e.g., in assessing the impacts of different outbreak and response scenarios as illustrated in figure 2 or effective routine immunization coverage thresholds required to prevent outbreaks) and help identify key characteristics of outbreaks to better focus future data collection efforts (e.g., more accurate information on the time between virus introduction and detection would improve confidence in other inputs chosen for the Albanian and Dutch outbreak models). Surveillance data provide critical information and we suggest that sustained monitoring of situations that create the types of subpopulations where outbreaks may occur represents an important opportunity to potentially preempt future outbreaks. Decisions regarding future use of IPV would benefit from additional data that could reduce uncertainties about the relative susceptibility and infectiousness of IPV-vaccinees, which drive the Dutch outbreak model. Finally, since one-way sensitivity analysis gives only a crude ranking of the importance of inputs and that different sensitivities may arise in other situations (e.g., prospectively) more advanced sensitivity and uncertainty analyses could also provide important insights.

To our knowledge, our model incorporates the most advanced analyses of poliovirus transmission dynamics yet developed; however, we note several important limitations. This model, like any model, remains limited by the quality of the information that goes into it. For the prospective model, the *a priori* choice of the size of an outbreak population determines the maximum potential outbreak magnitude, and modeling countries as homogeneous populations implies more rapidly growing outbreaks than with more heterogeneous mixing (48). The model does not incorporate the influence of heterogeneous mixing between age groups, in part because of difficulties obtaining such data. Although heterogeneous mixing between age groups possibly

played a role in the Dominican Republic, where all reported cases occurred in children (35), the age distribution in the two other outbreaks does not suggest more transmission among children than among adults (33, 43). The lack of reported paralytic cases in adults in the Dominican Republic outbreak may reflect the high level of population immunity among adults who experienced frequent exposure to wild or OPV viruses before the discontinuation of NIDs in 1996, or possibly the absence of routine surveillance of adults (49). Including adults in future reporting may become increasingly important as the time since the last wild virus isolation in a country grows. The assumption of continuously divisible populations demands cautious interpretation of absolute numbers, especially with low incidence. For example, the model could sustain transmission with less than one (partially) infected person (i.e., a physical impossibility) in each age group at the end of an outbreak that could resurge in the next peak season.

The three retrospective outbreak models demonstrate the use of situation-specific information (outbreak virus serotype, response, season) to help inform the modeling process. Using this model as a prospective tool to evaluate the consequences of different polio risk management policies in future outbreaks requires the use of generic inputs in place of the situation-specific inputs, or sets of scenarios that represent the spectrum of possible conditions prospectively. We expect that our average-based prospective model performs best in situations of widespread virus dissemination within a population (e.g., the Albania outbreak), when local heterogeneity and randomness average out. However, we did not test the model on outbreaks in very large populations and inferences from the prospective model for such situations must remain cautious. Analysts should develop specific models for those situations in which heterogeneous mixing exerts an important impact (48), and use appropriate inputs to prospectively model particular (i.e., "non-average") scenarios of interest.

In the context of prospective modeling, the time between virus introduction and detection and between detection and response emerge as critical inputs (8) for characterizing the impact of potential responses. The surveillance quality clearly influences the timeliness of detection; therefore, prospective models will need to carefully consider future changes in the surveillance network. This model can estimate the time until a threshold number of paralytic polio cases or infections occurs and model any appropriate dependence on the type and quality of surveillance. Clearly, response policies will need to consider the trade-offs associated with different strategies, and this model may help in the prediction of outbreak dynamics as a function of different response times and sizes, although its assumption of a pre-defined population means it cannot model a response that does not target entire (sub)populations at once. Until comprehensive outbreak response guidelines exist, our prospective model requires assumptions regarding the response that may not later prove consistent with the protocol.

Finally, when evaluating future outbreaks and responses, the question of availability of vaccine becomes very important, especially in countries that might cease all polio vaccination. In the Dutch outbreak, a vaccine shortage led to a restricted response (43), and inadequate supplies could similarly impact future responses. Assuming that a polio vaccine stockpile will exist, its size, location, and content will limit the number of available response options. With increasing numbers of susceptibles in the future, the existence of adequate response capabilities represents a crucial issue in mitigating the important risks that potential outbreaks pose.

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TABLE 1. Generic model inputs*

Model input	Value	Range	Sources	Notes
Rate of paralytic polio cases per infection, partially infectibles [proportion]	0			Assumes that persons in which vaccine "took" or with previous natural infection (i.e., those who seroconverted) cannot get paralytic polio
Average duration of latent period [days]	2	0.1-7	(17, 28, 29, 50-52)	Assumes equal duration for all groups of partially infectibles; another poliovirus transmission model uses 1 week (28), but in challenge studies (where date of exposure is known) as (17, Fig. 2), (50, Fig. 5) and those cited in (51, Fig. 3) the duration of latent period, even for children vaccinated prior to challenge, appears short but greater than 0, confirming (52, Fig. 1) and the estimate used in another transmission model for polio (29)
Average duration of infectious period for fully susceptibles [days]	35	20-50	(13, 16, 51, 53-55)	
Average duration of infectious period for partially infectibles group 1 (recent OPV† infection) [days]	7	3-9	(16, 17, 50)	
Average duration of infectious period for partially infectibles group 2 (historic OPV/wild infection) [days]	9	7-13	(51, 56)	
Average duration of infectious period for partially infectibles group 3 (IPV† only) [days]	20	12-35	(16, 17, 50)	
Relative susceptibility of partially infectibles group 1 (recent OPV infection) [proportion]	0.25	0.1-0.4	(16, 17)	See text for definition of this input; based on limited data from challenge studies
Relative susceptibility of partially infectibles group 2 (historic OPV/wild infection) [proportion]	0.8	0.6-1.0		See text for definition of this input; based on judgment
Relative susceptibility of partially infectibles group 3 (IPV only) [proportion]	0.95	0.7-1.0	(16, 17)	See text for definition of this input; based on limited data from challenge studies
Relative infectiousness of partially infectibles group 1 (recent OPV infection) [proportion]	0.1	0.05-0.25	(16, 17)	See text for definition of this input; based on limited data from challenge studies
Relative infectiousness of partially infectibles group 2 (historic OPV/wild infection) [proportion]	0. 5	0.3-0.7		See text for definition of this input; based on judgment
Relative infectiousness of partially infectibles group 3 (IPV only) [proportion]	0.75	0.5-1.0	(16, 17)	See text for definition of this input; based on limited data from challenge studies
Secondary OPV infection rate for children under age 5, due to routine OPV immunization [1/year]	0.1	0-0.3	(57)	Base case estimate represent a loosely interpreted "average" of the 3 serotypes in (57); upper end of range corresponds approximately to the type 2 rate (roughly derived from (57))
Secondary OPV infection rate for last age group, as a proportion of the rate for children under 5, for routine tOPV† immunization (rate declines linearly	0.3	0-1		Based on judgment

with age) [proportion]				
Average time from tOPV administration until individual immunity to infection and disease [days]	7	0-10		Neglects the difference between first and subsequent vaccine doses and between time until protection from infection or disease
Average time from eIPV† administration until individual immunity to infection and disease [days]	7	0-10		Neglects the difference between first and subsequent vaccine doses; reflects duration until protection to disease rather than to infection
Average duration of incubation period (time from infection until onset of paralysis) [days]	10	0-20	(13, 52, 58)	Base case same as in another poliovirus transmission model (13)

* Inputs and ranges represent averages over biological variability; refer to the technical appendix for additional information on how we obtain and use inputs

† eIPV = enhanced-potency inactivated polio vaccine; IPV= any inactivated polio vaccine; OPV = any oral polio vaccine; tOPV = trivalent oral polio vaccine

TABLE 2. Model inputs for the model of the Albanian wild poliovirus importation outbreak in 1996*

Model input	Value	Range	Sources	Notes
Number of virus introductions (in random age groups)	1		(33, 34)	
Date of virus introduction	02/12/'96	11/12/'95-04/03/'95		Based on judgment and iteration in the model with different possible values as part of model fitting; lower end of range is 3 months before the base case value, upper end is 2 weeks before the first reported case
Mean R_0† of the outbreak virus	11	10-12	(20, 32)	Approximate average of estimates in lower middle-income settings
Seasonal amplitude of R_0 [highest – lowest]	14	10-20		Assumes considerable seasonal variation in Eastern Mediterranean Europe
Peak day of seasonal transmission	July 6	July 1 – July 31		Based on judgment and iteration in the model with different possible values as part of model fitting
Size of the outbreak population	3,185,000		(59)	Equals 1995 of Albania population (medium variant)
Birth rate [per day per total population]	0.000054		(59)	Annual births/(population x 365 days)
First day of spring NID† round 1	04/08/'96		(33)	Estimated from (33, figure 2)
First day of spring NID round 2	05/13/'96		(33)	Estimated from (33, figure 2)
First day of mass immunization response round 1	10/07/'96		(33)	
First day of mass immunization response round 2	11/10/'96		(33)	
Age groups targeted by spring NID	0-4 yrs.		(33)	
Age groups targeted by mass immunization response	0-49 yrs.		(33)	
Duration of mass immunization rounds [days]	7		(33)	Exact dates for spring NID not given; this assumes same duration as response immunization rounds
Achieved mass immunization coverage (by round) [%]	98; 98, 82; 88%		(33)	
Half-life of secondary OPV† infection rate after mass immunization rounds [days]	8.6		(60)	Type 1 estimate
Proportion of susceptible children who will eventually get infected due to secondary OPV exposure from a mass immunization round [%]	46.4%	20%-60%	(60)	Type 1 estimate
Secondary OPV infection rate for last age group, as a proportion of the rate for children under 5 (rate declines linearly with age), during spring NID [proportion]	0.3			
Secondary OPV infection rate for last age group, as a proportion of the rate for children under 5 (rate declines linearly with age), during immunization response [proportion]	1	0.3-1.0		Assumes the rate of secondary infections was equal for all age groups because the response targeted adults as well
Routine immunization coverage (3 doses or more) at	90%	80%-98%	(33, 61)	Assumes that the true coverage was lower than the official

time of the outbreak [%]				figure of ≥ 99.5%
Take rate for 3 or more doses of polio vaccine (routine immunization) [%]		85%	75%-95%	(18)	Type 1 tOPV[†] estimate, corresponds approximately to average of middle-income country estimates cited in (18)
Take rate for 1 dose of tOPV (during response) [%]		60%	50%-70%	(18)	Type 1 estimate, corresponds approximately to average of middle-income country estimates derived from 2-dose take rates cited in (18)
Rate of paralytic polio cases per poliovirus infection for fully susceptibles [proportion]		1/100	1/200-1/50	(11, 62)	Type 1 estimate
Initial population immunity profile [age group in years;%]:					
Group 1 (recent live poliovirus infection[‡]):			Group 2 (historic live poliovirus infection);		Remaining percentages of each age group are fully susceptibles (i.e., we assume 0% in group 3 of IPV-vaccinees); estimates corrected for proportion of an age group exposed (recently or not) to secondary OPV, consistent with assumptions about secondary OPV infection rates in the outbreak model; sources include population data, vaccination coverage, vaccination history and seroimmunity data (33, 59, 61, 63)
0;76.5%	1;6.0%	2;6.2%	0;0.0%	1;69.0%	2;70.8%
3;6.4%	4;6.0%	5-9;6.6%	3;73.6%	4;69.0%	5-9;78.4%
10-14;5.2%	15-19;5.4%	20-24;4.5%	10-14;64.8%	15-19;69.6%	20-24;60.5%
25-29;5.0%	30-34;5.4%	35-39;5.7%	25-29;70.0%	30-34;79.6%	35-39;89.3%
40-44;5.5%	45-49;5.3%	>49;4.0%	40-44;90.5%	45-49;91.7%	>49;95.0%

[*]Refer to the technical appendix for additional information on how we obtain and use inputs

[†]NID = national immunization day; OPV = any oral polio vaccine; R_0=Basic reproductive number; tOPV = trivalent oral polio vaccine

[‡] Live poliovirus infection indicates wild, oral poliovirus vaccine or vaccine-derived polioviruses infection

TABLE 3. Inputs for the prospective model*

Model input	Value	Range/ Alternative values	Sources	Notes
Independent of income level and decisions:				
Average rate of paralytic polio cases per infection for fully susceptibles [proportion]	1/200	1/1000-1/100	(9, 11-13, 62, 64)	Range reflects variation among serotypes
Time from mOPV† administration until individual immunity to infection and disease [days]	7	0-10		Assumes that the delay is equal for the trivalent and the monovalent vaccine
Number of virus introductions	1	10, 100		
Half-life of secondary OPV† infection rate after the response [days]	13.1	8.6 -25.5	(60)	Serotype average
Detection trigger for AFP† surveillance [number of paralytic cases]	1	1-5		Judgment
Detection trigger for passive surveillance [number of paralytic cases]	5	5-15		Judgment
Detection trigger for environmental surveillance, all income levels [number of infections]	5,000	1,000-10,000		Assumption
Dependent on outbreak response decisions:				
Time between detection and response 1 and 2, respectively‡ [days]	45, 70	30-210	(8, 20, 43)	Judgment; assumes response time will decrease sharply post-certification compared to (8, Table 1 p. 50) where average is ~120 days in 17 recent outbreaks; neglects discrepancy between wild (93 days) and cVDPV† outbreaks (212 days) in (8, Table 1 p. 50); upper end of range corresponds to approximate average of the cVDPV outbreaks
Target age groups	All age groups born since OPV cessation	Include cohorts born up to15 year prior to OPV cessation	(20)	Assumes all cohorts born since cessation will be targeted regardless, rounded to the next multiple of 5.
Duration of response [days]	3	1-14		Assumption within range of commonly observed responses
Interval between rounds in response 1 or 2 [days]	30	20-60		Judgment; representative for intervals between current mass immunization rounds
Number of rounds in response 1 and 2, respectively	3, 2			Assumption
Achieved coverage [%]	90%	80%-99%		Judgment
Maximum age at which children experience full secondary OPV infection rate from mass	oldest targeted age	5-99		Assumption

immunization response (denote by A) [age]	group			
Secondary OPV infection rate for last age group due to mass immunization response, as a proportion of the rate for children under age A [proportion]	0.3	0-1		Judgment; rate declines linearly with increasing age
Dependent on income level:				
Proportion of susceptible children who will eventually get infected due to secondary OPV exposure from a response immunization round, LOW†	0.60	0.4-0.8	(60)	Judgment based on available data from Cuba (60) and assumption that secondary OPV exposure substantially greater in low-income settings
Proportion of susceptible children who will eventually get infected due to secondary OPV exposure from a response immunization round, LMI†	0.37	0.2-0.5	(60)	Judgment based on available data from Cuba (60), value of 0.37 corresponds to the average proportion secondarily infected across serotypes, range reflects serotype variability
Proportion of susceptible children who will eventually get infected due to secondary OPV exposure from a response immunization round, UMI†	0.30	0.15-0.5	(60)	Judgment based on available data from Cuba (60) and assumption that secondary OPV exposure somewhat lower in upper middle-income settings
Proportion of susceptible children who will eventually get infected due to secondary OPV exposure from a response immunization round, HIGH†	0.20	0.1-0.3	(60)	Judgment based on available data from Cuba (60) and assumption that secondary OPV exposure substantially lower in high-income settings
R_0† of the outbreak virus, LOW	10, 13	8, 16	(20, 32)	Consider two base case values to reflect large uncertainty and variability
R_0 of the outbreak virus, LMI	8, 11	6, 14	(20, 32)	Consider two base case values to reflect large uncertainty and variability
R_0 of the outbreak virus, UMI	6, 9	4, 12	(20, 32)	Consider two base case values to reflect large uncertainty and variability
R_0 of the outbreak virus, HIGH	4, 6	2, 9	(20, 32)	Consider two base case values to reflect large uncertainty and variability
Size of the outbreak population	variable			Run model for different population sizes, e.g. 500,000; 5 million, 10 million; 50million; 100million
Birth rate [per day per total population]	variable		(59)	Linear interpolation between pent-annual averages of medium variant estimates (of births/population*365) over income level
Age breakdown of the population	variable		(59)	Linear interpolation between pent-annual averages of medium variant estimates over income level
Routine immunization coverage, LOW [%]	68%	50%-80%	(65-67)	Average WHO projected DTP3 coverage for 2004 and beyond for low-income countries (2002 World Bank stratification)
Routine immunization coverage, LMI [%]	90%	75%-95%	(65-67)	Average WHO projected DTP3 coverage for 2004 and beyond for lower middle-income countries (2002 World Bank stratification)
Routine immunization coverage, UMI [%]	92%	90%-100%	(65-67)	Average WHO projected DTP3 coverage for 2004 and beyond for upper middle-income countries (2002 World Bank stratification)
Routine immunization coverage, HIGH [%]	94%	90%-100%	(65-67)	Average WHO projected DTP3 coverage for 2004 and beyond for high-income countries (2002 World Bank stratification)

Take rate for 3 tOPV[†] doses, LOW [%]	71%	40%-98%	(18)	Base case estimate corresponds approximately to unweighted average of studies in income level cited in (18, Table 1, p. 929), averaged over the three serotypes; range reflects variation among cited studies and the three serotypes
Take rate for 3 tOPV doses, LMI. UMI [%]	85%	60%-100%	(18)	Base case estimate corresponds approximately to unweighted average of studies in income level cited in (18, Table 1, p. 929), averaged over the three serotypes; range reflects variation among cited studies and the three serotypes; LMI and UMI lumped because few results (4 data sets) in UMI with somewhat lower rates than LMI
Take rate for 3 tOPV doses, HIGH [%]	95%	85%-100%	(12, 18)	Base case estimate corresponds approximately to unweighted average of studies cited in (18, Table 1, p. 929), averaged over the three serotypes; range reflects variation among cited studies and the three serotypes
Take rate for 3 eIPV[‡] doses, LOW, LMI, UMI [%]	95%	65%-100%	(19)	Assumes seroconversion rates similar when used in combination vaccines; base case estimate corresponds approximately to unweighted average of studies in income level cited in (19, Table 2, p. 35), averaged over the three serotypes; range reflects variation among cited studies and the three serotypes; we lumped LOW, LMI and UMI because differences between income levels in (19, Table 2, p. 35) are small
Take rate for 3 eIPV doses, HIGH [%]	99%	95%-100%	(15, 19)	Assumes seroconversion rates similar when used in combination vaccines; seroconversion estimates cited in (15) almost all close to 100%
Take rate per single dose[§] of tOPV, LOW [%]	45%	13%-65%	(18)	Base case estimate corresponds approximately to unweighted average of studies in income level cited in (18, Table 1, p. 929), averaged over the three serotypes; range reflects maximum variation among cited studies and the three serotypes
Take rate per single dose of tOPV (during response), LMI, UMI [%]	65%	35%-80%	(18)	Base case estimate corresponds approximately to unweighted average of studies in the income levels cited in (18, Table 1, p. 929), averaged over the three serotypes; range reflects maximum variation among cited studies and the three serotypes; LMI and UMI lumped because few results (4 data sets) in UMI with somewhat lower rates than LMI
Take rate per single dose of tOPV (during response), HIGH [%]	78%	40%-95%	(68)	Base case corresponds to average of 3 serotypes and ranges to maximum variation among serotypes in cited studies
Take rate per single dose of mOPV (during response), LOW [%]	76%	52%-93%	(69)	Base case estimate corresponds approximately to average of three serotypes of Uganda and India studies in (69, Table 3, p. 536); range reflects largest range in same table
Take rate per single dose of mOPV (during response), LMI, UMI, HIGH [%]	91%	67%-100%	(69)	Base case estimate corresponds approximately to average of three serotypes of all studies except Uganda and India in (69, Table 3, p. 536); range reflects largest range in same table
Inputs related to population immunity profile at time of certification[#]:				
Proportion with recent OPV infection if SIAs[†]	0.95	0.90-1.00		Judgment; this input represents the proportion of children under 5 that

continue until certification, ages 0 to 4, LOW, LMI, UMI [proportion]			seroconverted due to primary or secondary tOPV infection during recent SIAs
Proportion with historic OPV if SIAs continue until certification, ages 0 to 4, LOW, LMI, UMI [proportion]	0.005*(age in yrs.)	0-0.01*(age)	Judgment; this input represent the growing (with age) proportion of children that has immunity from OPV (vaccination or secondary exposure), but that escaped OPV (re)infection in the year prior to certification
Total proportion of partially infectibles if previously covered by SIAs, ages 5-19, LOW, LMI, UMI [proportion]	0.97	0.95-1.00	Judgment; assumes no influence of SIA policy until certification on immunity in persons older than 5
Total proportion of partially infectibles if previously covered by SIAs, ages 20 or more, LOW, LMI, UMI [proportion]	0.99	0.95-1.00	Judgment; assumes very good immunity due to frequent exposure to SIAs and/or endemic wild polioviruses
Total proportion of partially infectibles if SIAs were discontinued 10 years prior to certification, ages 20 or more LOW, LMI, UMI [proportion]	0.99	0.95-1.00	Judgment; estimate equal to previous input because both reflect age cohorts born at a time SIAs were still conducted and/or wild viruses still circulated
Proportion of partially infectibles (i.e. historic OPV/wild), ages 10 to 49, HIGH [proportion]	0.95	0.90-1.00	Judgment; assumes high-income countries switched to from tOPV to eIPV on average 10 years prior to certification of global polio eradication
Proportion of partially infectibles (i.e. historic OPV/wild), ages 50 or more HIGH [proportion]	0.98	0.95-1.00	Judgment; assumes very high immunity levels due to frequent exposure to OPV and/or endemic wild polioviruses

[*] Inputs and ranges represent averages over biological variability; refer to the technical appendix for additional information on how we obtain and use inputs

[†] AFP = acute flaccid paralysis; cVDPV = circulating vaccine-derived poliovirus; DTP3 = diphteria-tetanus pertussis vaccine (3 doses or more); eIPV = enhanced-potency inactivated polio vaccine; HIGH = high-income country; IPV= any inactivated polio vaccine; LOW = low-income country; LMI = lower middle-income country; mOPV = monovalent oral polio vaccine; OPV = any oral polio vaccine; R_0 = basic reproductive number; tOPV = trivalent oral polio vaccine; SIAs = supplemental immunization activities; UMI = upper middle-income country

[‡] We modeled two fairly arbitrary response scenarios, where response 2 represents an aggressive response scenario and response 1 is less aggressive

[§] Rather than using observed single-dose take rates, these estimates reflect the average take rate of the first two doses, so that the cumulative effect of two mass immunizations rounds in terms of seroconversion corresponds to the two-dose take rate. In mathematical terms, for a given two-dose take rate x (between 0 and 1), we estimate the single dose take rate as $1-\sqrt{(1-x)}$

[#] For the cohorts born after discontinuation of SIAs we estimate the population immunity profile based on the routine immunization coverage, and secondary OPV infection inputs from this table; the technical appendix explains the use of these inputs and displays the initial population immunity profiles at the time of certification

FIGURE 1. Weekly incidence of paralytic cases in the 1996 Albania outbreak; reported data from Ref. (33); NID = National Immunization Day.

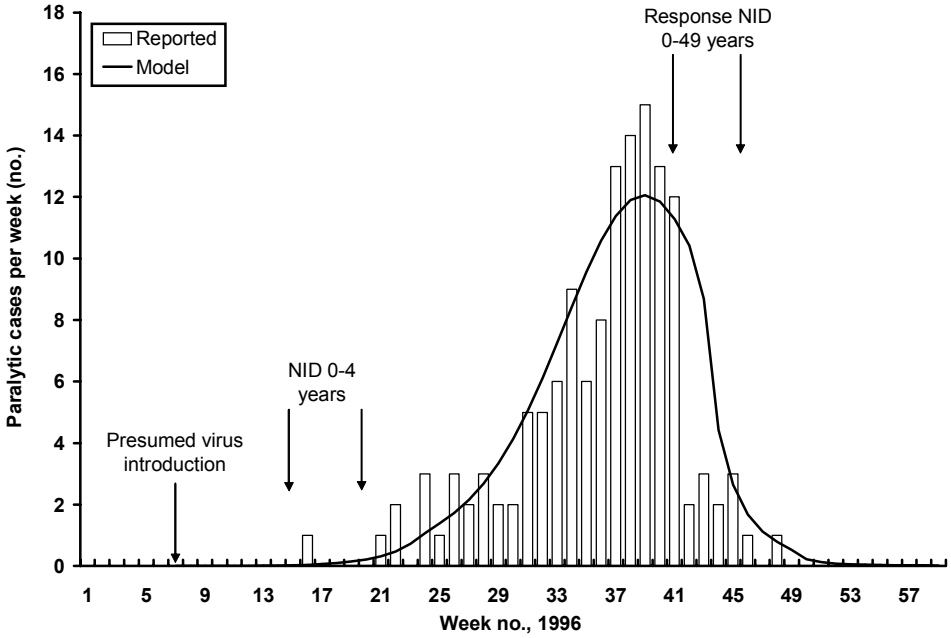
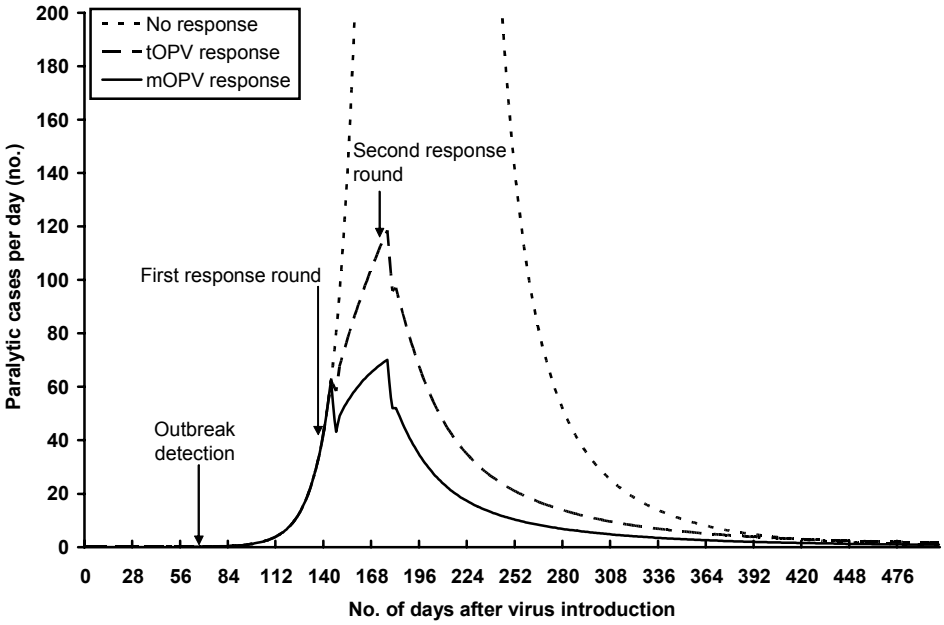


FIGURE 2. Example of a prospectively modeled outbreak after cessation in a hypothetical country. This model assumes a low-income country with R0=13 and a population of 100 million 5 years after cessation of all polio immunizations and 10 years after stopping supplemental immunization activities. Detection occurs as soon as the cumulative incidence reaches 1 paralytic case and the delay from detection to response is 70 days. The response scenarios assume two immunization rounds at a 30-day interval covering 90% of all children younger than 5 years of age in 3 days. The "no response" curve reaches a peak of over 1,700 cases on day 197. mOPV = monovalent oral polio vaccine; tOPV = trivalent oral polio vaccine.



TECHNICAL APPENDIX

Introduction

This technical appendix includes several sections that provide more details about the model and results. We use the same acronyms and reference numbers as in the main paper. Unless preceded by "A," table and figure numbers refer to the main paper. Section 2 presents the basic modeling approach and the actual equations. Section 3 presents the model assumptions. Section 4 presents additional details on our choices of model input values and section 5 presents additional details about the results for each retrospective case study and the sensitivity analyses.

Basic modeling approach and equations

Background on dynamic models for polio

A number of authors developed dynamic and stochastic models for poliovirus transmission. Fine and colleagues used deterministic, dynamic transmission models to investigate the persistence of vaccine viruses and some scenarios of post-certification polio outbreaks (13, 27). Eichner and Hadeler (1995) used deterministic models based on the same principles to calculate and compare theoretical thresholds for the required vaccination coverage to eradicate polioviruses with OPV versus IPV (26). Eichner and colleagues based their stochastic models on similar deterministic models to investigate the likelihood of silent poliovirus persistence (30) and the influence of population size (28). The former model included a population structured into a number of subpopulations (30). Elveback et al. (1976) published a pioneering stochastic computer simulation model for the investigation of influenza epidemics, and this model included heterogeneity by looking at a community of 1,000 individuals structured into families, preschool playgroups, schools, and neighborhoods (22). Elveback et al. (1971) developed two stochastic models for polio in a "community of families" (29) and Cvjetanovic and colleagues (1982) incorporated loss of immunity in their age-structured model for polio (25).

Model description

The main concept in transmission models centers on classifying each person in a population according to infection state at any point in time (i.e., susceptible, infectious, immune, etc.). Transition rates between these groups quantify what proportion of a group transfers to another group per time unit (e.g., from susceptible to infectious per day). Our model consists of a set of non-linear ordinary differential equations (see below) (31).

This type of deterministic transmission model assumes that the durations of infectious and latent periods are exponentially distributed, with means equal to the reciprocal of the transition rates of leaving these states. Given the memory-less property of the exponential distribution, this implies that the rate of leaving a state is independent of the time previously spent in this state. Although this assumption violates the true nature of infections at the individual level (i.e., persons are much more likely to become uninfectious after one month than

after one day of infectiousness), the population sizes in these compartments do change according to these rates (i.e., assuming homogeneous mixing and continuous divisibility of populations).

Given that protection to infection is incomplete, we refer to previously infected or successfully vaccinated persons as *partially infectibles* as opposed to *fully susceptibles* to distinguish them from people who have never been exposed to live or killed polioviruses. For convenience, we use *infectible* as a generic term for individuals of either group. We distinguish between recently live poliovirus (wild, OPV or VDPV) infected (group 1), historically live poliovirus infected (group 2) and only IPV-vaccinated (group 3) partially infectibles. We consider only those that acquired an infection during the outbreak (the *removeds*) as fully protected from re-infection with the outbreak virus such that they no longer participate in transmission during the outbreak after completing their infectious period.

The transition rates between infectible and infectious states represent the proportion of a given group of infectibles that gets infected per time unit, and are proportional to the (weighed) number of infectious persons (see equations below). The proportionality constant (i.e., the transmission coefficient β) directly relates to the basic reproductive number (R_0), defined as the average number of secondary infections caused by the introduction of one infectious person into an entirely susceptible population, a theoretical summary measure of transmissibility. We modeled R_0 as an oscillating function to reflect seasonal variations in the transmissibility of polioviruses (11). Before entering the infectious state, infected persons have a short latent period (an average 2 days, see below and table 1). As in the influenza model by Elveback et al. (1976) (22), we use parameters to reflect the relative susceptibility and relative infectiousness of each type of partially infectible compared to fully susceptibles. In our model, outbreaks start with a single infectious person in the population (the virus introduction).

Routine immunization places a proportion of newborns into the group of partially infectibles (group 1 or 3 with OPV or IPV, respectively) in accordance with the take rate (for 3 doses) and the vaccination coverage (with $\geq$ 3 doses by age 1). Mass immunization campaigns targeted at multiple age groups (e.g., the outbreak response) move individuals in a targeted age group to the appropriate group of partially infectibles, regardless of their prior susceptibility, at a rate determined from the one-dose take rate, coverage, and duration of the mass immunization activity. In the presence of routine or mass immunization with OPV, infectible individuals get secondarily infected due to exposure to OPV-viruses at rates estimated from US data (for routine immunization, see (57)) and Cuba (for mass immunization, see below). We modeled these rates as functions of time and age (see below). We assume that any group 1 partially infectible (recent OPV) remains in this group for the duration of the outbreak unless or until acquiring an infection from the outbreak virus.

We model 25 age groups. The first 5 age groups represent 1 year each, while the remaining 20 age groups each span 5 years. We denote the age group of a variable with a subscript $_a$, with *a* between 1 and 25. Superscript ^{s} denotes the number of the subpopulation to which an individual belongs, with *s* between 1 and *n*, where *n* is the number of subpopulations. Another subscript $_i$ stands for the group of partially infectibles (and we place this in front of the age subscript in case of ambiguity):

i=1: immunity derives from recent live poliovirus (wild, OPV, or VDPV) infection
i=2: immunity derives from a historic poliovirus (wild , OPV or VDPV) infection
i=3: immunity derives from IPV vaccination only

Variables
n = number of subpopulations
$S^s_a(t)$ = fully susceptibles in age group *a* and subpopulation *s*
$L^s_a(t)$ = "regular" latents in age group *a* and subpopulation *s*
$I^s_a(t)$ = "regular" infecteds (those that acquired infection as fully susceptibles) in age group *a* and subpopulation *s*
$PI^s_{i,a}(t)$ = partially infectibles of group *i* in age group *a* and subpopulation *s*
$LPI^s_{i,a}(t)$ = latent partially infectibles of group *i* in age group *a* and subpopulation *s*
$IPI^s_{i,a}(t)$ = infected partially infectibles of group *i* in age group *a* and subpopulation *s*
$R^s_a(t)$ = removeds in age group *a* and subpopulation *s* (those that recovered or died from infection with the outbreak virus)
b^s = birth rate in subpopulation *s [births per population per day]*
N = size of the total population affected by outbreak and response
N^s = size of subpopulation *s*
$covopv^s$ = routine tOPV vaccination coverage in subpopulation *s [proportion]*
$covipv^s$ = routine eIPV vaccination coverage in subpopulation *s [proportion]*
$irrateipv^s_a(t)$ = vaccination rate in age group *a* and subpopulation *s,* with eIPV, during the immunization response *[1/day]*
$irrateopv^s_a(t)$ = vaccination rate in age group *a* and subpopulation *s,* with OPV, during the immunization response *[1/day]*
$secopvrate^s_a(t)$ = rate of acquiring immunity from secondary OPV exposure in age group *a* and subpopulation *s* as a result of routine immunization and/or immunization response with OPV *[1/day]*
$\varepsilon opv3$ = take rate of three doses of OPV by age 1 *[proportion]*
$\varepsilon ipv3$ = take rate of three doses of eIPV by age 1 *[proportion]*
$\varepsilon opv1$ = take rate of a single doses of OPV during the outbreak response (except in the Dutch outbreak where this represents the three-dose tOPV take rate) *[proportion]*
$\varepsilon ipv1$ = take rate of a two doses of eIPV during the outbreak response (applies only to the Dutch outbreak) *[proportion]*
$\beta_{ij}(t)$ = rate of potentially infectious contacts for individuals in subpopulation *i* with individuals in subpopulation *j [1/day]*
α = transfer rate from the latent to the infectious stage of the infection (= 1 over the duration of the latent period) *[1/day]*
γ = recovery rate for fully susceptibles (= 1 over the duration of infectiousness for fully susceptibles) *[1/day]*
γ_i = recovery rate for partially infectibles of group *i* (= 1 over the duration of infectiousness for partially infectibles of group *i*) *[1/day]*
i_i^{rel} = relative infectiousness for partially infectibles of group *i [proportion]*
s_i^{rel} = relative susceptibility for partially infectibles of group *i [proportion]*
w_a = width of age group *a [days]*
incubationperiod = average duration of the incubation period between infection and onset of paralysis *[days]*
pptoasympsus = rate of paralytic cases per polio infection for fully susceptibles *[proportion]*
$pptoasymppi_i$ = rate of paralytic cases per polio infection for partially infectibles of group *i [proportion]*

$Incsus_a^s$(d) = daily incidence of infections in fully susceptibles of age *a* and subpopulation *s [infections/ day]*
$Incpi_{i,a}^s$(d) = daily incidence of infections in partially infectibles of group *i,* with *i*= 1,2,3, and age *a* and subpopulation *s [infections/ day]*
$Incpp_a^s$(w) = weekly incidence of paralytic cases in age group *a* and subpopulation *s [paralytic cases/ week]*
p = proportion of an individual's potentially infectious contacts that are within its own subpopulation (equals 1 in models with only 1 subpopulation)
$R_0^{average}$ = average annual basic reproductive number of the outbreak virus in the outbreak population
R_0^{seas}(t) = basic reproductive number as a function of time, reflecting seasonal variations in transmissibility
ampl = amplitude of R_0^{seas}(t), defined as maximum minus minimum value of R_0 in a year
pd = day of year on which R_0^{seas}(t) reaches its maximum
$covnid^i$ = coverage of ith response NID round among its target group
$duration^i$ = duration of ith response round
A = last age group for which secondary OPV infection rate is at the maximum level
$secrate^{rel}$ = relative rate of secondary OPV infection for adults in last age group compared to individuals in age groups 1 to A *[proportion]*
sec_0 = daily rate of secondary OPV infections during a response round, among persons up to age A *[1/year]*
$yrate^{routine}$ = yearly rate of secondary OPV infections as a result of routine immunization, among persons up to age A *[1/year]*
psec = proportion of children under age A that eventually gets secondarily OPV infected as a result of a mass immunization round *[proportion]*
h = half life of secondary OPV exposure after each round *[days]*
t^i_{begin} = start of ith response round *[day]*
t^i_{end} = end of ith response round *[day]*
delayipv = delay between administration of eIPV and immune response *[days]*
delayopv = delay between administration of OPV and immune response *[days]*

Differential equations for the first age group (0 year old infants)

$$\frac{dS_1^s(t)}{dt} = b^s \times N^s \times (1 - covopv^s \times \varepsilon opv3^s - covipv^s \times \varepsilon ipv3^s) - \left\{ \frac{1}{w_1} + secopvrate_1^s(t) + irrateipv_1^s(t) + irrateopv_1^s(t) + \sum_{j=1}^{n} \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I_a^j(t) + \sum_i^3 i_i^{rel} IPI_{i,a}^j(t) \right) \right] \right\} S_1^s(t)$$

$$\frac{dL_1^s(t)}{dt} = \sum_{j=1}^{n} \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I_a^j(t) + \sum_i^3 i_i^{rel} IPI_{i,a}^j(t) \right) \right] S_1^s(t) - \left\{ \frac{1}{w_1} + \alpha \right\} L_1^s(t)$$

$$\frac{dI_1^s(t)}{dt} = \alpha L_1^s(t) - \left\{ \frac{1}{w_1} + \gamma \right\} I_1^s(t)$$

$$\frac{dR_1^s(t)}{dt} = \gamma I_1^s(t) + \sum_{i=1}^{3} [\gamma_i IPI_{i,1}^s(t)] - (1/w_1) R_1^s(t)$$

$$\frac{dPI_{1,1}^s(t)}{dt} = b^s \times N^s \times covopv^s \times \varepsilon opv3^s + (secopvrate_1^s(t) + irrateopv_1^s(t)) \left(S_1^s(t) + s_2^{rel} PI_1^2(t) + s_3^{rel} PI_1^3(t) \right) - \left\{ \frac{1}{w_1} + s_1^{rel} \sum_{j=1}^{n} \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I_a^j(t) + \sum_i^3 i_i^{rel} IPI_{i,a}^j(t) \right) \right] \right\} PI_{1,1}^s(t)$$

$$\frac{dPI_{2,1}^s(t)}{dt} = -\left\{ \frac{1}{w_1} + s_2^{rel} secopvrate_1^s(t) + s_2^{rel} irrateopv_1^s(t) + s_2^{rel} \sum_{j=1}^{n} \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I_a^j(t) + \sum_i^3 i_i^{rel} IPI_{i,a}^j(t) \right) \right] \right\} PI_{2,1}^s(t)$$

$$\frac{dPI_{3,1}^s(t)}{dt} = b^s \times N^s \times covipv^s \times \varepsilon ipv3^s + irrateipv_1^s(t) S_1^s(t) - \left\{ \frac{1}{w_1} + s_3^{rel} secopvrate_1^s(t) + s_3^{rel} irrateopv_1^s(t) + s_3^{rel} \sum_{j=1}^{n} \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I_a^j(t) + \sum_i^3 i_i^{rel} IPI_{i,a}^j(t) \right) \right] \right\} PI_{3,1}^s(t)$$

$$\frac{dLPI_{i,1}^s(t)}{dt} = s_i^{rel} \sum_{j=1}^{n} \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I_a^j(t) + \sum_i^3 i_i^{rel} IPI_{i,a}^j(t) \right) \right] PI_{i,1}^s(t) - \left(\frac{1}{w_1} + \alpha \right) LPI_{i,1}^s(t), \quad i = 1,2,3$$

$$\frac{dIPI_{i,1}^s(t)}{dt} = \alpha\, LPI_{i,1}^s(t) - \left(\frac{1}{w_1} + \gamma_i \right) IPI_{i,1}^s(t), \quad i = 1,2,3$$

Differential equations for subsequent age groups (people older than 1; *age = 2,…,25*)

$$\frac{dS^{s}_{age}(t)}{dt} = (1/w_{age-1})\,S^{s}_{age-1}(t) - \left\{\frac{1}{w_{age}} + secopvrate^{s}_{age}(t) + irrateipv^{s}_{age}(t) + irrateopv^{s}_{age}(t) + \sum_{j=1}^{n}\left[\beta_{sj}(t)\sum_{a=1}^{25}\left(I^{j}_{a}(t) + \sum_{i}^{3} i^{rel}_{i}\, IPI^{j}_{i,a}(t)\right)\right]\right\} S^{s}_{age}(t)$$

$$\frac{dL^{s}_{age}(t)}{dt} = (1/w_{age-1})L^{s}_{age-1}(t) + \sum_{j=1}^{n}\left[\beta_{sj}(t)\sum_{a=1}^{25}\left(I^{j}_{a}(t) + \sum_{i}^{3} i^{rel}_{i}\, IPI^{j}_{i,a}(t)\right)\right] S^{s}_{age}(t) - \left\{\frac{1}{w_{age}} + \alpha\right\} L^{s}_{age}(t)$$

$$\frac{dI^{s}_{age}(t)}{dt} = (1/w_{age-1})I^{s}_{age-1}(t) + \alpha L^{s}_{age}(t) - \left\{\frac{1}{w_{age}} + \gamma\right\} I^{s}_{age}(t)$$

$$\frac{dR^{s}_{age}(t)}{dt} = (1/w_{age-1})R^{s}_{age-1}(t) + \gamma I^{s}_{age}(t) + \sum_{i=1}^{3}[\gamma_{i} IPI^{s}_{i,age}(t)] - (1/w_{age})\,R^{s}_{age}(t)$$

$$\frac{dPI^{s}_{1,age}(t)}{dt} = (1/w_{age-1})PI^{s}_{1,age-1}(t) + (secopvrate^{s}_{age}(t) + irrateopv^{s}_{age}(t))\left(S^{s}_{age}(t) + s^{rel}_{2} PI^{2}_{age}(t) + s^{rel}_{3} PI^{3}_{age}(t)\right) - \left\{\frac{1}{w_{age}} + s^{rel}_{1}\sum_{j=1}^{n}\left[\beta_{sj}(t)\sum_{a=1}^{25}\left(I^{j}_{a}(t) + \sum_{i}^{3} i^{rel}_{i}\, IPI^{j}_{i,a}(t)\right)\right]\right\} PI^{s}_{1,age}(t)$$

$$\frac{dPI^{s}_{2,age}(t)}{dt} = (1/w_{age-1})PI^{s}_{2,age-1}(t) - \left(\frac{1}{w_{age}} + s^{rel}_{2}\, secopvrate^{s}_{age}(t) + s^{rel}_{2}\, irrateopv^{s}_{age}(t)\right) PI^{s}_{2,age}(t) + s^{rel}_{2}\sum_{j=1}^{n}\left[\beta_{sj}(t)\sum_{a=1}^{25}\left(I^{j}_{a}(t) + \sum_{i}^{3} i^{rel}_{i}\, IPI^{j}_{i,a}(t)\right)\right] PI^{s}_{2,age}(t)$$

$$\frac{dPI^{s}_{3,age}(t)}{dt} = (1/w_{age-1})PI^{s}_{3,age-1}(t) + irrateipv^{s}_{age}(t)S^{s}_{age}(t) - \left\{\frac{1}{w_{age}} + s^{rel}_{3}\, secopvrate^{s}_{age}(t) + s^{rel}_{3}\, irrateopv^{s}_{age}(t) + s^{rel}_{3}\sum_{j=1}^{n}\left[\beta_{sj}(t)\sum_{a=1}^{25}\left(I^{j}_{a}(t) + \sum_{i}^{3} i^{rel}_{i}\, IPI^{j}_{i,a}(t)\right)\right]\right\} PI^{s}_{3,age}(t)$$

$$\frac{dLPI^{s}_{i,age}(t)}{dt} = (1/w_{age-1})ILI^{s}_{i,age-1}(t) - (\frac{1}{w_{age}} + \alpha) LPI^{s}_{age,1}(t) + s^{rel}_{i}\sum_{j=1}^{n}\left[\beta_{sj}(t)\sum_{a=1}^{25}\left(I^{j}_{a}(t) + \sum_{i}^{3} i^{rel}_{i}\, IPI^{j}_{i,a}(t)\right)\right] PI^{s}_{i,age}(t), \quad i = 1,2,3$$

$$\frac{dIPI^{s}_{i,age}(t)}{dt} = (1/w_{age-1})IPI^{s}_{age-1}(t) + \alpha\, LPI^{s}_{i,age}(t) - (\frac{1}{w_{age}} + \gamma_{i}) IPI^{s}_{i,age}(t), \quad i = 1,2,3$$

Incidence

The time unit model inputs are expressed in is days. The incidence of infections on a day d in age group *age* of subpopulation s consists of the number of newly acquired infections in fully susceptibles and partially infectibles on that day:

$$Incsus^{s}_{age}(d) = \int_{t=d}^{d+1} \sum_{j=1}^{n} \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I^{j}_{a}(t) + \sum_{i}^{3} i^{rel}_{i} IPI^{j}_{i,a}(t) \right) \right] S^{s}_{age}(t)\,dt$$

$$Incpi^{s}_{i,age}(d) = s^{rel}_{i} \int_{t=d}^{d+1} \sum_{j=1}^{n} \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I^{j}_{a}(t) + \sum_{i}^{3} i^{rel}_{i} IPI^{j}_{i,a}(t) \right) \right] PI^{s}_{i,age}(t)\,dt, \quad i = 1,2,3$$

The incidence of paralytic cases during week w in an age group *age* and subpopulation s is:

$$Incpp^{s}_{age}(w) = \sum_{d=7(w-1)+incubationperiod}^{7w+incubationperiod-1} pptoasympsus \times Incsus^{s}_{age}(d) + \sum_{i=1}^{3} pptoasymppi_{i} \times Incpi^{s}_{i,age}(d)$$

The second term equals zero since we assumed that partially infectibles cannot get paralytic polio. To obtain the total weekly incidence of paralytic cases in subpopulation s we sum over the 25 age groups.

Transmission rates

We model the seasonal periodicity of the basic reproductive number (R_0) as follows:

$$R_0^{seas}(t) = R_0^{average} + 0.5 \times ampl \times \mathrm{Sin}\left[2\pi \times (t - pd)/365 + \pi/2\right]$$

which is an oscillating function with an amplitude of *ampl* around $R_0^{average}$, reaching its maximum value at the peak day *pd*. For the remainder of this section, we denote this function shortly as R_0.

R_0 represents the number of persons that an initial infectious person can infect when mixed in a totally susceptible population. With $1/\gamma$ days of infectiousness, it must therefore have on average γR_0 potentially infectious contacts per day ('potentially infectious' meaning that the contact transmits the virus if it happens between an infectious and a susceptible person). Given n subpopulations of equal size and that a proportion p of contacts are within an individual's subpopulation, the rate of potentially infectious contacts for individuals in subpopulation i with individuals in subpopulation j, looks as follows:

$$\beta_{ij}(t) = \gamma R_0 p / N_i, \quad i = j$$

$$\beta_{ij}(t) = \gamma R_0 (1-p)/(N - N_i), \quad i \neq j$$

In above formulas, we multiply the number of potentially infectious contacts per day, γR_0, by p (or *1-p*) to obtain the number of potentially infectious contacts per day within (or outside) the subpopulation. We then divide this by the size of the subpopulation with which contacts occur at this rate to reflect the chance that a potentially infectious contact is with a given person per day (N is the size of the total population and N_i is the size of subpopulation i). If there is only one subpopulation, *p=1* and the formula collapses into

$$\beta_{11}(t) = \gamma R_0 / N$$

In the Dutch outbreak sub-model, however, subpopulation 1 has 300,000 and subpopulation 2 has14,928,500 inhabitants. For the calculation of the transmission coefficients

in this situation, we conceptually think of the Dutch population as 50 subpopulations (define m=50) of size 300,000 (define N_1=300,000), of which the first subpopulation is subpopulation 1 (the religious communities) and all other subpopulations together represent subpopulation 2 (the general population). As before, p is the proportion of contacts within the subpopulation for an individual in one of 50 small subpopulations. For subpopulation 1, the transmission coefficients remain the same. For any of the 49 smaller subpopulations within the general population, 48 out of 49 contacts outside its subpopulation are with individuals in small subpopulations belonging to the general population. This implies that 1 out of 49 of these contacts is with members of subpopulation 1. All within-subpopulation contacts for a member of a small subpopulation (within the general population) are of course also contacts within the general population. Thus, the formulas for the transmission coefficients in the Dutch outbreak are:

$$\beta_{11} = \frac{\gamma R_0}{N_1} p \qquad \beta_{21} = \frac{\gamma R_0}{N - N_1} \times \frac{(1-p)}{m}$$

$$\beta_{12} = \frac{\gamma R_0}{N - N_1}(1-p) \qquad \beta_{22} = \frac{\gamma R_0}{N - N_1} \times \left\{ (1-p)\frac{m-2}{m-1} + p \right\}$$

Mass immunization and secondary OPV infection rates

If the i[the] OPV (IPV) outbreak response round is held between t^i_{begin} and t^i_{end}, the immunization response rates in a given subpopulation s and a targeted age group a are equal to the constants (Ln denotes the natural logarithm):

$$irrateopv^s_a(t) = -\frac{\mathrm{Ln}(1 - covnid^i \times \varepsilon opv1)}{duration^i} \quad , t^i_{begin} \le t - delayopv < t^i_{end}, \quad i = 1,...,\#\ of\ rounds$$

$$irrateipv^s_a(t) = -\frac{\mathrm{Ln}(1 - covnid^i \times \varepsilon ipv1)}{duration^i} \quad , t^i_{begin} \le t - delayipv < t^i_{end}, \quad i = 1,...,\#\ of\ rounds$$

and 0 elsewhere. With the exception of the Dutch outbreak, where we assume the secondary OPV infection rate equals a constant function (=-Ln(1-psec)/response duration) during the response round and 0 elsewhere, the secondary OPV infection rate as a result of the response with OPV, in the first A age groups, equals:

$$secopvrate\ nid^s_{age}(t) = 0\ , \qquad t < t^i_{end} + opvdelay + 1/\alpha,\ i = 1,...,\#\ of\ rounds,\ age = 1,...,A$$

$$secopvrate\ nid^s_{age}(t) = -sec_0\ \mathrm{Exp}\left[-\mathrm{Ln}(0.5) \times (t - t^i_{end})/h\right], \qquad t \ge t^i_{end} + opvdelay + 1/\alpha,\ i = 1,...,\#\ of\ rounds,\ age = 1,...,A$$

$opvdelay+\alpha$ accounts for the delay between secondary OPV immunization and individual immunity and the latent period before vaccine recipients can infect others. We explains below how we use data from Cuba (60) to estimate sec_0 and h and that for a given half life h and a given proportion $psec$ of susceptibles that eventually gets infected due to secondary OPV exposure after the outbreak response round, the formula for sec_0 is:

$$sec_0 = \frac{\mathrm{Ln}(0.5)}{h}\mathrm{Ln}(1 - psec)$$

The function $secopvratenid^s_{age}(t)$ decays from the value sec_0 after the first round and resumes at that level after each subsequent round (i.e., we do not add secondary OPV exposure from the first to the next rounds). The secondary OPV rate as a result of routine OPV immunization equals a constant (=-Ln(1-$yrate^{routine}$)/365) and the total secondary OPV rate for

persons up to age group A is the sum of the rates for routine immunization and outbreak response. In subsequent age groups, the rate equals:

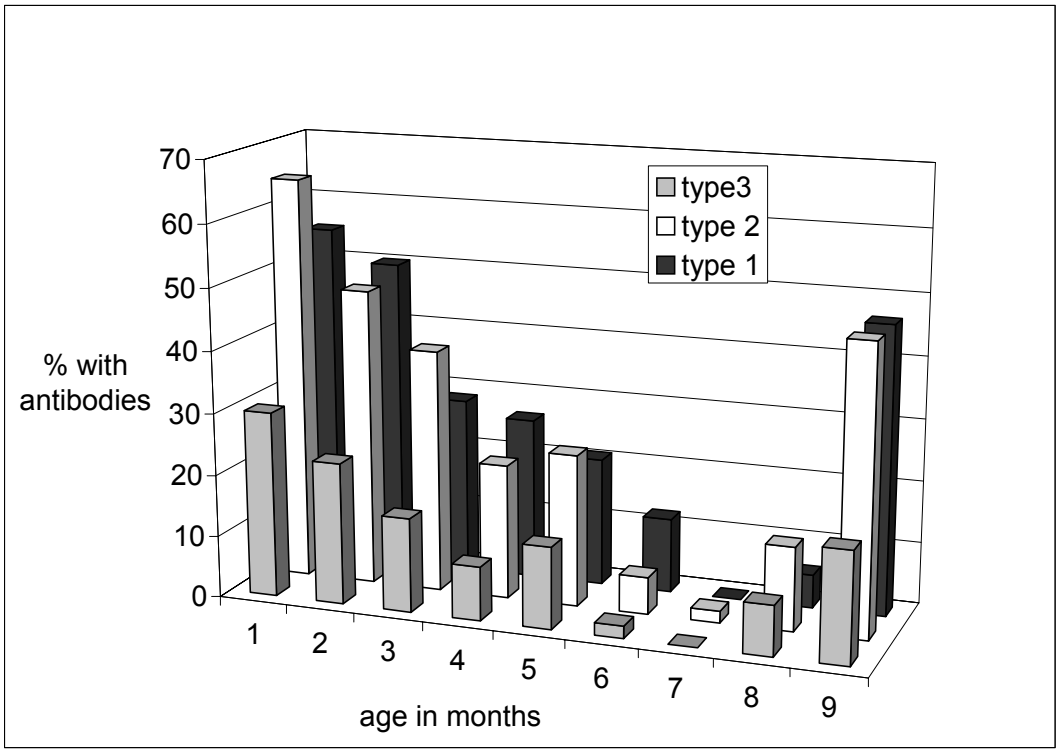
$$secopvrate^{s}_{age}(t) = secopvrate^{s}_{1}(t)\frac{(secrate^{rel} - 1) \times age + 25 - A - secrate^{rel}}{25 - A}, \quad age = A+1,...,25$$

which corresponds to a linear decrease in the rate down to a proportion of $secrate^{rel}$ of the rate for children under A years of age in the last age group. In some instances, $secrate^{rel}$ and A may be defined separately for the response and routine immunization, in which case we apply the above formula to both secondary OPV rates separately before adding the functions.

Estimation of the decay curve for the secondary OPV infection rate after immunization rounds

Más Lago et al. (1994) published a unique data set reflecting the effect of secondary OPV spread on antibody prevalence (60). Given that Cuba is free of wild polio and relies solely on semiannual NIDs (i.e., no OPV is available between NIDs), antibodies in children born between successive NIDs can only reflect maternal antibodies or secondary poliovirus infections resulting from OPV viruses introduced during the previous NID. Sera collected just before an NID from children born since the previous NID (9 months earlier) reveal that a declining proportion of children aged less than 7 months has antibodies, with almost no children aged 7 months having antibodies at a titer of 8 or more. However, studies detect antibodies in children born less than 3 months after the previous NID (ages 8 to 9 months) (see figure A1) that presumably derive from OPV-viruses circulating after the NID.

FIGURE A1. Maternally-derived antibodies and antibodies from secondary OPV infections in Cuban children (data from Ref. (60))



Assuming that antibodies in all children aged 7, 8 and 9 months derive from secondary OPV infections (i.e. there has been no wild poliovirus exposure and all maternal antibodies have

waned by age 7 months) and neglecting the effect that maternal antibodies may have had on their secondary OPV infection rates, these data provide 3 data points for each serotype on which we can base our secondary OPV infection curve. We assume this curve starts at the maximum level soon after the NID and then declines according to an exponential decay. Defining $t_{end} = 0$ as the end of an NID round, we approximate the secondary OPV infection rate due to the NID round by:

$$sec(t) = 0, \qquad t < 0$$
$$sec(t) = sec_0 e^{-kt}, \qquad t \geq 0$$

sec_0 is the rate of secondary OPV infections per day and $k>0$ is the decay constant. For children born at a point of time $t>t_{end}$, the remaining proportion susceptible after exposure to the OPV viruses from the NID equals:

$$s(t) = e^{-\int_{s=t}^{\infty} sec\{s\}\, ds} = e^{-\frac{sec_0}{k} e^{-kt}}$$

The data points for children aged 7, 8 and 9 months correspond approximately to one minus the percentage susceptible at times 60, 30, and 0 days after the NID, respectively (i.e., we assume that the 9 month-old children were born during a time when the secondary OPV rate was still peaking from the NID). We obtain the following solution for k and sec_0 from the set of equations at $t_1=0$ and $t_2=30$:

$$k = \mathrm{Ln}\left[\frac{\mathrm{Ln}(1-ab1)}{\mathrm{Ln}(1-ab2)}\right] / t_2$$

$$sec_0 = -k\,\mathrm{Ln}(1-ab1)$$

where $ab1$ and $ab2$ are the proportions with antibodies for children born at t_1 and t_2, respectively. Figure A2 shows the serotype-specific fits and figure A3 shows the fit where we used the averages of the proportions with antibodies over the 3 serotypes.

FIGURE A2. Proportion of susceptibles getting infected due to secondary OPV infection rate as a function of the number of days born after an NID round (small circles show data from Ref. (60) , lines show the decay curve fits for type 1 (dashed), type 2 (dotted), and type 3 (solid)

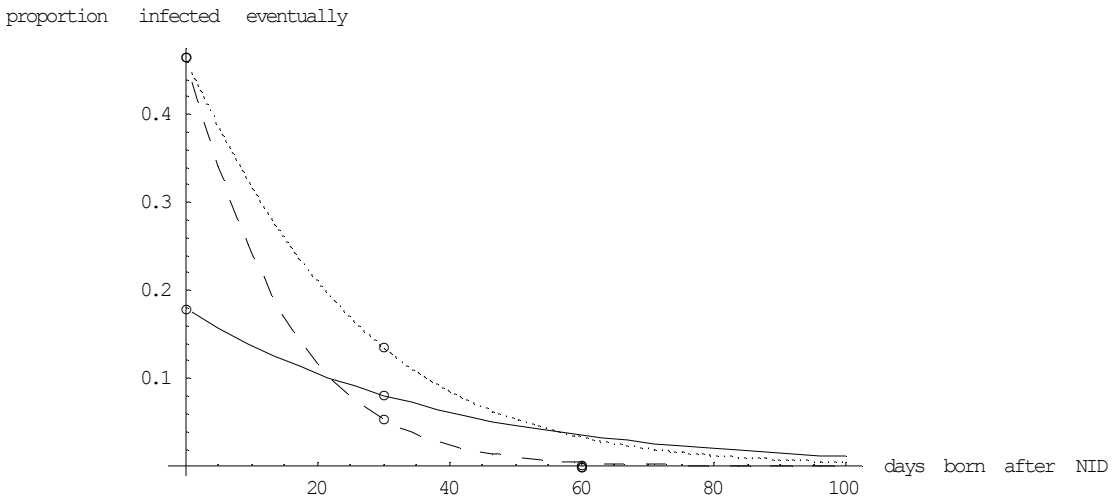


FIGURE A3. Decay curve fit for serotype average (line) and measured average (small circles show data from Ref. (60))

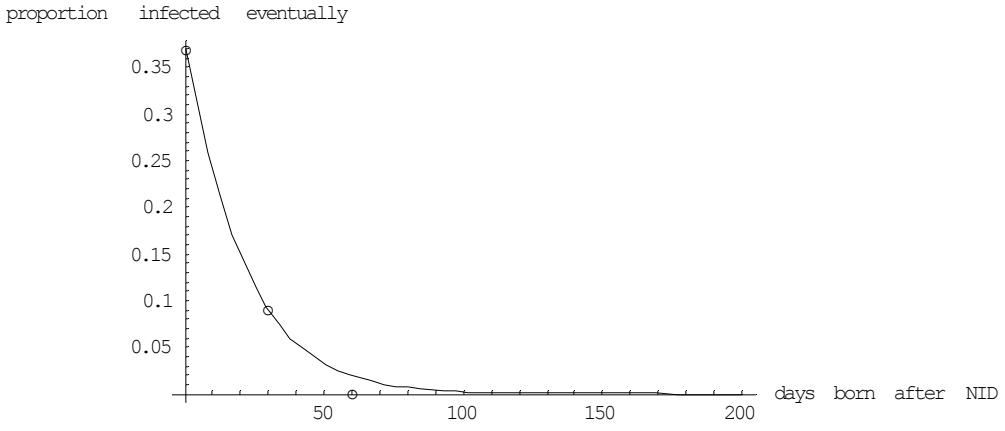


Table A1 shows the half lifes and the daily secondary OPV infection rates during the NIDs (sec_0). The half life equals h=-Ln(1/2)/k, so that sec_0 =Ln(1/2)×Ln(1-$ab1$)/h.

TABLE A1. Fitted secondary OPV infection rate values for the decay curve

	type 1	type 2	type 3	average
Half life *[days]*	8.6	14.3	25.5	13.1
Infection rate during NID (sec_0) *[1/day]*	0.050	0.030	0.006	0.024

Model Assumptions

1. Mixing within subpopulations is instantaneous and homogeneous. If there is more than one subpopulation, we assume that for each individual a fixed ratio of potentially infectious contacts within its subpopulation to potentially infectious contacts outside its subpopulation.
2. The population is continuously divisible in every compartment.
3. The latent and infectious periods are exponentially distributed, with the rate of leaving a state independent of the time previously spent in that state.
4. Infectiousness is constant over the entire infectious period.
5. The transmission coefficient(s) (β_{ij}) change over time according to the seasonal variation of R_0, which we characterize by a sine function with a peak day and positive amplitude. An amplitude of 0 corresponds to the model with no seasonality, and an amplitude of $2\times R_0^{average}$ corresponds to the largest possible amplitude.
6. An individual infected and recovered during the outbreak cannot become infected with the same outbreak virus strain again.
7. All outbreaks (wild or VDPV) are caused by a single initiating infection.
8. The outbreak is contained in the outbreak population, which may or may not consist of several subpopulations.
9. Outbreak-causing vaccine-derived polioviruses are as transmissible and neurovirulent as wild poliovirus.
10. The duration of the latent period is equal for each type of infection (wild, VDPV, serotypes) and for each group of infectibles.
11. Secondary OPV infection moves susceptibles and partially infectibles of all age groups into the group 1 of partially infectibles at a constant rate in the event of routine OPV vaccination.
12. The rate of secondary OPV infection caused by the response equals a constant during the response and then decreases exponentially according to some half-life of the secondary exposure rate (except for the outbreak in the Netherlands, where the long duration of the response prompted us to model the secondary OPV infection rate as a constant during the response and 0 elsewhere, i.e., with no decay after the response).
13. Both secondary OPV infection rates (i.e., routine and response related) decline linearly with age.
14. The secondary OPV infection rate for a group of partially infectibles equals the relative susceptibility of that group of partially infectibles times the secondary OPV infection rate for fully susceptibles.
15. Each round of an OPV outbreak response moves a fixed proportion of fully susceptibles and partially infectibles of group 2 or 3 into the group of partially infectibles from recent OPV

exposure (partial immunity group 1). This proportion equals *coverage× single-dose take rate of OPV* and is the same during all rounds.

16. The eIPV response in the Dutch outbreak moves a fixed proportion of fully susceptibles in the general population into the group of partially infectibles from IPV-vaccination. This proportion equals *coverage× two-dose take rate of eIPV*.
17. The immunization response rate for a group of partially infectibles equals the relative susceptibility of that group of partially infectibles times the immunization response rate for fully susceptibles.
18. The population sizes are constant. Individuals eventually all move to the next age group until age 100, after which they leave the model (i.e. there is no premature mortality). The influence of premature mortality over the short time horizon of an outbreak is small.
19. In the model, "covered through routine vaccination" means completion of the minimal immunization schedule (3 doses in the first year of life) at birth. The take rate of a vaccination during routine immunization equals its seroconversion rate after administration of 3 doses in the relevant setting (income level, schedule). We neglect the influence of booster doses on the transmission of the outbreak virus. Given that the outbreak response commonly includes at least two rounds, we derive single-dose take rates from the two-dose take rate, assuming that the first dose seroconverts at the same rate as the second dose.
20. The secondary OPV infection rate does not depend on the intensity of immunization.
21. We neglect the presence of maternal antibodies in infants during the first six months of their lives.
22. The incubation period and delays between (OPV or IPV) immunization and individual immunity are constants and independent of age or group of infectibles.
23. Any group 1 partially infectible (recent OPV) remains in this group for the duration of the outbreak unless (s)he acquires an infection from the outbreak virus.

Additional Model Input Details

Generic model inputs (see table 1)

We recognize that biological variability exists for all inputs in table 1, however for practical purposes our models uses estimates of population averages. In addition to biological variability between humans, inputs also vary according to serotypes (and virus strains within serotypes), hygiene levels, vaccine formulations, time since vaccination and possibly other factors. The inputs reflect typical values that one may see for polioviruses. The ranges still represent population averages, but reflect both uncertainty and variability across settings and serotypes. For most inputs we estimate input values based on the expected rank order, total range, simplification of biological variability and detection factors, and limited data in specific cases.

We base our estimates of the average R_0 on other studies that calculated R_0 from data from the pre-vaccine era under a number of assumptions (20, 32). The estimates differ by population because of variation in contact rates and the survival of polioviruses in different settings. Even for specific populations, methods and data for the estimation of R_0 are imperfect and based on assumptions that are often violated (e.g., methods assume that populations are at endemic equilibrium, that seronegativity indicates absence of previous infection and that seropositives are fully protected against reinfection; seroimmunity data use different titres to determine seropositivity, often lack large samples (if any) from the adult population and waning

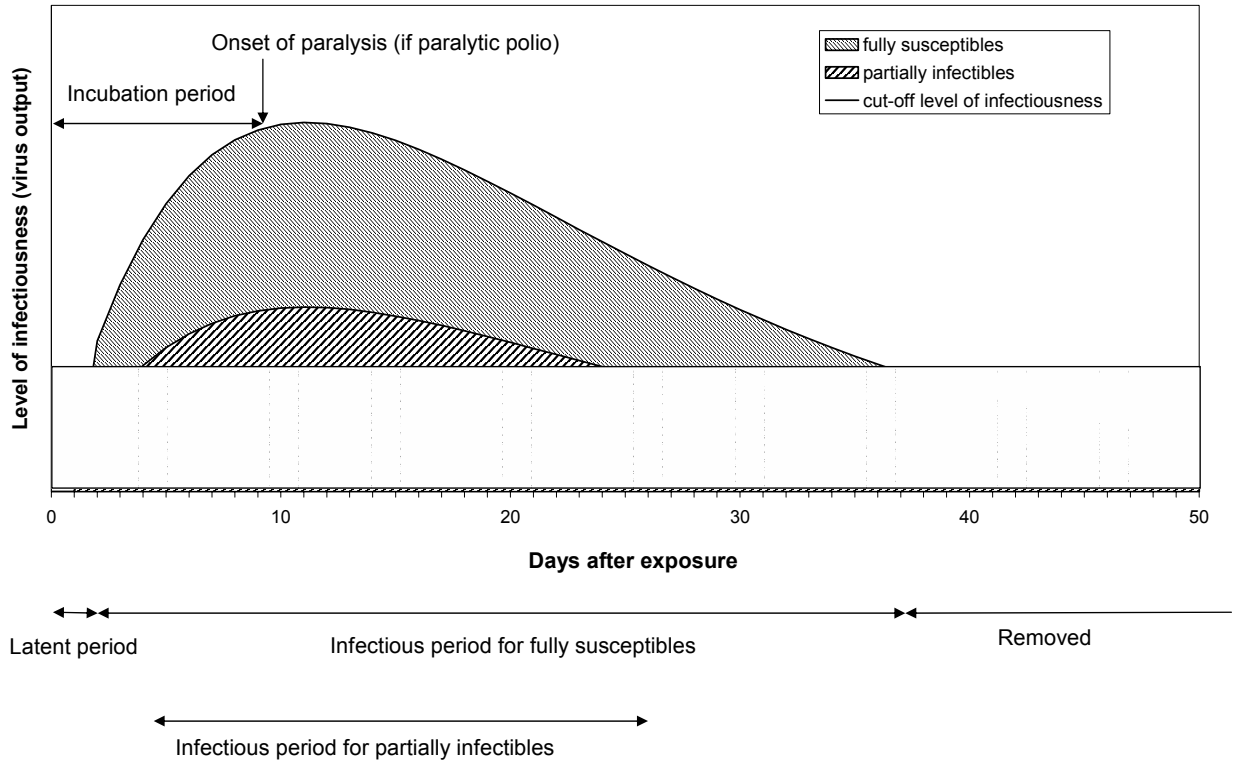
antibodies may make it impossible to detect seroimmunity long past infection). Consequently, R_0 estimates remain highly uncertain and we suggest testing at least the two base cases in table 3, which we believe represent a consensus about the best estimates.

Very limited data exist to estimate the relative susceptibility and infectiousness and the duration of the infectious period for each group of infectibles. Below, we discuss these key inputs in further detail to support our estimates in table 1.

Duration of the infectious period

The duration of the infectious period is the time during the course of infection (of a fully susceptible or partially infectible) during which contact with another person can lead to transmission. One can view this as the period during which an infected person excretes high enough virus loads to infect others. As the model does not include different stages of infectiousness representing different amounts of virus loads, the model assumes that a person is equally infectious throughout the entire duration of the infectious period. In reality, infectiousness changes over time and therefore our estimates implicitly use cut-off levels of infectiousness between which the model considers an individual as infectious (see figure A4).

Figure A4: A hypothetical infection curve



Relevant studies report the proportion of paralytic patients still excreting at discrete points of time relative to onset of paralysis. However, given that in the challenge studies the date of exposure is known, they report the time relative to exposure, which is not the same. Looking at figure A4, if we believe that the latent period is 2 days and that the incubation period is 10 days (see table 1), onset of paralysis occurs on average 8 days after the beginning of the

infectious period. Furthermore, all data are right-censored since there is always a certain duration of time between last positive and first negative sample. This implies that using the time of last positive sample represents an underestimation.

Duration of the infectious period for fully susceptibles. Alexander et al. (1997) reviewed studies of poliovirus excretion over time in three categories: cross-sectional studies of wild poliovirus excretion, longitudinal studies of wild poliovirus excretion and longitudinal studies of Sabin virus excretion (51). They fit regression curves to data from each study category to obtain excretion rates at days 0, 7, 14, 21 and 28 after onset of paralysis in the index case. Table A2 below summarizes the mean excretion rates at these points of time:

Table A2: Summary of excretion rates based on fitted regression curves in Alexander et al. (1997) and estimation of mean duration of excretion from the excretion rates (51).

Excretion rate from regression curve				Proportion of excretors stopping to excrete during given week				Length of excretion (midpoint)×frequency			
Day*	Wild, cross-sectional	Wild, longi-tudinal	Sabin, longi-tudinal	Week*	Wild, cross-sectional	Wild, longi-tudinal	Sabin, longi-tudinal	Midpoint of interval (day*)	Wild, cross-sectional	Wild, longi-tudinal	Sabin, longi-tudinal
0	0.82	0.94	0.92	0	0.11	0.06	0.24	3.5	0.38	0.22	0.84
7	0.73	0.88	0.7	1	0.12	0.14	0.21	10.5	1.28	1.45	2.17
14	0.63	0.75	0.51	2	0.11	0.16	0.16	17.5	1.92	2.79	2.85
21	0.54	0.6	0.36	3	0.11	0.16	0.14	24.5	2.69	3.91	3.46
28	0.45	0.45	0.23	≥ 4	0.55	0.48	0.25	31.5	17.29	15.08	7.88
				Sum	1	1	1	**Sum=mean:**	**23.56**	**23.46**	**17.20**

* After onset of paralysis or Sabin challenge

We can estimate the mean by looking at the proportion that stops excreting during given weeks. For example, for the wild, cross-sectional studies, a proportion 0.82 excretes at day 0 and 0.73 at day 7, so a proportion (0.82-0.73)/0.82 = 0.11 of excretors stopped excreting during the first week. Dividing by 0.82 implies that we exclude subjects for which no virus was isolated from further analysis. If we assign for each week the midpoint of the week as the estimated duration of excretion for the proportion stopping to excrete during that week, we can calculate the average duration of excretion as given in the last 3 columns (where the average is the sum of the estimated length of excretion multiplied by the proportion/frequency with each length of excretion). For the wild virus studies, we should add 8 days to the means (since excretion length is relative to the day of paralysis onset), while for the Sabin studies we should substract 2 days (to account for the latent period). Consequently, it appears that the true duration of excretion was much shorter after Sabin challenge than after wild poliovirus exposure. Note that for the last interval (those excreting 4 weeks or more), we assigned a midpoint of 31.5 days, i.e., the middle of the fifth week. If we set the midpoint at the middle of the sixth week (day 38.5), we obtain higher means of 27.40, 26.80 and 18.95 days for the wild cross-sectional, wild longitudinal and Sabin longitudinal data sets, respectively. We do not know the true average duration of excretion beyond day 28, but the data in Alexander et al. (1991) reveal frequent excretion beyond day 35 among those studies that measure excretion this far out (51):

- for wild, cross-sectional, 2 data points: 25 percent and 50 percent still excreting after 35 days
- for wild, longitudinal, 4 data points ranging from 14 percent to 32 percent still excreting after 35 days

- for Sabin, longitudinal, 4 data points ranging from 12 percent to 14 percent still excreting after 35 days.

In addition, a recent challenge study with a more sensitivity detection method revealed higher proportions excreting for many more weeks than previously measured: beyond 28 days after vaccination, 68.8 percent, 93.8 percent and 43.8 percent of first-dose tOPV recipients were positive for serotypes 1, 2, and 3, respectively (54). Therefore, the averages in the table may be underestimates. Adding 8 days for the time between the end of the latent period and onset of paralysis yields an estimate of 31.5 days.

For one of the original, longitudinal studies (53), the point taken as day 0 was not the onset of paralysis in the index patient but the first positive isolate, where stool samples were routinely taken every month. Given that the subject could have started excretion at any time between monthly sample collections, we should add two weeks to the interval of excretion. The authors also included the fact that there was an average time between last positive and first negative sample and concluded that the true average duration of excretion was 51 days. However, since this does include the full period of infectiousness, no pre-onset period of excretion should be added. All things considered, the base case estimate of 35 days with a range from 20 to 50 days (table 1) appears reasonable.

Duration of the infectious period for recent OPV vaccinees. Onorato et al. (1991) collected the last positive stool specimen of recent OPV vaccinees on average 6.4 days after challenge (17). They took samples at 1, 3, 7, 14, 21 and 42 days after challenge. Again, these are right-censored data, but the resulting underestimation may be at least in part offset by the latent period. Ghendon and Sanakoyeva (1961) took samples every other day up to 28 days after challenge(16). They calculated an average duration of excretion of 4.6 days without explaining how they dealt with any subjects still excreting after 28 days. Given that the average duration is shorter for Sabin than wild poliovirus infections (table A2), the average duration of 5.5 days from both studies is likely an underestimate. If we corrected for Sabin vs. wild poliovirus infection, we would approximately have to double this estimate, given the durations in table A2 (i.e., multiply by $(23.5+8)/(17.2-2) \approx 2$). In Onorato et al. (1991), we can also directly estimate the ratio of the duration of infectiousness for recent OPV vaccinees to fully susceptibles, which equals $4.6/20.4=0.23$ (16). With 35 days of excretion for wild polioviruses, this would translate into a duration of infectiousness of 7.9 days. A recent study of the kinetics of poliovirus excretion for recent OPV-vaccinees reveals a complex serotype-specific and dose-specific picture of excretion, but excretion beyond the first week after re-vaccination is frequent in this data set as well (55). Thus, despite the actual measurements of 4.6 and 6.4 (16, 17) after Sabin challenge of recent OPV vaccinees, we estimate the true average duration of their infectious period at 9 days (table 1).

Duration of the infectious period for the group of historic OPV/wild partially infectibles. No study has investigated the duration of excretion for this group. However, based on a typical anamnestic response after 7-10 days, we estimated a duration of excretion of about 9 days (56).

Duration of the infectious period for IPV vaccinees. Onorato at al. (1991) collected the last positive stool specimen of recent IPV vaccinees on average 15.5 days after challenge (17). Ghendon and Sanakoyeva (1961) estimated a mean duration of 12.3 days (16). However, as for recent OPV vaccinees this is based on challenge with a Sabin strain and the duration with wild

poliovirus exposure may be longer based on the data in table A2. Alternatively, from Ghendon and Sanakoyeva (1961) we obtain a ratio of the duration of infectiousness for IPV vaccinees to fully susceptibles of 12.3/20.4=0.60 (16), which based on a wild poliovirus excretion of 35 days for fully susceptibles would translate into a duration of excretion of 21.1 days for IPV-vaccinees. Hence our estimate of 20 days appears a reasonable compromise.

Relative susceptibility

The relative susceptibility of partially infectibles group *i* (i=1, 2, or 3) is the probability that a partially infectible person of group *i* acquires an infection divided by the probability that a fully susceptible person acquires an infection in an identical situation. We based the relative susceptibility estimates on data from challenge studies, although for the group of historic OPV/wild partially infectibles to our knowledge no suitable studies exist. These studies in general focus on fecal excretion. Pharyngeal excretion is rare for both OPV and IPV vaccinees (17) and consequently measuring pharyngeal excretion is not likely to reveal much about the proportion becoming infectious.

The relative susceptibility for fully susceptibles. The relative susceptibility for fully susceptibles equals 1, by definition.

The relative susceptibility for recent OPV vaccinees. In Onorato et al. (1991), 20/79 (25 percent) of children immunized with 3 doses of OPV in the year preceding the study had virus isolated after challenge with Sabin 1 (14/45 for a high and 6/34 for a low dose of exposure)(17). This gives an indication of the proportion getting infected upon challenge, but since the study included no fully susceptibles we cannot determine the *relative* susceptibility compared to fully susceptibles. Data from Modlin et al. (1997) reveal generally lower excretion rates upon challenge, but in this study the challenge was with trivalent OPV (50). The challenge study by Ghendon and Sanakoyeva (1961) included 30 susceptibles (i.e., children with no detected antibodies prior to the challenge) and of those 24 (80 percent) excreted poliovirus in their stools (16). For the group of recent OPV vaccinees (aged 1-3 years), 12 of 33 (36 percent) excreted virus in their stools. Thus, the relative susceptibility based on these 64 children equals 12/33 divided by 24/30, or 45 percent. However, given that in this study the "fully susceptible" group may have been partially protected due to prior exposure to OPV viruses, we estimate the relative susceptibility for recent OPV vaccinees at 0.25.

The relative susceptibility for the group of historic OPV/wild partially infectibles. We have no firm data to support estimates for this group. W based on our estimate on the assumption that gut immunity does wane over time. With the last exposure dating back to anywhere between 1 year and a lifetime, the estimate of 0.8 represents an estimate of the average over this entire population.

The relative susceptibility for IPV-vaccinees. In Onorato et al. (1991), 59/93 (63 percent) of IPV-vaccinees excreted in the stool upon challenge (37/45 after high, 22/48 after low-dose exposure) (17). As for recent OPV-vaccinees, this study lacks data to compare this to fully susceptibles. In Ghendon and Sanakoyeva (1961), 23/31 (74 percent) of IPV-vaccinees excreted after exposure (16), and comparing this to the 80 percent of non-immunes excreting leads to an estimate of 0.93 for the relative susceptibility. Given our assumption that the susceptibility

increases with time since IPV vaccination, we estimate the average relative susceptibility for this group at 0.95.

Relative infectiousness

The relative infectiousness of partially infectibles of group *i* (i=1, 2, or 3) is the probability that a partially infectible person of group *i* who acquired an infection transmits the infection divided by the probability that a fully susceptible transmits an infection in an identical situation. The relative infectiousness accounts for the fact that even for the period where a partially infectible has a level of infectiousness above the cut-off, s/he is still not as infectious as fully susceptibles due to a lower virus output (see figure A4). However, we do not know the actual shape of the curves in the figure and even if we knew the virus output over time we would not know how this translates into the probability of transmitting the virus to others (e.g., we do not know whether or not 1 log difference in titres also corresponds to a ten-fold increase in the probability of infecting others).

Although both R_0 and the excreted virus titres affect the probability of transmission for any infected individual, the relative infectiousness is a model input intended to characterize only the relative difference between the different groups of partially infectibles. Since R_0 is defined as a measure of overall transmissibility of a virus in a certain setting in terms of the number of secondary infections that an infectious person *would* infect *if* the population were entirely susceptible, it is not meaningful to think of different R_0's for different immunity groups (e.g., recent OPV-vaccinees). R_0 averages over all types of contacts, e.g. intra-household, school, or community. While R_0 is intended to capture the differences between populations (in terms of social-economic status, population density, climate etc.), we assume that the relative infectiousness is independent of the setting. The length of the infectious period obviously also influences the number of successful transmissions. We may view the relative infectiousness as the number of infections caused *per day* by an infectious person of a certain group of partially infectibles divided by the number of persons an infected fully susceptible would infect per day, *given* a certain R_0.

The study by Onorato et al. (1991) indicates that the intensity of exposure clearly influences the probability of infection (17). They challenged recent IPV and OPV vaccinees with either a high or a low dose of Sabin 1 and observed the infection rates given in table A3.

Table A3: The impact of exposure dose on infection rates*

	Previously eIPV-vaccinated	*Previously tOPV-vaccinated*
Low dose (500-800 $TCID_{50}$)	22/48 (46%)	6/34 (18%)
High dose (560,000-600,000 $TCID_{50}$)	37/45 (82%)	14/45 (31%)

* Data from Onorato et al. (1991) (17)

IPV = enhanced-potency inactivated polio vaccine; TCID = tissue culture infective doses; tOPV = trivalent oral polio vaccine

Thus, an approximately 1000-fold increase in exposure lead approximately to a two-fold increase in the proportion infected. Given that we know that the virus titres excreted by different groups of partially infectibles are not the same and less than those of fully susceptibles (16), we can suppose 2 things: (i) the relative infectiousness is not the same for each group (i.e., not 1), and (ii) the relationship between virus output and probability of infection is not linear. Direct

measurement of the relative infectiousness is impossible because of the effect of dilution in the time from virus excretion by the infected person to intake by the contact, but we can reasonably estimate the values as "much greater" than the relative virus output and smaller than 1.

The study by Ghendon and Sanakoyeva (1961) indicates much higher virus titres in the stools for those IPV-vaccinees that excrete compared to OPV-vaccinees and fully susceptibles: 5.2 log virus titres ($TCID_{50}$) per gram of faeces for susceptibles, 4.1 for IPV-vaccinees and 2.2 for OPV vaccinees (and naturally immune children) (16). The study by Onorato et al. (1991) confirms the relative difference between OPV and IPV vaccinees (17). This forms the basis of our estimates for the relative infectiousness of 0.1 for recent OPV, 0.5 for historic OPV/wild and 0.75 for IPV-vaccineees, although clearly these values remain highly uncertain.

The Albania outbreak

The first cases in the Albania outbreak in 1996 occurred shortly after a National Immunization Day (NID) that immunized 98 percent of all children less than 5 years of age (33). Albania conducted this NID based on concerns that increased migration after the opening of the country in 1991 and past problems with vaccine supply interruptions and the cold chain posed a threat for virus reintroduction. The first reported case showed onset of paralysis on 17 April 1996, between the two rounds of this preventive NID (33). Field workers originally identified the case as a potential VAPP case given the timing of the Spring NID, but subsequent investigation confirmed a wild virus infection. We suspect that the virus may have already caused large numbers of infections without detection before the Spring NID and could therefore survive the immunization campaigns targeted only at children. Between the first case and 25 November 1996, 138 confirmed paralytic cases occurred including 78 percent in persons aged 11-36. Two rounds of mass immunization on 7-14 October (81 percent coverage) and 10-17 November (88 percent coverage) targeted all persons up to age 50 and controlled the outbreak (33).

The age distribution of outbreak cases, a review of immunization practices (33), and a seroimmunity study performed before the outbreak all strongly suggest "a major failure in immunization practices before the year 1980" (34, p. 1916), including problems with the cold chain and vaccine quality. We incorporate this information along with vaccination coverage and population data in estimates of the initial population immunity profile (table A4). We correct these results roughly for the influence of recent and cumulative exposure to OPV-viruses.

The Dominican Republic outbreak

Table A5 shows the inputs for the model of the cVDPV outbreak in the Dominican Republic in 2000-2001. Reported estimates of the national immunization coverage in the Dominican Republic since the last NIDs conducted in 1996 present inconsistent information that suggests the true routine immunization coverage may have averaged about 60-80 percent during 1996-2000 (Pedreira MC, Pan American Health Organization, personal communication, 2003). Because we limit the outbreak population to those provinces with confirmed cases and immunity gaps, we estimate the average coverage at 60 percent during the 5 years preceding the outbreak. Based on this coverage estimate, the take rates of three doses of tOPV type 1 in middle-income settings and the years of secondary OPV exposure, table A4 displays the initial population immunity profile in the Dominican Republic. For persons born during the time of on-going NID activities and/or circulating wild polioviruses, we assume much higher proportions of immunes.

The outbreak in the Netherlands

Table A4 shows the initial population immunity profile and table A6 the other inputs for the Dutch outbreak model. A few days after confirmation of the first case in the outbreak in the Netherlands in 1992-3, public health authorities started offering additional vaccination with both tOPV and eIPV to the Dutch population. Because of the high demand during the first days of the outbreak, the Netherlands restricted vaccination with tOPV to persons at highest risk (i.e. mainly children who had refused vaccination on religious grounds) (43). However, with the report of two paralytic cases in older adults, authorities dropped the age restriction on the response with tOPV and throughout the outbreak they used eIPV for susceptibles in the general population (van der Avoort HGAM, Rijksinstituut voor Volksgezondheid en Milieukunde (RIVM), personal communication, 2003). While vaccination of susceptibles in the religious communities occurred most intensely from September to November 1992 (van Loon AM, Universitair Medisch Centrum Utrecht, personal communication, 2003), some received a third dose six months after receiving the first two doses, and increased immunization activity lasted well over a year (Bosman A, RIVM, personal communication, 2003). Based on this information and estimates of polio vaccine use (46), we modeled a response lasting 365 days with three tOPV doses targeted at all members of the religious communities and a response lasting 365 days with two eIPV doses targeted only at unvaccinated persons (all ages) in the general population. Although reports from some parts of the country indicated an immunization coverage of 60 percent for the tOPV response (van der Avoort HGAM, Rijksinstituut voor Volksgezondheid en Milieukunde (RIVM), personal communication, 2003), we assume that the average tOPV response coverage in the religious coverage was as low as 35 percent (Oostvogel PM, Medisch Centrum Haaglanden, personal communication, 2004).

Estimation of the population immunity profiles in the prospective model

Our approach to estimate the income level dependent population immunity profiles consists of two steps, the first being to determine the profile at the point of certification and the second to update the profile on a yearly basis taking into account the vaccination decision taken at the point of certification. For the first step, we make several assumptions regarding the immunity status of typical populations at certification, as characterized by the inputs in the last section of table 3. WHO projected as the most realistic scenario that coverage with three or more doses of diphteria-tetanus-pertussis vaccine (DTP3) remains almost constant beyond 2004 (65). Based on the current small difference between DTP3 coverage and coverage with 3 or more doses of tOPV (66), we use for our future coverage for both eIPV and tOPV the income-level averages projection for DTP3 in 2004, using 2002 World Bank income levels (67). A key determinant of population immunity in high-income countries (assumed to already be using eIPV at the time of certification) is the year of the switch to IPV. We assume that a typical high-income country will have used eIPV for the last 10 years prior to certification of global polio eradication. For eIPV-using countries, the immunity profile for cohorts born since the switch to eIPV follows directly from the take rate for three eIPV doses and the routine immunization coverage. For older age groups, table 3 displays the assumed proportions whose immunity derives from the OPV or wild polio eras.

For the countries in the low and middle-income levels (which we assume will not switch to eIPV before certification), the last year with supplemental immunization activities (SIAs) is a

key factor for the population profile at certification and beyond. If the year of certification is greater than the last year with SIAs, the initial proportions in partially immunity group 1 (recent OPV) and 2 (historic OPV/wild) for cohorts not covered by SIAs derive from the routine immunization coverage, the take rates and the cumulative secondary OPV infection rate due to routine immunization applied on a yearly basis for 10 years. We use the same linearly decreasing (by age) secondary OPV infection rate function as in the outbreak model. For cohorts previously covered by SIAs we assume a fixed total proportion of partially infectibles and estimate how many of them and the fully susceptibles would have had a recent secondary OPV infections. In the event of continued SIAs (assumed to be targeted at children less than 5 years of age only) until certification, we assume the proportions of children less than 5 years of age in partially infectibles group 1 and 2 directly, as given in the last section of table 3. For older persons, the approach is similar to the approach for countries that discontinued SIAs, except that the secondary OPV infection rates are higher to include the effect of the continued SIAs. Table A7 gives the population immunity profiles at the time of certification obtained with this approach and all inputs from table 3 kept at their base case value.

After defining the population immunity profiles at the time of certification, the profile in future years of the post-certification era follows from any take rates, immunization coverage and secondary OPV infection rates that apply to the chosen strategy.

TABLE A4. Initial population immunity profiles for the retrospective case studies*

Age group	Albania 1996†				Dominican Republic 2000-2001‡				Netherlands 1992-1993§							
	Entire country				The 5 provinces with reported cases				Religious communities				General population			
(years)	Size (x1000)	Group 1 (recent OPV#)	Group 2 (historic OPV/wild)	Fully suscep-tibles	Size (x1000)	Group 1 (recent OPV)	Group 2 (historic OPV/wild)	Fully suscep-tibles	Size (x1000)	Group 2 (historic OPV/wild)	Group 3 (IPV# only)	Fully suscep-tibles	Size (x1000)	Group 2 (historic OPV/wild)	Group 3 (IPV only)	Fully suscep-tibles
0	63	76.5%	0.0%	23.5%	87	51.0%	0.0%	49.0%	3.9	5.0%	35.0%	60.0%	192	5.0%	91.0%	4.0%
1	73	6.0%	69.0%	25.0%	79	4.9%	51.0%	44.1%	3.8	5.0%	35.0%	60.0%	187	5.0%	91.0%	4.0%
2	73	6.2%	70.8%	23.0%	79	4.4%	55.9%	39.7%	3.8	5.0%	35.0%	60.0%	187	5.0%	91.0%	4.0%
3	73	6.4%	73.6%	20.0%	79	4.0%	60.3%	35.7%	3.8	5.0%	35.0%	60.0%	187	5.0%	91.0%	4.0%
4	73	6.0%	69.0%	25.0%	79	3.6%	64.3%	32.1%	3.8	5.0%	35.0%	60.0%	187	5.0%	91.0%	4.0%
5-9	342	6.6%	78.4%	15.0%	399	0.6%	93.4%	6.0%	18	10.0%	37.0%	53.0%	903	10.0%	87.0%	3.0%
10-14	310	5.2%	64.8%	30.0%	404	0.3%	96.6%	3.1%	18	15.0%	35.0%	50.0%	885	15.0%	82.0%	3.0%
15-19	297	5.4%	69.6%	25.0%	388	0.0%	99.2%	0.8%	20	20.0%	33.0%	47.0%	981	20.0%	78.0%	2.0%
20-24	287	4.5%	60.5%	35.0%	328	0.0%	99.2%	0.8%	23	24.0%	31.0%	45.0%	1,166	24.0%	73.0%	3.0%
25-29	278	5.0%	70.0%	25.0%	302	0.0%	99.2%	0.8%	26	29.0%	30.0%	41.0%	1,274	29.0%	69.0%	2.0%
30-34	275	5.4%	79.6%	15.0%	281	0.0%	99.2%	0.8%	25	34.0%	28.0%	38.0%	1,245	34.0%	64.0%	2.0%
35-39	232	5.7%	89.3%	5.0%	247	0.0%	99.2%	0.8%	23	59.0%	18.0%	23.0%	1,167	59.0%	39.0%	2.0%
40-44	174	5.5%	90.5%	4.0%	206	0.0%	99.2%	0.8%	23	69.0%	14.0%	17.0%	1,149	69.0%	30.0%	1.0%
45-49	131	5.3%	91.7%	3.0%	165	0.0%	99.2%	0.8%	21	78.0%	10.0%	12.0%	1,026	78.0%	21.0%	1.0%
> 49	505	4.0%	95.0%	1.0%	475	0.0%	99.2%	0.8%	84	94.0%	2.0%	4.0%	4,192	94.0%	5.0%	1.0%

*All estimates are subjectively corrected for proportion of an age group exposed (recently or not) to secondary OPV, consistent with assumptions about secondary OPV infection rates (as function of age and group of partially infectibles) used in the outbreak model

†Assumes no one is in partial infectivity group 3 (IPV-only). Sources include population data, vaccination coverage, vaccination history and seroimmunity data (33, 59, 61, 63)

‡Assumes no one is in partial infectivity group 3 (IPV-only). Sources include population data, vaccination coverage and vaccination history (35, 39, 59, 61, 66) and unpublished data on vaccination coverage (Pedreira MC, Pan American Health Organization, personal communication 2003)

§Assume no one is in partial infectivity group 1 (recent OPV). Sources include population data, vaccination coverage data, estimates of unvaccinated persons among the religious communities by age group and seroimmunity data (43, 44, 47, 59, 61)

#IPV= any inactivated polio vaccine; OPV = any oral polio vaccine

TABLE A5. Model inputs for the model of the outbreak of circulating vaccine-derived poliovirus in the Dominican Republic in 2000-2001*

Model input	Value	Range	Sources	Notes
Number of virus introductions (in random age groups)	1		(35)	
Date of virus introduction	05/27/'00	04/16/'00-06/28/'00	(35)	Estimated date of introduction derived from regression of observed isolate sequences in Viral Protein 1 region back to common ancestral node, with the presumption that this ancestral infection occurred in the Dominican Republic; lower end of range is six weeks before the base case value, upper end is 2 weeks before the first reported case
Mean R_0† of the outbreak virus	11	5-13	(20, 32)	Approximate average of estimates in lower middle-income settings
Seasonal amplitude of R_0 [highest – lowest]	2	0-6		Assumes little seasonal variation in tropical setting
Peak day of seasonal transmission	July 1	June 1-Sep 1		Mid-year
Size of the outbreak population	3,600,000	1-9 million	(35, 36)	Equals the sum of 1993 estimates of population of provinces with at least one case during the outbreak
Birth rate [per day per total population]	0.000066		(66)	Annual births/(population * 365) (medium variants)
First day of mass immunization response round 1	12/15/'00		(37)	
First day of mass immunization response round 2	02/04/'01		(35)	Estimated this from (35, Fig.1)
First day of mass immunization response round 3	04/29/'01		(35, 40)	Estimated from figures
Age groups targeted by mass immunization response	0-4 yrs.		(35)	
Duration of mass immunization rounds [days]	3		(37, 38)	Exact dates for rounds 2 and 3 are not given; assume same duration as round 1
Achieved mass immunization coverage (by round) [%]	99.9;99.9; 95%		(38)	99.9% instead of reported 100% for mathematical reasons
Half-life of secondary OPV infection rate after mass immunization rounds [days]	8.6		(60)	Type 1 estimate
Proportion of susceptible children who will eventually get infected due to secondary OPV† exposure from a mass immunization round [%]	46.4%	20%-60%	(60)	Type 1 estimate
Secondary OPV infection rate for last age group, as a proportion of the rate for children under 5, during immunization response (rate declines linearly with age) [proportion]	0.3	0-1		
Routine immunization coverage (3 doses or more) since 1996 [%]	60%	40%-80%	(61)	Lower than reported figures of ca. 80% or more, based on (Pedreira MC, Pan American Health Organization, personal communication, 2003)
Take rate for 3 or more doses of polio vaccine (routine	85%	75%-95%	(18)	Type 1 tOPV† estimate, corresponds approximately to

immunization)[%]				average of middle-income country estimates cited in (18)
Take rate for 1 dose of tOPV (during response)[%]	60%	50%-70%	(18)	Type 1 estimate, corresponds approximately to average of middle-income country derived from 2-dose estimates cited in (18)
Rate of paralytic polio cases per poliovirus infection for fully susceptibles [proportion]	1/100	1/200-1/50	(11, 62)	Type 1 estimate
Proportion of children aged 5-9 who were infected/vaccinated by 1996 [%]	90%	80%-95%		Based on judgment; input used for estimation of initial population immunity profile
Proportion of children aged 10-14 who were infected/vaccinated by 1996 [%]	95%	90%-98%		Based on judgment; input used for estimation of initial population immunity profile
Proportion of children aged ≥15 who were infected/vaccinated by 1996 [%]	98%	99%-100%		Based on judgment; input used for estimation of initial population immunity profile

*Refer to the technical appendix for additional information on how we obtain and use inputs

†OPV = any oral polio vaccine; R_0 = basic reproductive number; tOPV = trivalent oral polio vaccine

TABLE A6. Model inputs for the model of the Dutch wild poliovirus importation outbreak in 1992-1993*

Model input	Value		Sources	Notes
Number of virus introductions (in random age groups)	1			Assume introduction in subpopulation 1
Date of virus introduction	06/10/'92	02/27-08/27/'92		Based on judgment and iteration in the model with different possible values as part of model fitting. Lower end of range is 3 months before the base case value, upper end is 3 months after the base case value.
Mean R_0† of the outbreak virus	5	4-7	(20, 32)	Approximate average of estimates in high-income settings.
Seasonal amplitude of R_0 [highest – lowest]	8	5-10		Assumes substantial seasonal variation in temperate climate setting.
Peak day of seasonal transmission	September 1	July 1 – Sep 30		Start of school year
Size of the outbreak population	15,228,500		(59)	Linear interpolation between medium variants of Dutch population (by 5-year age groups) in 1990 and 1995
Size of subpopulation 1: the religious communities	300,000		(47)	
Size of subpopulation 2: the general population	14,928,500			Total population – subpopulation 1
Birth rate (both subpopulations) [per day per total population]	0.000035		(59)	Annual births/(population x 365)
First day of immunization response	09/22/'92		(43)	
Age groups targeted by immunization response	all ages	0-15 yrs.-0-45 yrs.	(43)	Although the main focus of immunization may have been children at some stage, this restriction was dropped after the occurrence 2 paralytic cases in older adults (van der Avoort HGAM, Rijksinstituut voor Volksgezondheid en Milieukunde, personal communication, 2003)
Duration of immunization response [days]	365	100-400		Main immunization activity may have been from September to November (van Loon AM, Universitair Medisch Centrum Utrecht ,personal communication, 2003), but third doses were given 6 months later and the total duration of immunization activity was at least one year (Bosman A, Rijksinstituut voor Volksgezondheid en Milieukunde, personal communication, 2003)
Achieved immunization response coverage (tOPV in subpopulation 1, eIPV in the general population) [%]	tOPV†: 35% eIPV†: 50%	tOPV: 40%-80% eIPV: 30%-70%	(46)	35% estimate for tOPV vaccination in subpopulation 1 based on judgment (Oostvogel PM, Medisch Centrum Haaglanden, personal communication, 2004); assuming that the ~ 500,000 eIPV doses (46) were used only for those unvaccinated other than for religious reasons (van der Avoort HGAM, Rijksinstituut voor Volksgezondheid en Milieukunde, personal communication, 2003), we estimate that 2 eIPV doses were given to ~ 50% of the ~ 500,000 susceptibles in the general population
Half-life of secondary OPV† infection rate after mass immunization rounds [days]	NA†	NA	NA	Because of the long duration of the response in this outbreak, we model the secondary OPV spread as a constant function during the response and 0 afterwards
Proportion of susceptible children who will eventually get infected due to secondary OPV	17.9%	0-45%	(60)	Type 3 estimate; applies only to subpopulation 1

exposure from a mass immunization response [%]				
Secondary OPV infection rate for last age group, as a proportion of the rate for children under 5, during immunization response (rate declines linearly with age) [proportion]	1	0.3-1.0		We assume all age groups in subpopulation 1 benefited from secondary OPV exposure at the same rate because the tOPV response reached all age groups.
Routine immunization coverage in subpopulation 1 (3 doses or more) [%]	41.7%	30%-50%	(44, 47)	Estimated as the estimated number of unvaccinated persons under age 50 in the religious communities divided by the population under age 50
Routine immunization coverage in subpopulation 2 (3 doses or more) [%]	97%	95%-100%	(43, 61)	National coverage with 3 or more doses of IPV
Take rate for 3 or more doses of eIPV (routine immunization)[%]	99%	95%-100%	(15, 19, 45)	A Dutch study showed only 77.1% of children had antibodies to type 3 poliovirus before administration of the 4th doses of IPV around 1980 (cited in 45); however, after booster doses, antibodies were close to 100%; other more recent studies (cited in (15, 19)) in high-income settings also showed close to 100% seroconversion
Take rate for 3 doses of tOPV (during response in subpopulation 1) [%]	82.5%	80%-85%		15 to 20% of children who received 3 doses during the response lacked antibodies to type 3 poliovirus (Bosman A, Rijksinstituut voor Volksgezondheid en Milieukunde, personal communication, 2003)
Take rate for 2 eIPV doses (during response in subpopulation 2)	97%	95%-100%	(15, Table 24-5)	Type 3 estimate; equals rounded sample-size-weighed average of study results cited in (15, Table 24-5)
Rate of paralytic polio cases per poliovirus infection for fully susceptibles [proportion]	1/1000	1/1000-1/200	(11, 64)	Type 3 estimate
Proportion of potentially infectious contacts of persons in subpopulation 1 that are with persons in subpopulation 2	1%	0%-20%		Based on judgment

*Refer to the technical appendix for additional information on how we obtain and use inputs

†eIPV = enhanced-potency inactivated polio vaccine; NA = not applicable; OPV = any oral polio vaccine; R_0 = basicc reproductive number; tOPV = trivalent oral polio vaccine

TABLE A7. Base case population immunity profile at the time of certification for use in the prospective model*

Age group	Low -income countries assuming continuation of SIAs† until certification			Low-income countries assuming no SIAs since 5 years prior to certification			Lower middle -income countries assuming continuation of SIAs until certification			Lower middle-income countries assuming no SIAs since 5 years prior to certification			Upper middle -income countries assuming continuation of SIAs until certification			Upper middle-income countries assuming no SIAs since 5 years prior to certification			High-income countries (assuming switch to IPV† 10 years prior to certification, no SIAs)		
	Grp. 1‡ [%]	Grp. 2§ [%]	Fully susc. [%]	Grp. 1 [%]	Grp. 2 [%]	Fully susc. [%]	Grp. 1 [%]	Grp. 2 [%]	Fully susc. [%]	Grp. 1 [%]	Grp. 2 [%]	Fully susc. [%]	Grp. 1 [%]	Grp. 2 [%]	Fully susc. [%]	Grp. 1 [%]	Grp. 2 [%]	Fully susc. [%]	Grp. 1 [%]	Grp. 3# [%]	Fully susc. [%]
0	95.0	0.0	5.0	48.3	0.0	51.7	95.0	0.0	5.0	76.5	0.0	23.5	78.2	0.0	21.8	95.0	0.0	5.0	0.0	93.1	6.9
1	95.0	0.5	4.5	6.4	47.1	46.5	95.0	0.5	4.5	4.3	74.6	21.2	4.1	76.2	19.6	95.0	0.5	4.5	0.0	93.1	6.9
2	95.0	1.0	4.0	8.6	49.5	41.9	95.0	1.0	4.0	8.2	72.8	19.0	8.2	74.2	17.7	95.0	1.0	4.0	0.0	93.1	6.9
3	95.0	1.5	3.5	8.4	53.9	37.7	95.0	1.5	3.5	7.9	74.9	17.1	7.9	76.2	15.9	95.0	1.5	3.5	0.0	93.1	6.9
4	95.0	2.0	3.0	8.3	57.8	33.9	95.0	2.0	3.0	7.9	76.7	15.4	7.9	77.8	14.3	95.0	2.0	3.0	0.0	93.1	6.9
5-9	45.5	51.5	3.0	7.6	89.4	3.0	28.0	69.0	3.0	7.6	89.4	3.0	7.6	89.4	3.0	22.8	74.2	3.0	0.0	93.1	6.9
10-14	43.8	53.2	3.0	7.3	89.7	3.0	26.9	70.1	3.0	7.3	89.7	3.0	7.3	89.7	3.0	21.9	75.1	3.0	95.0	0.0	5.0
15-19	42.1	54.9	3.0	7.0	90.0	3.0	25.9	71.1	3.0	7.0	90.0	3.0	7.0	90.0	3.0	21.1	75.9	3.0	95.0	0.0	5.0
20-24	41.2	57.8	1.0	6.9	92.1	1.0	25.3	73.7	1.0	6.9	92.1	1.0	6.9	92.1	1.0	20.6	78.4	1.0	95.0	0.0	5.0
25-29	39.5	59.5	1.0	6.6	92.4	1.0	24.3	74.7	1.0	6.6	92.4	1.0	6.6	92.4	1.0	19.7	79.3	1.0	95.0	0.0	5.0
30-34	37.7	61.3	1.0	6.3	92.7	1.0	23.2	75.8	1.0	6.3	92.7	1.0	6.3	92.7	1.0	18.9	80.1	1.0	95.0	0.0	5.0
35-39	36.0	63.0	1.0	6.0	93.0	1.0	22.1	76.9	1.0	6.0	93.0	1.0	6.0	93.0	1.0	18.0	81.0	1.0	95.0	0.0	5.0
40-44	34.2	64.8	1.0	5.7	93.3	1.0	21.0	78.0	1.0	5.7	93.3	1.0	5.7	93.3	1.0	17.1	81.9	1.0	95.0	0.0	5.0
45-49	32.5	66.5	1.0	5.4	93.6	1.0	20.0	79.0	1.0	5.4	93.6	1.0	5.4	93.6	1.0	16.2	82.8	1.0	95.0	0.0	5.0
50-54	30.7	68.3	1.0	5.1	93.9	1.0	18.9	80.1	1.0	5.1	93.9	1.0	5.1	93.9	1.0	15.4	83.6	1.0	98.0	0.0	2.0
55-59	29.0	70.0	1.0	4.8	94.2	1.0	17.8	81.2	1.0	4.8	94.2	1.0	4.8	94.2	1.0	14.5	84.5	1.0	98.0	0.0	2.0
60-64	27.2	71.8	1.0	4.5	94.5	1.0	16.7	82.3	1.0	4.5	94.5	1.0	4.5	94.5	1.0	13.6	85.4	1.0	98.0	0.0	2.0
65-69	25.5	73.5	1.0	4.2	94.8	1.0	15.7	83.3	1.0	4.2	94.8	1.0	4.2	94.8	1.0	12.7	86.3	1.0	98.0	0.0	2.0
70-74	23.7	75.3	1.0	4.0	95.0	1.0	14.6	84.4	1.0	4.0	95.0	1.0	4.0	95.0	1.0	11.9	87.1	1.0	98.0	0.0	2.0
75-79	22.0	77.0	1.0	3.7	95.3	1.0	13.5	85.5	1.0	3.7	95.3	1.0	3.7	95.3	1.0	11.0	88.0	1.0	98.0	0.0	2.0
80-84	20.2	78.8	1.0	3.4	95.6	1.0	12.4	86.6	1.0	3.4	95.6	1.0	3.4	95.6	1.0	10.1	88.9	1.0	98.0	0.0	2.0
85-89	18.5	80.5	1.0	3.1	95.9	1.0	11.4	87.6	1.0	3.1	95.9	1.0	3.1	95.9	1.0	9.2	89.8	1.0	98.0	0.0	2.0
90-94	16.7	82.3	1.0	2.8	96.2	1.0	10.3	88.7	1.0	2.8	96.2	1.0	2.8	96.2	1.0	8.4	90.6	1.0	98.0	0.0	2.0
95-99	15.0	84.0	1.0	2.5	96.5	1.0	9.2	89.8	1.0	2.5	96.5	1.0	2.5	96.5	1.0	7.5	91.5	1.0	98.0	0.0	2.0
>100	14.3	84.7	1.0	2.4	96.6	1.0	8.8	90.2	1.0	2.4	96.6	1.0	2.4	96.6	1.0	7.1	91.9	1.0	98.0	0.0	2.0

*Refer to the technical appendix for additional information on how we obtain the estimates

†IPV = any inactivated polio vaccine; OPV = any oral polio vaccine; SIAs = supplemental immunization activities; susc. = susceptible

‡ Recent OPV partially infectibles

§ Historic OPV/wild partially infectibles

Only IPV-vaccinated partially infectibles

Additional model output details

Table A8 summarizes the main results of our simulations of the three outbreaks.

TABLE A8. Summary of base case results of the three retrospective case studies (reported numbers from Refs. (33, 35, 43)).

	Week number when cumulative incidence exceeds 1	Cumulative number of cases until the week of the first mass immunization response	Cumulative number of cases up to and including the week of the last reported case	Cumulative number of cases at end of simulation	Mean absolute difference model vs. reported, by week (n=52 weeks)
Albania, reported	16	113	138	138	
Albania, model at base case	22	112.8	153.8	155	
Relative difference*	0.38	0.00	0.11	0.12	0.96
Dominican Republic, confirmed cases	28	10	13	13	
Dominican Republic, polio-compatible cases	30	12	13	13	
Dominican Republic, total reported cases	28	22	26	26	
Dominican Republic, model at base case	37	18.3	30.3	35.6	
Relative difference*	0.24	-0.20	0.14	0.27	0.75
The Netherlands, reported	38	1	71	71	
The Netherlands, model at base case	38	0.7	59.5	60.1	
Relative difference*	0.00	-0.43	-0.19	-0.18	0.62

*(model-reported)/reported

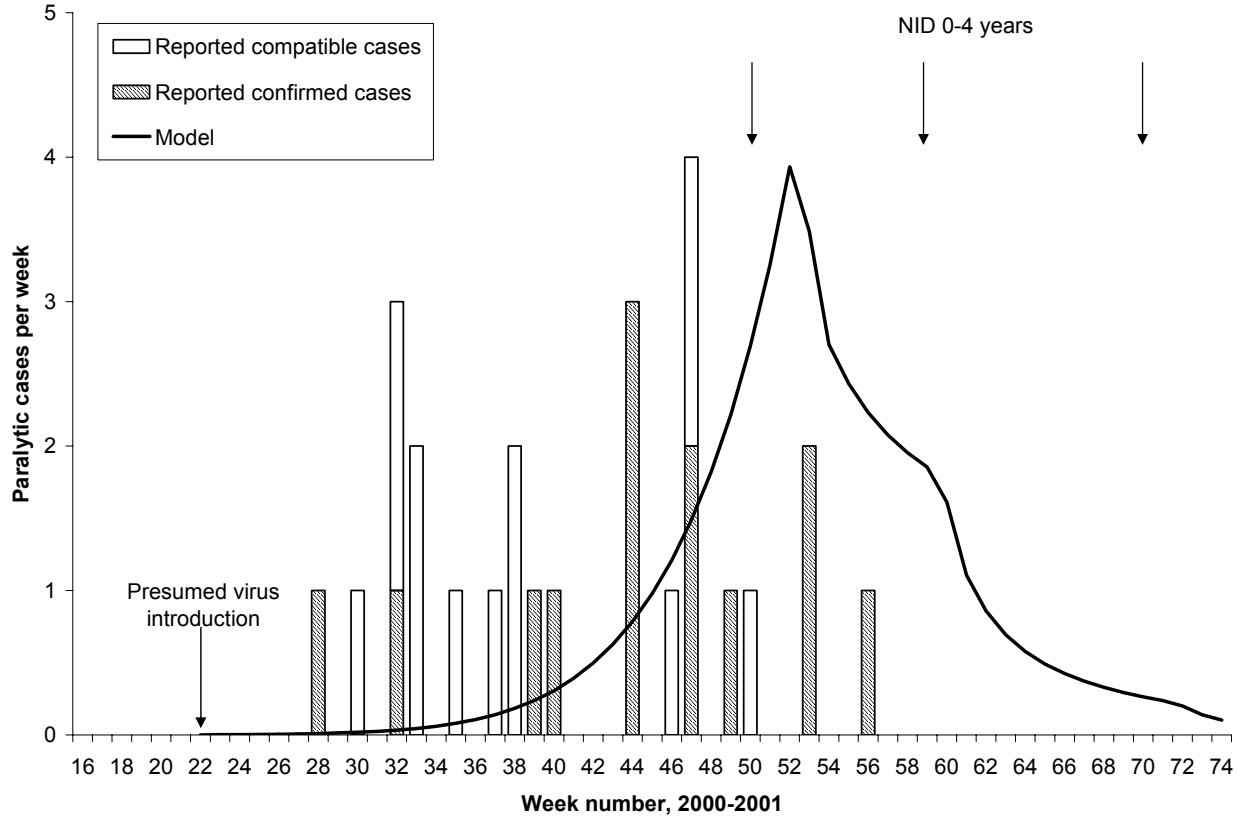
Notes about the Albania outbreak simulation

During the initial stages of the outbreak we observe a small discrepancy between the model and the reported cases, with the simulated cumulative number of 0.1 paralytic polio cases up to the week of onset of paralysis of the first reported case (week 16). By week 20 (second reported case), the model still obtains a cumulative incidence of only 0.6 paralytic polio cases. Although interpretation of such small numbers in a continuous population model as actual infections remains meaningless, this could indicate a discrepancy in the modeled and actual transmissibility of polioviruses during the spring in Albania or between the modeled and actual initial population immunity profile.

Notes about the Dominican Republic outbreak simulation

Figure A5 shows the results of the outbreak simulation of the cVDPV outbreak in the Dominican Republic. The uncertainty about the true R_0 for cVDPVs is even greater than for wild polioviruses since so few data exist. We tested values as low as $R_0 = 5$ (which led to less than 10 cumulative infections) for this outbreak as well as other values up to the base case value of 11. Given our assumptions about population immunity and other attributes of the outbreak, we did not obtain a better visual fit. Only with better district-level data could we investigate this issue further with a more heterogeneous model.

FIGURE A5. Weekly incidence of confirmed and polio-compatible cases in the 2000-2001 Dominican Republic outbreak; reported data from Ref. (35)



Notes about the simulation of the outbreak in the Netherlands

Figure A6 shows the results of the simulation of the Dutch outbreak. When we ran an otherwise similar model characterizing the entire population of the Netherlands as one homogeneous block, this failed to result in any notable outbreak (< 0.5 cumulative cases after more than 1.5 years), which underscores the importance of considering real heterogeneities in the population.

The reported numbers include 10 non-paralytic cases while the model derives cases from the (type 3) rate of paralytic cases per infection, which varies according to virus strain and outbreak population (11, 62). Figure A7 demonstrates the impact of varying the rate of paralytic cases per infection.

Figure A8 reveals a small resurgence in the incidence in the general population ("2.84 cases" in the second year) and this demonstrates a drawback of a continuous population model in which the prevalence of infectious persons never reaches zero. The virus prevalence in the general population remains very low during the winter of 1993 (6 infections including 4 in IPV vaccinees), but when R_0 starts to increase when the seasons change the model predicts a very small outbreak in the general population in the second year, an event that did not occur in reality. We emphasize that this example demonstrates the fact that the model allows fractional numbers of infections and cases, where in fact individual people either do or do not become infected. In a real situation, different chains of transmission within the outbreak end dead when the virus does not transmit to a next person because of a combination of a lack of contacts with susceptible

persons, environmental conditions and chance. After all transmission chains die out, the outbreak is obviously over. The fact that outbreaks die out of their own accord provides an indication that dynamic modelers must report low fractional numbers cautiously with the realization that infection thresholds exist (at least at the level of individuals in the population).

FIGURE A6. Weekly incidence of polio cases in the 1992-1993 outbreak in the Netherlands; reported data from Ref. (43)

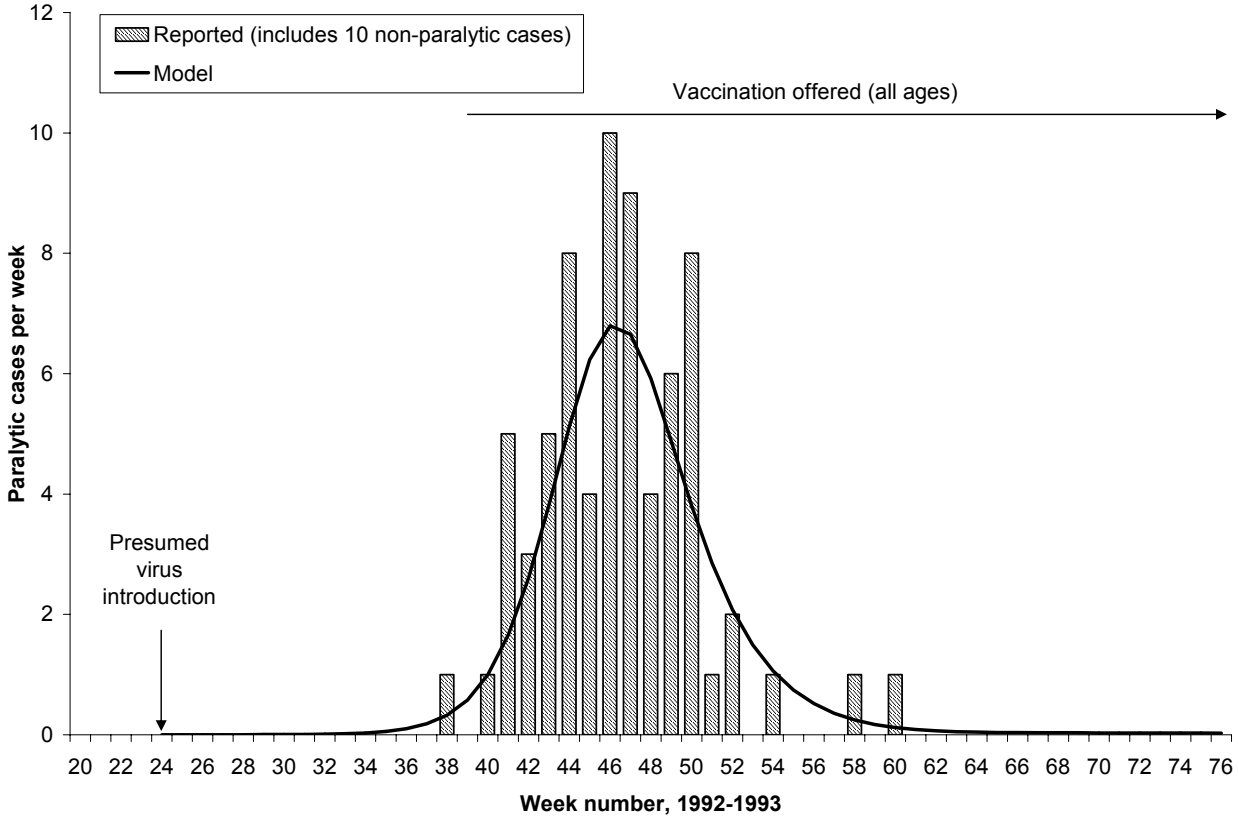


FIGURE A7. Influence of rate of paralytic polio per infection on weekly incidence of polio cases in the Dutch outbreak; reported data from Ref. (43)

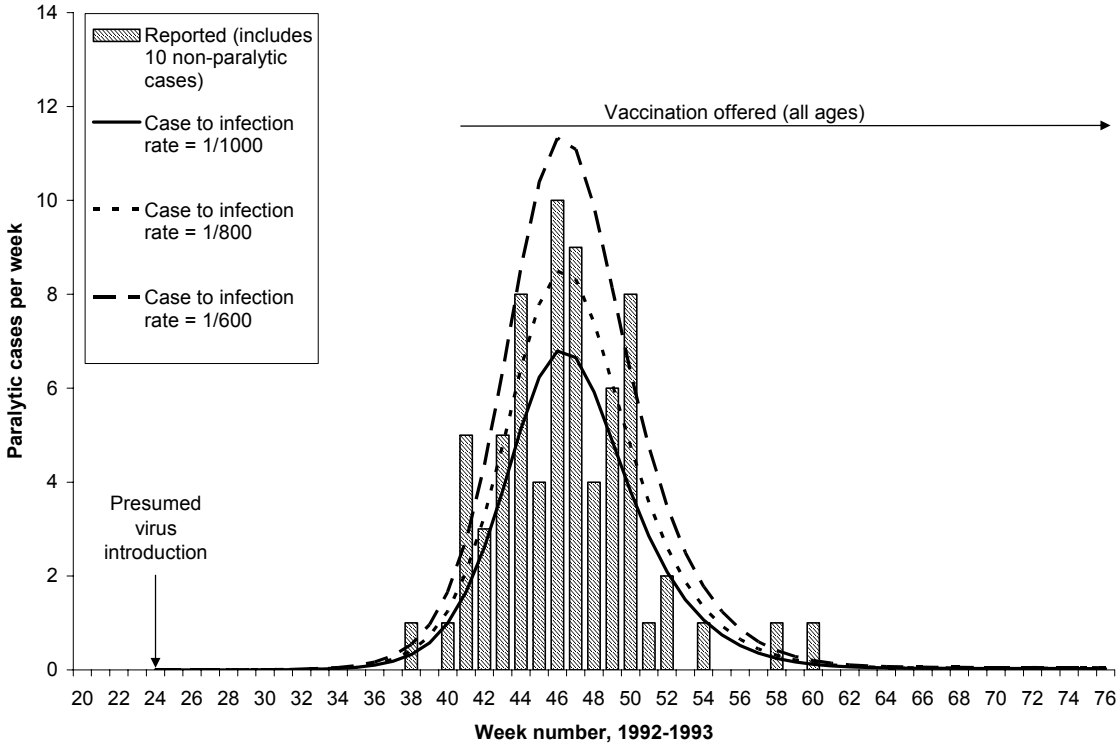
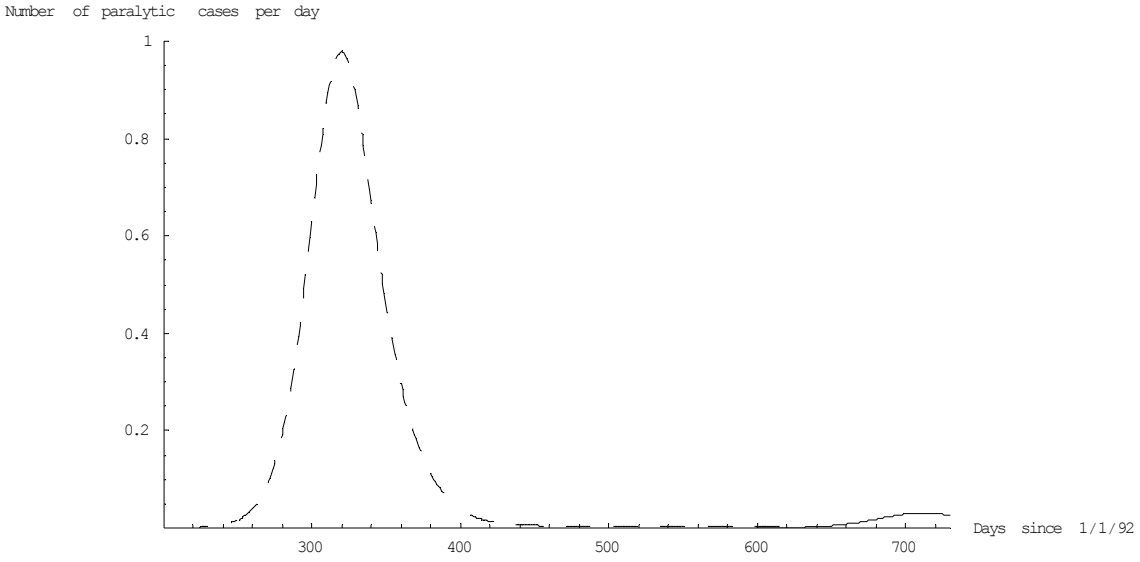


FIGURE A8. Modeled daily incidence of paralytic cases during the Dutch outbreak in the religious communities (dashed line) and the general population (solid line)



Sensitivity analysis

Using the total number of outbreak cases as the outcome measure, we performed one-way sensitivity analyses on inputs in each of the outbreaks based on the ranges in tables 1-2 and A5-A6. Our focus on the outbreak magnitude as the modeling outcome of interest means that our sensitivity analyses may not identify all inputs substantially impacting other potential outcome choices (e.g., the height of the outbreak peak or the overall match of the model curve to the reported cases). Of the three outbreaks that we modeled, we find that the sensitivity analysis results show less uncertainty in the Dutch outbreak than in the other two outbreaks, consistent with our understanding of these outbreaks.

The sensitivity analysis identified several key uncertain inputs. Variation of the duration of the infectious period over its range produces the greatest impact on the total number of cases at the end of the simulation in the Dominican Republic and Dutch outbreaks, and the second greatest impact in the Albanian outbreak. In the Albanian outbreak, the proportion secondarily immunized by an NID represents a more influential input because of the spring NID that Albania conducted during the initial phase of the outbreak. However, the proportion secondarily immunized due to the response immunization activities shows a much lower impact in all three outbreaks given the range we used in the sensitivity analysis. The importance of the duration of the infectious period results from the large range for which we ran this input in the sensitivity analysis (20 to 50 days for fully susceptibles; for comparison we ran the average R_0 only from 10 to 12, 5 to 13 and 4 to 7 in Albania, the Dominican Republic and the Netherlands, respectively). The relative infectiousness and relative susceptibility of the most prevalent type of partially infectibles (i.e., historic OPV/wild in Albania and Dominican Republic, IPV-only in the Netherlands) and the average R_0 represent the next most influential inputs overall. In the Dutch outbreak, the infectious period of IPV-immunes and the rate of paralytic cases per infection show

similar magnitudes of impact. In the Dominican Republic, the date of virus introduction also ranked among the most important inputs. In the Dutch and the Albania outbreaks the very low transmissibility of the virus in winter reduces the impact of decreasing the date of the virus introduction.

Varying several other inputs also yields important changes, but the model shows less sensitivity to these inputs than to the ones mentioned above. For all of the outbreaks, the amplitude and peak day of seasonal transmission, and the duration of the latent period all represent inputs in this second tier. Similarly, the infectious period for partially infectibles with historic OPV/wild infection falls in this tier for both the Albanian and Dominican Republic outbreaks. In Albania, the delay between tOPV administration and individual protection falls within this same second tier of inputs due to the spring NID. In the Dominican Republic, other inputs in this tier include the routine immunization coverage, the secondary OPV infection rate due to routine immunization, and the take rates of three tOPV doses. This reflects our use of those inputs to estimate the initial population immunity profile in children under 5 years of age (as opposed to the two other outbreaks where we did not model the population immunity profile as a function of those inputs). In the Netherlands, the relative susceptibility and infectiousness for partially infectibles with recent OPV/wild infection, the proportion of outside-subpopulation contacts, and the duration of the response (because of the large uncertainty concerning that input in the Dutch outbreak) also fit in this second tier.

Overall, given the ranges we used in this analysis, the take rates (apart from the three-dose tOPV take rate in the Dominican Republic), the relative infectiousness, relative susceptibility and duration of infectiousness of partially infectibles with recent OPV infection, and the duration of the incubation period yielded little influence on the number of cases. We note that although the incubation period does not influence the final outcome of estimated paralytic polio cases, it does influence the time at which cases occur and can influence the matching of data in intermediate time points.

In the Dominican Republic model only, we tested the influence of the population immunity profile in people older than 5 years of age, but this showed little influence on the number of cases. Some key inputs interact in very important ways, and for this reason we considered them in combination. The date of introduction and peak day of seasonal transmission both interact importantly with each other, R_0, and its amplitude. In Albania, variation of the date of introduction at intermediate points in the range revealed non-monotonic behavior of the model output as a function of this input. Depending on the peak day, an early virus introduction did not lead to more cases because the seasonal transmissibility at time of introduction was too low to allow for expansion of the outbreak in its initial stages. In the Netherlands, the minimum and maximum values for the peak day of seasonal transmission both lead to a lower number of total cases than the base case estimate, revealing that the model output is not monotonic in that input.

CHAPTER 6

Sensitivity Analyses of a Dynamic Economic Evaluation Model for Vaccination Programs

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ABSTRACT

With public policy increasingly relying on mathematical models to provide insights about the impacts of potential policy options, the demand for sensitivity analyses that explore the implications of different assumptions in the model continues to expand. While analysts develop methods to meet the demand, remarkably most modelers rely on a single method in the context of their assessments and presentations of results, and few analysts provide results that facilitate comparisons between the sensitivity analysis methods. Sensitivity analyses vary in their degree of analytical difficulty and in the nature of the information that they provide, and analysts must communicate their results while noting that not all sensitivity analysis methods might necessarily yield the same insights. This paper uses the dynamic cost-effectiveness model of a hypothetical infectious disease as the basis to perform one-way and multi-way sensitivity analyses, design-of-experiments, and Morris' method. We also compute partial derivatives as well as a number of probabilistic sensitivity measures, including correlations, regression coefficients and the correlation ratio to demonstrate the existing methods and to compare them. For this model, we obtained a range of importance rankings for different sensitivity analysis methods and characterizations of uncertainty, although each measure, with the exception of unit-dependent measures (partial derivatives and regression coefficients), correctly identified the three most important inputs. Sensitivity analyses remain a critical part of any model used to inform policy decisions, and appropriate methods exist for a wide array of practical constraints, characterizations of uncertainty, and desired insights.

Keywords: sensitivity analysis; uncertainty analysis; cost-effectiveness analysis; economic evaluation; decision analysis; design-of-experiments; dynamic infection transmission model

INTRODUCTION

Risk management in public health often involves difficult decisions and high stakes. Applied mathematics plays an increasingly important role in assisting decision makers by providing estimates of future risks and trade-offs associated with different options, and the methods analysts use continue to evolve.[1] Mathematical models for infectious disease transmission play a critical role in appropriately characterizing the impacts of diseases and potential interventions in a population.[2] Edmunds and colleagues emphasized the need for analysts to use these models in their economic analyses to appropriately account for the important dynamics inherent in infectious disease control.[3, 4] Recent experience demonstrates that such models can indeed provide a much more realistic picture than static (linear) models in real economic evaluations.[5]

Both analysts and decision makers must deal with the uncertainties inherent in models, but doing so requires characterizing uncertainty.[6] The Panel on Cost-effectiveness in Health and Medicine recommended performing both sensitivity and uncertainty analyses to quantify the importance of the lack of knowledge about the inputs on the outcome of the analysis.[7] The panel discusses some aspects of doing uncertainty and sensitivity analysis in the context of results in the form of a (cost-effectiveness) ratio. With computational power and the level of sophistication of sensitivity analysis methods continuing to evolve, understanding and interpretation of available methods becomes crucial to choose the most appropriate method for a given model.

In general, sensitivity analysis aims to answer the following questions:

1. Which of the uncertain inputs impact the model output the most (i.e., can we rank them)?
2. How importantly do interactions between inputs affect the output?
3. How much of the uncertainty in the output can we attribute to the uncertainty of different inputs?

Thus, a sensitivity analysis gives the model user a sense of the absolute and relative impact of the uncertainty in the various model inputs on the model output. This insight can help target further research aimed at reducing the uncertainty of specific model inputs and provide an idea about the robustness of the analytical outcome. In real problems, modelers face limits in their choice of appropriate sensitivity analysis methods based on the types of information they have about the uncertainty of the model inputs and the computational cost of the model. We consider four cases that represent realistic situations in ascending order of the amount of prior knowledge about the uncertainty:

1. The modeler professes complete ignorance about the amount of uncertainty in each model input,
2. The modeler asserts knowledge about the ranges for each input, but remains ignorant about the shape of input distributions and the probabilities of the possible values within these ranges,
3. The modeler has a sense of the marginal uncertainty distributions for individual inputs and can reasonably assume independence between the model inputs, and
4. The modeler has a sense of the marginal uncertainty distributions and the dependence structure of the model inputs.

We explore available sensitivity analysis methods for each case on a generic dynamic economic evaluation model of vaccination against a hypothetical infectious disease.[3] This

example illustrates important considerations in choosing a sensitivity analysis method and demonstrates the insights one can gain from performing a sensitivity analysis using different methods. For purposes of this analysis, we assume that agreement exists on the structure of the model (i.e., lack of *model uncertainty)* and focus solely on the uncertainty about the inputs (*parameter uncertainty)*, although we emphasize that the model structure also plays a critical role in the context of most real models.

We first provide a brief description of each method with references to further reading on them. Then, we present and explain the results with each different sensitivity analysis method. We conclude with a discussion of the insights we obtained through these analyses.

METHODS

We first discuss the basic model on which we explore the sensitivity analysis methods and then describe these methods.

The basic model (Edmunds et al., 1999)

A sensitivity analysis explores how a given model $y = y(\mathbf{x}) = y(x_1,\ldots,x_k)$ reacts to variations in the k uncertain model inputs $x_1,\ldots,x_k$. We refer to the k-dimensional space spanned by $(x_1,\ldots,x_k)$ as the *input space*. In this paper, we use as the basic model y a proposed generic model that estimates the costs and benefits of a hypothetical vaccination program against a hypothetical infectious disease (see appendix).[3] This model first calculates the number of disease cases that a vaccination program would prevent compared to the situation without vaccination using a dynamic infectious disease transmission model.[2, 3, 8] Edmunds et al. (1999) then calculate the cost-effectiveness ratio (CER) of this vaccination program as the discounted costs of the vaccination program divided by the discounted number of disease cases prevented by vaccination.[3] However, the CER can be a problematic endpoint in the context of performing a sensitivity analysis. First, ambiguity exists with a negative CER since in that case the magnitude of the CER does not reveal whether the intervention is very beneficial (costs < 0 and effectiveness > 0) or completely undesirable (costs > 0 and effectiveness < 0). Furthermore, it is possible that the denominator of the CER equals zero at some point of the input space, in which case the CER is undefined.[5] Given these irregularities, we modify the original model[3] to a net benefit (NB) formulation, which requires attributing a monetary amount H to a disease case in order to express both economic and health outcomes on the same scale. If the analysis takes a societal perspective, then H includes all health-care and non health-care related costs of a disease case.

Table 1 shows the base case values (i.e., the best estimates) of each input in the basic model, which we abbreviate functionally as $NB = y = y(\mathbf{x}) = y(N,\gamma,\mu,\beta,vc,tr,\delta,c,H)$, and the uncertainty ranges and distributions we chose for them. We chose bounded distributions such that the bounds correspond to the uncertainty ranges and the means were close, but not always equal to the base case value (e.g., for the discount rate we chose the base case value of 0.03 as the most likely value in a triangular distribution, although its mean equals approximately 0.043 and its median approximately 0.041). We use these distributions and uncertainty ranges solely for the purpose of demonstrating sensitivity analysis methods; other choices would lead to different results. We assume a constant population size N, and consequently we exclude this input from the sensitivity analysis. We consider the remaining inputs as the set of $k = 8$ uncertain inputs, so the input space consists of the 8-dimensional space spanned by (γ, μ, β, vc,

tr, δ, *c*, *H*). We assume a time horizon of 10 years from the beginning of the vaccination program. At the base case, the model estimates a net benefit of approximately $11 million.

Table 1: Model inputs and characterization of the uncertainty.

Model input [symbol]	Base case value*	Unit	Range	Distribution
Population size [*N*]	1 million	-	No uncertainty assumed	
Recovery rate [γ]	50	1/year	30-70	Beta(6,6,30,70)
Mortality/birth rate [μ]	0.02	1/year	0.019-0.021	Triangular(0.019,0.02,0.021)
Transmission coefficient [β]	0.000246	1/year	0.0001-0.0004	Beta(1.8,2,0.0001,0.0004)
Vaccination coverage [*vc*]	0.9487	proportion	0.75-0.99	Beta(6,1.5,0.75,0.99)
Vaccine take rate [*tr*]	0.9487	proportion	0.85-0.99	Beta(5,2,0.85,0.99)
Discount rate [δ]	0.03	1/year	0-0.1	Triangular(0,0.03,0.1)
Cost per immunized child [*c*]	10.54	dollars	8-15	Triangular(8,10.54,15)
Health cost per disease case [*H*]	100	dollars	75-125	Beta(1.25,1.25,75,125)

* Base case values (except *H*) adapted from Table I in Edmunds et al. (1999): we chose *vc, tr* and *c* such that for the base case $vc \times tr = 0.9$, i.e., the "vaccination efficacy", and $vc \times c \times \mu \times N = 200{,}000$, i.e., the annual "net cost."[3] The estimates for *H* reflect a mild, transient disease.

Sensitivity analysis methods

Table 2 lists the methods we used for each case. For the first case (i.e., complete ignorance about the uncertainty) we computed partial derivatives at the base case, for the second case (i.e., availability of uncertainty ranges only) we performed one-way sensitivity analyses (OWSA), multi-way sensitivity analyses (MWSA), design-of-experiments (DOE) methods, and Morris' method, and for the third and fourth case (i.e., availability of information about the joint uncertainty distribution of the inputs) we computed a number of probabilistic sensitivity measures. We briefly describe each approach and refer to the appendices for additional details. We denote the minimum value of input x_i by x_i^{min}, the maximum value by x_i^{max}, and the base case value by x_i^{base}. We computed model evaluations in Mathematica™ and sensitivity measures for cases 1 and 2 in MS Excel™ (partial derivatives, OWSA, Morris) or Design-Ease™ (DOE).

Table 2: Summary of sensitivity analysis methods for each case

Case	Characterization of the uncertainty	Approach/Methods	Number of model evaluations used
1	Ignorance about model inputs	Partial derivatives	$k+1=9$
2	Uncertainty ranges for each input	One-way sensitivity analysis (OWSA) Multi-way sensitivity analysis (MWSA) Morris' method Design-of-Experiments (DOE)	$2k=16$ 30 $r\times(k+1)=900$ (i.e., $r=100$) variable from $2^{k-2}=64$ to $2^4 3^4=1296$
3	Independent marginal distributions for each input	Correlation ratio (CR) Regression coefficients Correlation coefficients	10,000
4	Marginal distributions and dependence structure	Same as case 3, but includes a dependence specification (here in the form of a vine)	10,000

Partial derivatives. Given that the basic model has no closed form solution, we have to approximate the partial derivatives. We computed the k partial derivatives using the following formula:

$$\frac{\partial y}{\partial x_i}(\mathbf{x}^{base}) = \frac{y(x_1^{base},...,x_i^{base}+\varepsilon,...,x_k^{base}) - y(\mathbf{x}^{base})}{\varepsilon} \quad (1)$$

where we took an arbitrary small value for ε (i.e., 10^{-7}, other small values did not alter the estimates substantially).

One-way sensitivity analysis (OWSA). OWSA evaluates each input independently at the lower and upper end of the uncertainty range with all other inputs kept at their base case values, implying $2k$ model evaluations. In OWSA, the measure of importance of input x_i is the difference between $y(x_i^{max}) = y(x_1^{base}, x_2^{base}, ..., x_i^{max},..., x_k^{base})$ and $y(x_i^{min}) = y(x_1^{base}, x_2^{base}, ..., x_i^{min},..., x_k^{base})$, i.e., which we shall refer to as the *one-way effect*. We ranked the inputs according to the absolute value $|y(x_i^{max}) - y(x_i^{min})|$.

Multiway sensitivity analysis (MWSA). To illustrate MWSA, we chose two inputs, vc and β, and varied these simultaneously at 5 and 6 different levels, respectively, while keeping all other inputs at their base case values.

Design of experiments (DOE). We refer to the appendix for additional information and to the literature[9, 10] for a complete description of DOE methods. DOE designs a set of model evaluations (i.e., experiments) for all or a fraction of possible combinations of input values, where each input can take a finite number of different values (i.e., *levels*, usually 2 or 3 per input, corresponding to low, medium, and high estimates). A two-level design varies the endpoints in the hypercube that bounds the input space. A three-level design (or more) explores

the interior points (at the medium level) and provides more coverage of the space. In a two-level design, the *main effect me(x_i)* of an input is defined as the average output of all model runs with the input at the maximum level minus the average output with the input at the minimum level. The two-way interaction between two inputs x_i and x_j is defined as half the difference between the main effect of x_i at x_j^{max} and the main effect of x_i at x_j^{min}. Higher order interactions are defined analogously. We start with a 2^8 full factorial design (requiring 256 evaluations of the basic model) to illustrate the main idea of DOE. We demonstrate how a fractional design could reveal much of this information with fewer model evaluations by assuming that higher-order interactions are of negligible magnitude. These two-level designs implicitly assume that the model responds in a linear way to variation of the inputs. However, addition of a center point to the full factorial design reveals the existence of non-linearities, motivating us to run a 3^{13} Taguchi design[9, 11] requiring 27 model runs that has a highly aliased structure but is useful to quickly explore the form (i.e. linear or non-linear) of the model for each input.[i] Based on the insights from that design, we construct a $2^4 3^4$ mixed factorial design (1296 model runs) to explore some of the behavior of the model in response to the inputs at the interior of the input space.

Morris' method. Morris (1991) proposed this method as an efficient algorithm to screen inputs for their overall importance.[12] We discretize the range of each input into (p-1) intervals of equal length, such that the input space consists of $(p\text{-}1)^k$ hypercubes. On this grid and for an appropriate choice of Δ and p (see appendix), we define the *elementary effect* $d_i(\mathbf{x})$ of the i^{th} input at point $\mathbf{x}$ as:

$$d_i(\mathbf{x}) = \frac{y(x_1, \ldots, x_i + \Delta(x_i^{max} - x_i^{min}), \ldots, x_k) - y(\mathbf{x})}{\Delta} \qquad (2)$$

This represents an approximation of the effect of the model with respect to x_i, at the point $\mathbf{x}$. Note that if we would instead divide by $\Delta(x_i^{max}\text{-}x_i^{min})$, we would get an approximation of the partial derivate instead of an effect, although it would for common choice of Δ be much less local than the partial derivatives calculated in equation (1) with small ε. Morris' method evaluates the elementary effects at pseudo-randomly sampled points on the grid. The sampling algorithm randomly samples a starting point, and then selects a next point that differs by $\Delta(x_i^{max}\text{-}x_i^{min})$ from the previous point in exactly one direction (i.e., input). By assuring that each direction changes once, the algorithm requires only k+1 model evaluations to compute one set of k elementary effects (i.e., one for each input). Repeating this procedure r times yields r

[i] A partial design (i.e., less than full factorial) consists of less model runs than there are effects (i.e., main effects and interactions) and thus yields more unknowns than equations. The relationship between effects that emerges from the equations is the aliasing structure. A much reduced design will contain many such aliasing relationships between effects, since there will be many more effects than model runs, but in efficient designs the aliasing structure always relates low order effects (i.e., main effects and interaction between few inputs) to effects of much higher order (that we may assume negligible compared to the low order effects) and therefore still enables good approximation of the low order effects. Like fractional factorial designs, Taguchi designs also try to capture the input space with fewer points while still maintaining statistical efficiencies (refer to the appendix for additional descriptions).

elementary effects for each input. The mean of the elementary effects of an input at different points of the input space gives an indication of its overall importance. A large standard deviation may indicate either curvature (nonlinearities) or strong interactions with other inputs, or both. We used Δ=5/9, p=10, and r=100.

Probabilistic sensitivity measures. For the probabilistic sensitivity analyses, we explicitly consider the model output y and inputs x_i as random variables, i.e., we write $Y = Y(X_1,...,X_k)$. In case 3 we assume the X_i are independent, while in case 4 we specify a different dependence structure. To evaluate the probabilistic model sensitivities we used Unicorn™ to obtain a large sample of size 10,000 for $(X_1,...,X_k)$ according to their distribution and to compute the probabilistic sensitivity measures, except for the correlation ratio which we computed in Mathematica.™ In case 3, with independent marginals, the sampling is equivalent to Monte Carlo sampling, but for case 4, we use a graphical representation of the dependence structure called a vine, along with an algorithm in Unicorn™ that can generate a sample that satisfies these dependence constraints.

Figure 1 shows the dependence structure we assumed for case 4, in the form of a vine (more specifically a D-vine).[13, 14] A regular vine is a nested set of trees, where the edges of a tree of one level represent the nodes of the tree of the next level and edges are joined by an edge in the next level only if they share a common node. A regular vine on n variables specifies a set of bivariate and conditional bivariate constraints in the form of copulae[ii] and conditional copulae.[15] A convenient way to realize these constraints is to choose a family of copulae (here we chose diagonal band copulae) indexed by correlation and assign a conditional rank correlation to each edge as shown in Figure 1. With given marginal distributions, the sampling algorithm can realize any arbitrary combination of constant conditional rank correlations in the interval [-1,1]. This is a considerable advantage over a specification using a correlation matrix, where the requirement that the correlation matrix be positive semidefinite[iii] imposes strong limitations on specified correlations. Compared to dependence trees or correlation matrices, vines have the additional advantage that we can enforce conditional correlations involving more than 2 inputs.

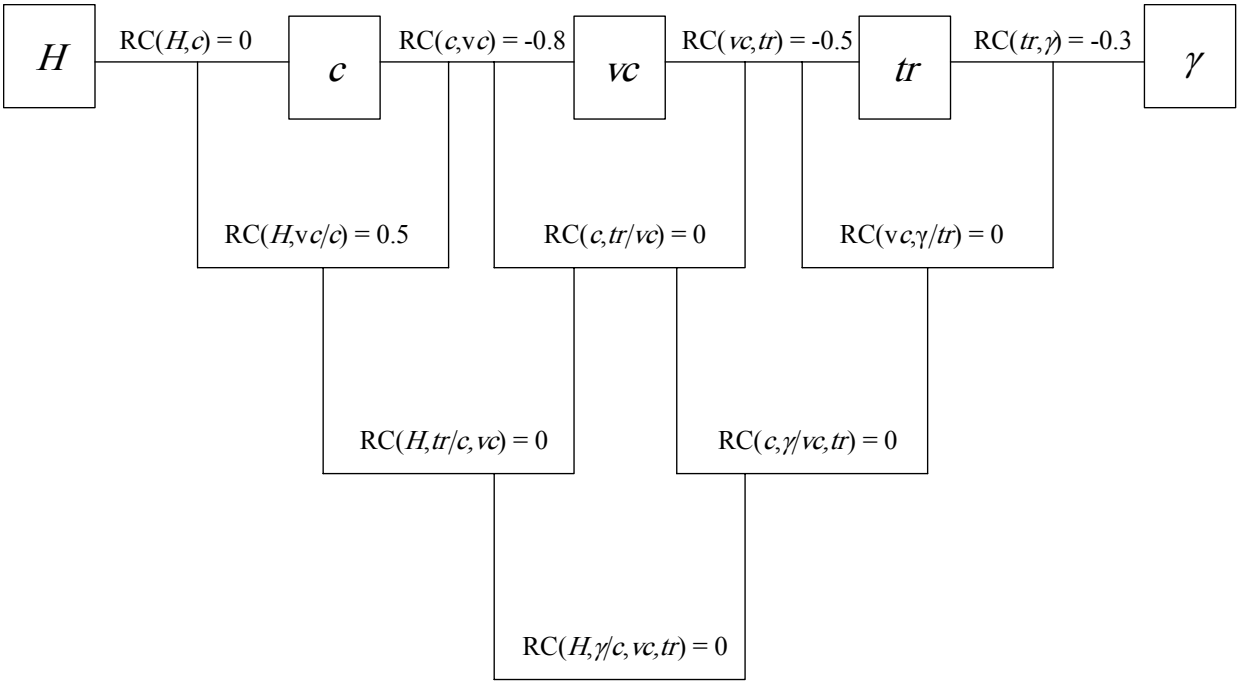
While the mortality and birth rate (μ) may not be perfectly certain for the given population, we assume this input to be completely independent of the other inputs. Similarly, the discount rate (δ) reflects the decision maker's time preference, which is independent of the values of other inputs, and the transmission coefficient (β), while highly uncertain, reflects the properties of the pathogen and contact pattern of the population but in a given population will not depend on any of the other inputs. Therefore we did not include these inputs in the vine. Given that a longer duration of infectiousness (smaller γ) might lead to a better take of the vaccine (because of a longer opportunity for the vaccine recipient to produce antibodies), we assign a moderate negative correlation between γ and tr, as shown in Figure 1. A successful take of the vaccine implies less need for high vaccination coverage and this may influence the behaviour of

[ii] A copula is a bivariate distribution with uniform marginals. Given two random variables with arbitrary continuous marginal distributions and correlation, we can use a copula to join or "couple" these variables in a joint distribution that satisfies these constraints.

[iii] For any arbitrary vector of random variables, its correlation matrix R is positive semidefinite, i.e., $a^T Ra \geq 0$ for every vector a (a^T denotes transposition of a). Thus, a consistent specification of a correlation matrix must also have this property.

the population, which we reflect with a correlation of -0.5. Likely, the cost, *c*, of a vaccination is the most important driver of the vaccination coverage, which we reflect in a strong negative correlation between *vc* and *c*. Furthermore, a very dreadful disease (i.e., a high *H*) might encourage people to vaccinate against it, implying that we should assign a moderate positive correlation of about 0.3 between *vc* and *H*. However, we believe there should be no correlation between *H* and *c* (e.g., because very cheap vaccines exist for deadly diseases). Using the vine, we can realize this by forcing zero correlation between *H* and *c*, while choosing a conditional rank correlation between *vc* and *H* given *c* such that the unconditional correlation between *vc* and *H* equals 0.3 (this corresponds to a conditional rank correlation of 0.5; see appendix). Note that this would be impossible in a tree specification that assigns rank correlations involving pairs of inputs but cannot assign conditional rank correlations involving more than two inputs. We assume conditional correlations of zero for all other edges, e.g., γ is (conditionally) uncorrelated with *vc* given *tr*.

Figure 1: Vine used for case 4 (RC = rank correlation)



Linear regression coefficient (LRC) and partial regression coefficient (PRC). $LRC(Y,X_i)$ equals the slope *a* in the least-square fit of the linear model $Y = aX_i + b$. If *Y* and X_i have zero mean, $LRC(Y,X_i)$ equals the coefficient *a* that minimizes $E((Y-aX_i)^2)$, where *E* denotes the expectation. $PRC(Y,X_i)$ is the coefficient a_i of input X_i when we linearly regress the output on all *k* inputs: $Y = a_1 X_1 + ... + a_i X_i + ... a_k X_k + b$. If *Y* and $X_1,...,X_k$ have zero mean, $PRC(Y,X_i)$ equals the coefficient a_i out of the set $\{a_1,..,a_k\}$ that minimizes $E((Y-a_1X_1-...-a_kX_k)^2)$. We can compute the LRCs using least-square fitting and the PRCs from the matrix of product moment correlations between the inputs $Y,X_1,...,X_k$ (see appendix).

Product moment correlation (PMC), rank correlation (RC) and partial correlation coefficient (PCC). While LRC and PRC describe the absolute effect that a unit change in an input exerts on the output, PMC and RC provide an indication of the type of functional relationship between input and output. The product moment correlation between the output Y and an input X_i equals:

$$PMC(Y, X_i) = \frac{E(YX_i) - E(Y)E(X_i)}{\sigma_Y \sigma_{X_i}} \tag{3}$$

where E denotes the expectation and σ the standard deviation of a random variable, and both must be finite for each variable. If Y and X_i have mean zero (which we can assume without loss of generality since $PMC(Y,X_i) = PMC(Y\text{-}E(Y), X_i\text{-}E(X_i))$), we can alternatively define PMC in terms of regression coefficients as:

$$PMC(Y, X_i) = \text{sgn}(LRC(Y, X_i))\sqrt{(LRC(Y, X_i)\, LRC(X_i, Y))} \tag{4}$$

$PMC(Y,X_i)$ equals 1 (-1) if and only if the relationship between the two random variables is of the form $Y = aX_i+b$ for some constant $a>0$ ($a<0$). If Y and X_i are independent, then $PMC(Y,X_i) = 0$, although the converse is not always true. Thus, $PMC(Y,X_i)$ provides a directional measure of the degree of linearity between Y and X_i. $PMC(Y,X_i)$ equals the *standardized regression coefficient* $LRC(Y,X_i)\times\sigma_{Xi}/\sigma_Y$. The standardized regression coefficient is the LRC after normalizing each variable v (inputs and output) according to the transformation $v^* = (v\text{-}E(v))/\sigma_v$ and is commonly interpreted in sensitivity analysis as the average number of standard deviations of change in the output per standard deviation change in an input.[16]

The rank correlation gives an indication of the degree of monotone relationship between the inputs and equals:

$$RC(Y, X_i) = PMC(F_Y(Y), F_{X_i}(X_i)) \tag{5}$$

where F_Y and F_{X_i} are the marginal cumulative distribution functions of Y and X_i, respectively. $RC(Y,X_i)$ equals 1 (-1) if there exists a strictly increasing (decreasing) function G such that $G(X_i) = Y$.

Similar to the difference between LRC and PRC, PCC reflects the PMC between an input and an output with respect to the linear relationship between the output and *all* inputs. Assuming (without loss of generality) that $Y, X_1,..,X_k$ have zero mean, we define PMC in terms of regression coefficients as:

$$PCC(Y, X_i) = \text{sgn}(PRC(Y, X_i))\sqrt{PRC(Y, X_i)\, PRC(X_i, Y)} \tag{6}$$

We can compute the PCCs from the matrix of PMCs between the inputs $Y,X_1,...,X_k$ (see appendix).

Correlation ratio (CR) and linearity index (LI). The correlation ratio of Y to X_i equals:

$$CR(Y, X_i) = \frac{\sigma^2_{E(Y|X_i)}}{\sigma^2_Y} = PMC^2(Y, E(Y|\, X_i)) \tag{7}$$

where the random variable $E(Y|X_i)$ is the conditional expectation of Y given X_i, which a function of X_i. $CR(Y,X_i)$ coincides with the maximum of $PMC^2(Y,f(X_i))$ over all functions $f(X_i)$ and therefore provides an adequate measure of the general sensitivity of Y to X_i. Furthermore, since $PMC^2(Y,X_i) \le CR^2(Y,X_i)$, where equality holds if $E(Y|X_i)$ is a linear function in X_i, we define the linearity index as a measure of the degree of linearity of $E(Y|X_i)$ as follows:

$$LI(Y, X_i) = CR(Y, X_i) - PMC^2(Y, X_i) \tag{8}$$

We approximate the function f with a polynomial of suitable degree (see appendix).

RESULTS

In this section, we discuss the results of performing sensitivity analyses on the net benefit model for each of the four cases.

Case 1: Ignorance about the amount of uncertainty in each model input

In the case of complete ignorance about the amount of uncertainty in each model input, the modeler might take partial derivatives at some location of the input space (usually the base case). This gives an idea of how the model reacts to infinitesimally small deviations around only one point of the input space. Table 3 shows approximations of the partial derivatives with respect to the 8 uncertain inputs.

Table 3: Partial derivatives of y with respect to each input

Input	*Partial derivative*[1]	*Rank based on $\lvert\partial y/\partial x_i\rvert$*
Recovery rate [γ]	-6.47×10^{4}	8
Mortality/birth rate [μ]	5.76×10^{7}	2
Transmission coefficient [β]	1.51×10^{10}	1
Vaccination coverage [vc]	-1.11×10^{6}	4
Vaccine take rate [tr]	7.11×10^{5}	5
Discount rate [δ]	-5.67×10^{8}	3
Cost per immunized child [c]	-1.64×10^{5}	6
Health cost per disease case [H]	1.27×10^{5}	7

[1] Using $\varepsilon = 10^{-7}$ in equation (1)

We see that changes in the transmission coefficient β lead by far to the greatest difference in net benefit per unit change, while a unit change in the recovery rate has little impact on the output. This depends largely on the choice of units used for each of the inputs. For example, expressing H in cents instead of dollars yields a 100-fold lower partial derivative for H. To avoid this, analysts can normalize all inputs to the unit interval, but doing so requires knowledge about the range for each input, which by assumption we do not have in this case. The rank provides an indication of the local impact of unit changes in inputs on the model. This method may be helpful for situations where one is interested in a certain point or area of the input space, although more sophisticated local measures exist.[17] Partial derivatives also provide a good approximation of the global response of the model to changes in inputs in near-linear models. However, this method gives no indication as to how linear the model is.

Case 2: Only ranges available for each model input

We discuss the results of OWSA, MWSA, DOE and Morris' method assuming that the ranges in Table 1 characterize the uncertainty of inputs.

OWSA. Table 4 shows the results of the OWSA. The ranking suggests that the transmission coefficient β, the cost per disease case H and the discount rate δ are the most influential factors and varying these inputs individually leads to a change in the net benefit of \$6.6, \$6.4 and \$5.0 million, respectively. Varying the recovery rate, the birth and mortality rate and the cost per immunized child results in net benefit changes between \$1.1 and \$2.6 million, while for the vaccination coverage and vaccine take rate the change in the net benefit is less than

$0.3 million. Table 3 and Table 4 show differences in ranking between partial derivatives and OWSA, respectively. Unlike partial derivatives, OWSA yields an *effect*, i.e., an absolute change in output resulting from changing an input over its range, and does not depend on the unit of the input.

Provided that the ranges of inputs indeed reflect a similar level of confidence in each input (e.g., for each input we are 95% certain that the value lies within the range), the OWSA yields a first look at the impact of uncertainty of the model inputs on the model output. However, the analysis completely ignores curvature and interactions. Curvature arises when the model output is non-linear with respect to the input considered. For example, the change in output associated with variation in the input may be much greater between x_i^{min} and x_i^{base} than between x_i^{base} and x_i^{max} (or vice versa), or if the model does not respond monotonically to x_i the model output may be equal for x_i^{min} and x_i^{max} (i.e., $y(x_i^{max}) - y(x_i^{min}) = 0$) but not the same for values in between. Interactions arise if the value of $(y(x_i^{max}) - y(x_i^{min}))$ varies with the choice of the values of other inputs. Since OWSA keeps the other values fixed at their base case values, this type of analysis does not reveal interactions. MWSA is a first step towards investigating the importance of interactions.

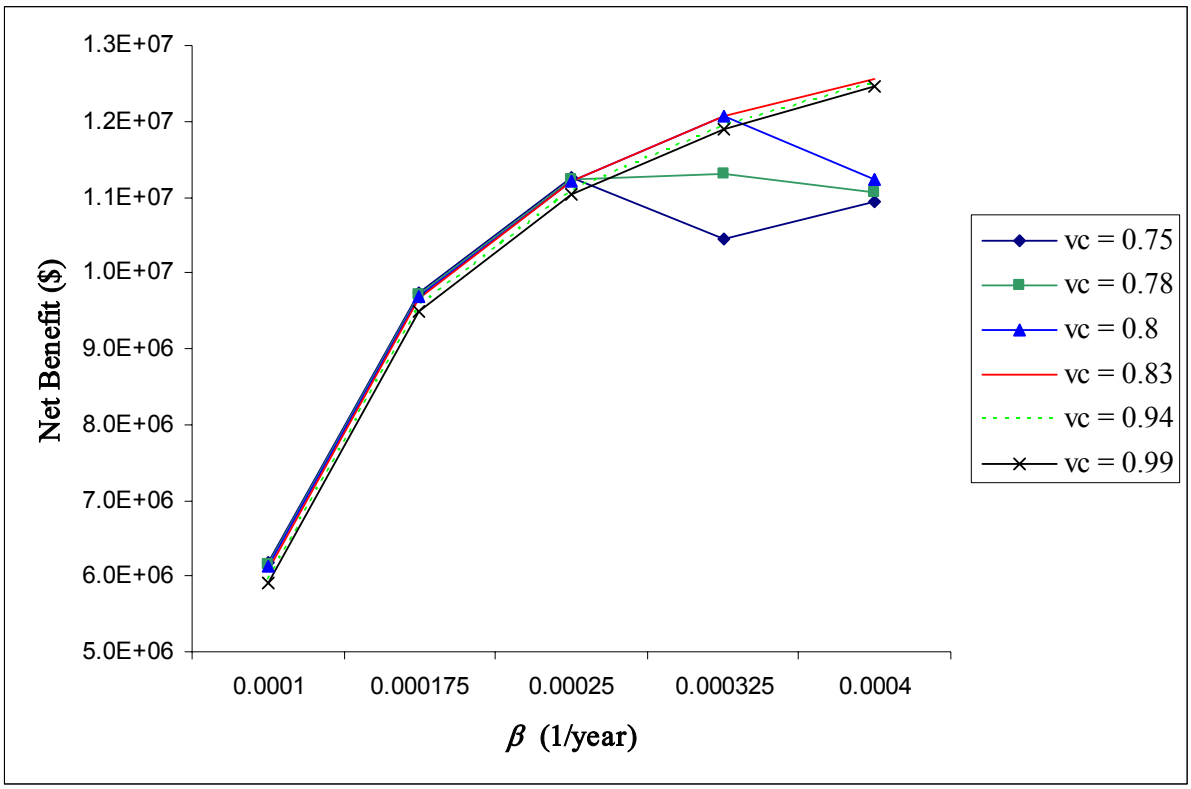
Table 4: One-way sensitivity analysis results

Input	One-way effect*	One-way partial derivative**	Rank based on |effect|	Rank based on |derivative|
Recovery rate [γ]	$-2/59\times10^{6}$	-6.47×10^{4}	4	8
Mortality/birth rate [μ]	1.15×10^{6}	5.76×10^{7}	5	2
Transmission coefficient [β]	6.55×10^{6}	1.51×10^{10}	1	1
Vaccination coverage [vc]	-2.18×10^{5}	-1.11×10^{6}	7	4
Vaccine take rate [tr]	1.07×10^{5}	7.11×10^{5}	8	5
Discount rate [δ]	-5.08×10^{5}	-5.67×10^{8}	3	3
Cost per immunized child [c]	-1.15×10^{6}	-1.64×10^{5}	6	6
Health cost per disease case [H]	6.37×10^{6}	1.27×10^{5}	2	7

* $y(x_i^{max}) - y(x_i^{min})$
** $(y(x_i^{max}) - y(x_i^{min}))/(x_i^{max} - x_i^{min})$

MWSA. In MWSA, one changes more than one input at a time to investigate how they interact. The model user usually chooses inputs that are particularly interesting or where (s)he expects important interactions. For example, Figure 2 shows how the net benefit changes when we simultaneously vary β and vc (the model user may choose these inputs because the vaccination coverage vc is somewhat controllable and the transmission coefficient β appears the most important input based on the OWSA). We see that for low values of β, vc has very little impact, while with higher β clearly lower coverage implies lower benefits. This reflects the fact that a certain coverage threshold exists for each β above which the disease gets permanently eradicated and below which epidemics can still occur.[18] Thus, a two-way sensitivity analysis as in Figure 2 helps the model user understand such interactions. However, the figure would look different if we alter the values of the other 6 inputs from their base case value. Furthermore, MWSA typically shows only a number of such interaction plots for combinations of inputs the model user *a priori* decided to be of interest and the method also lacks a quantitative measure of the sensitivity of the model to one or more inputs.

Figure 2: Example of a multi-way sensitivity analysis result simultaneously varying the transmission coefficient (β) and the vaccination coverage (vc).



DOE. DOE provides a more comprehensive approach to performing a multi-way sensitivity analysis by systemically varying inputs and measuring the main effects and interactions. The first three columns in Table 5 list the 20 most important effects in the full factorial design, which evaluates the model at all corners of the input space (i.e., $2^8 = 256$ model evaluations for 8 inputs) to assess the effect of variations in inputs or combinations of inputs. With the exception of μ and c, the ranking of the main effects remained unchanged compared to the OWSA (Table 4), although the magnitudes of the effects are different. For example, β and H have much lower main effects than OWSA effects due to the fact that they substantially interact with each other, δ and γ, and the effects of vc and tr increased due to their interactions with other inputs. Remarkably, the direction of the influence of the vaccination coverage (vc) is different in the OWSA and the full factorial DOE. Given that increasing vc leads to more prevented disease cases while at the same time also increasing the costs, it is not surprising that the values of the other inputs may alter the direction of the influence of vc. Table 5 further reveals that the main effects of β, H, δ and γ are greater than any multi-way interaction, but several two-way interactions involving β or H have more impact on the model output than any of the remaining inputs considered individually. Only two three-way interactions ($\beta\delta\gamma$ and $\gamma\beta H$) and no interactions of order four or more rank among the 20 most important effects.

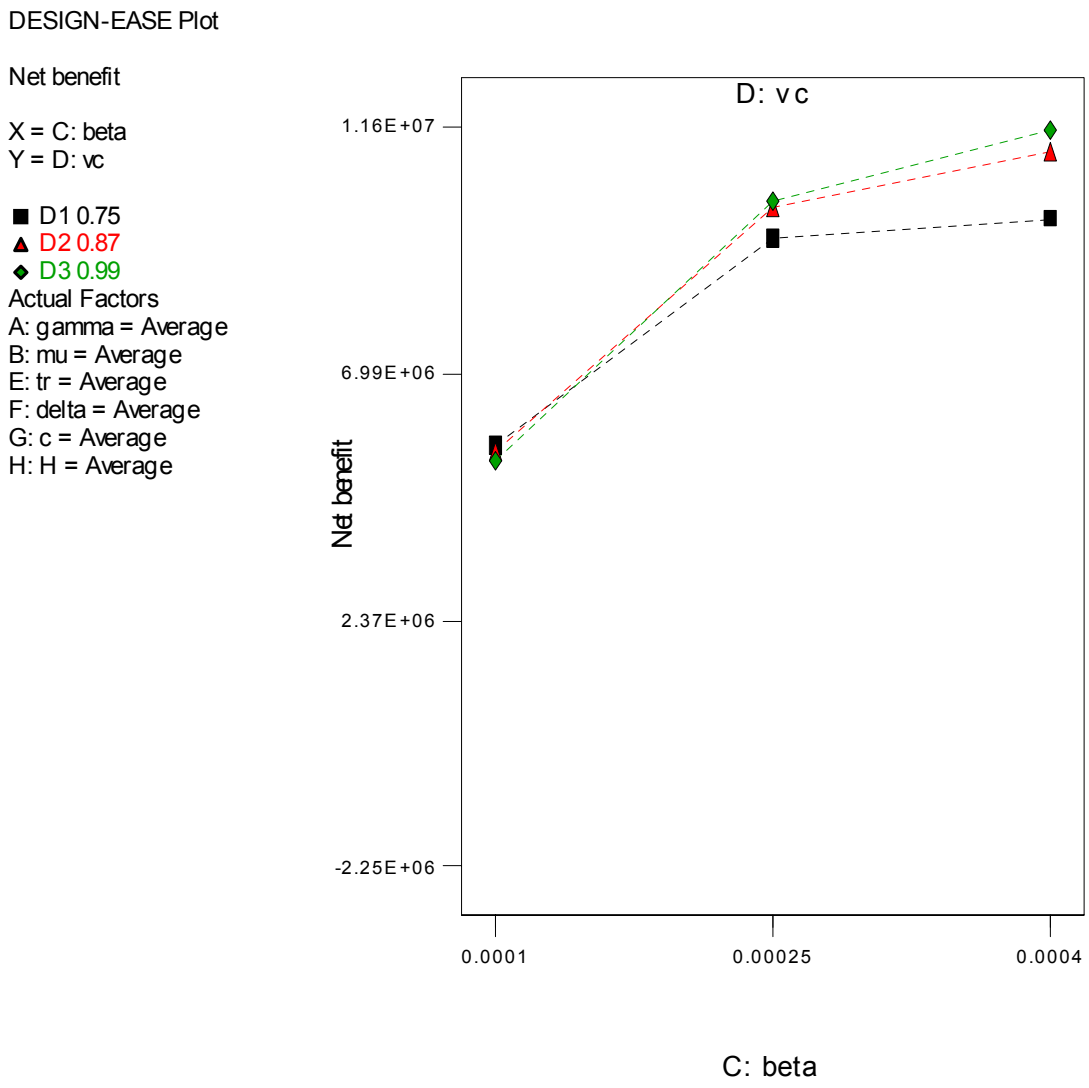
Table 5: Summary of results of the two-level designs

2^8 Full factorial			¼ fractional factorial design generated by:							
			G=ABCD; H=ABEF		G=-ABCD; H=ABEF		G=ABCD; H=-ABEF		G=-ABCD; H=-ABEF	
Rank	Term	Effect	Term	Effect	Term	Effect	Term	Effect	Term	Effect
1	C=β	5,278,938	C	5,279,750	C	5,279,750	C	5,278,127	C	5,278,127
2	H=H	4,878,953	H	4,882,228	H	4,882,228	H	4,875,678	H	4,875,678
3	F=δ	-3,994,106	F	-3,996,229	F	-3,996,229	F	-3,991,983	F	-3,991,983
4	A=γ	-3,122,945	A	-3,124,097	A	-3,124,097	A	-3,121,793	A	-3,121,793
5	AC	2,523,801	AC	2,515,803	AC	2,529,513	AC	2,518,088	AC	2,531,799
6	CH	1,319,735	CH	1,322,980	CH	1,322,980	CH	1,316,489	CH	1,316,489
7	FH	-1,182,515	FH	-1,191,007	FH	-1,191,007	FH	-1,174,023	FH	-1,174,023
8	CF	-1,129,656	CF	-1,131,410	CF	-1,131,410	CF	-1,127,902	CF	-1,127,902
9	G=c	-994,014	G	-976,893	G	-1,011,135	G	-1,043,881	G	-944,147
10	CD	913,470	CD	912,941	CD	912,941	CD	914,000	CD	914,000
11	B=μ	865,457	B	869,216	B	869,216	B	861,697	B	861,697
12	AH	-780,736	AH	-785,345	AH	-785,345	AH	-776,128	AH	-776,128
13	AF	762,146	AF	768,316	AF	768,316	AF	755,976	AF	755,976
14	ACF	-672,738	ACF	-665,719	ACF	-668,808	ACF	-676,668	ACF	-679,757
15	D=vc	642,517	D	641,983	D	641,983	D	643,052	D	643,052
16	ACH	630,950	ACH	626,379	ACH	626,379	ACH	635,522	ACH	635,522
17	E=tr	571,364	E	581,894	E	581,894	E	560,834	E	560,834
18	AD	-508,065	AD	-507,199	AD	-507,199	AD	-508,931	AD	-508,931
19	DE	-476,192	DE	-475,513	DE	-475,513	CE	479,245	CE	479,245
20	CE	471,401	BG	-465,698	CE	463,558	DE	-476,871	DE	-476,871

Besides the full-factorial two-level design, a large number of designs can either approximate the results of the full factorial design or provide additional insights. Table 5 includes the results of four ¼ fractional factorial designs of 64 runs, that approximate main effects and interactions by assuming that higher order interactions are negligible compared to lower order interactions. We design these experiments by considering only those combinations of inputs (i.e., rows of the design) that satisfy a certain condition, which we refer to as the generator (see appendix). In this case, the fractional factorial designs all maintain the rank order of the first 18 effects, and did not alter the magnitude of effects substantially compared to the full factorial design. Only for ranks 19 and 20, we see different effects in the various designs. This suggests that a ¼ fractional factorial design of only 64 runs would probably have sufficed for a two-level sensitivity analysis of this model. If one is interested in whether curvature is important in the model, a center point design that includes the middle of each interval $[x_i^{min}, x_i^{max}]$ allows for testing of the existence of non-linearities. We performed the full factorial analysis with a center point and concluded that in fact curvature is significant (see appendix). We identified γ, μ, β, vc as four inputs involved in strong curvature and tr, δ, c and H as inputs exerting a more linear impact on the output using a highly fractional Taguchi 3^{13} design of 27 model runs.[9, 11] Using this information, we performed a full $2^4 3^4$ mixed design (1296 model evaluations), where we defined three levels for the four inputs with strong curvature and two levels for the other four. Automatically generated interaction plots such as in Figure 3 and statistical analysis of a regression model of y to the most significant effects can reveal a fairly complete picture of how

the model responds to inputs and interactions based on this design (see appendix). The data points for different values of β and vc in Figure 3 show the net benefit averaged over the different values of the remaining 6 inputs, yielding a different picture than with the MWSA that kept those inputs at their base case values (Figure 2). The graph illustrates the nonlinear response and the effect of the interaction between β and vc. That is, the value of the net benefit rises more steeply with higher values of both.

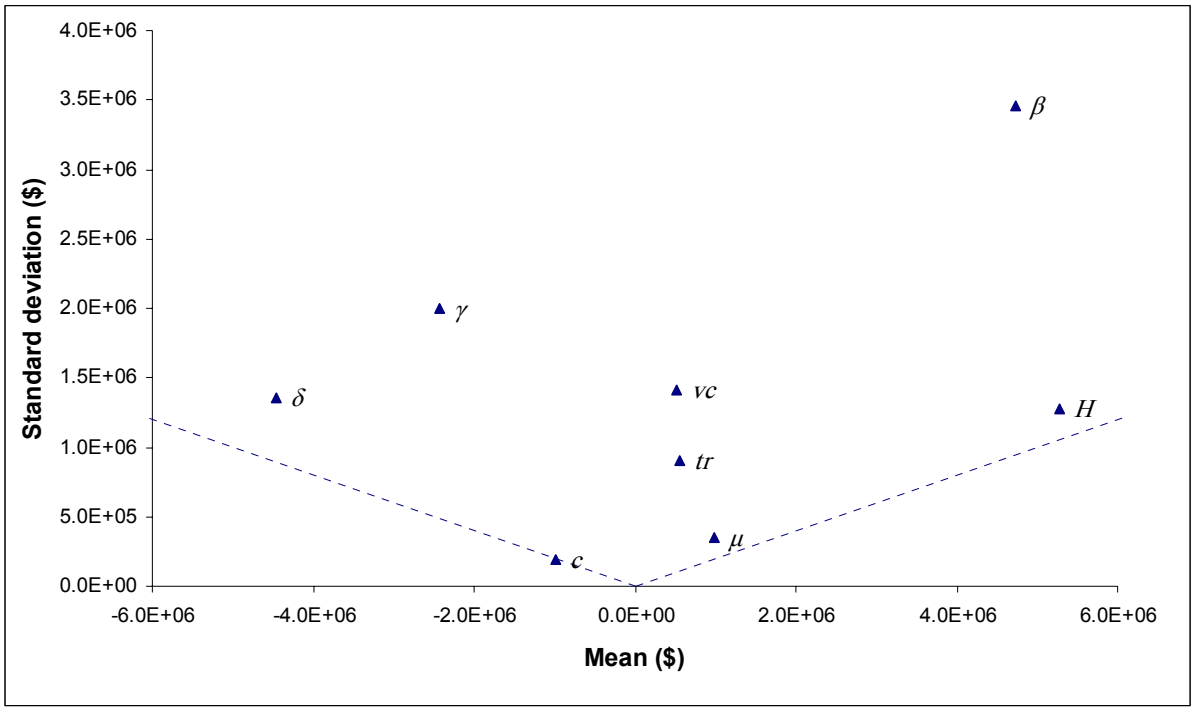
Figure 3: Example of an interaction plot in the mixed full factorial design: interaction between the transmission coefficient (β) and the vaccination coverage (vc).



Morris' method. Figure 4 shows the results of Morris' method in terms of the means and standard deviations of the elementary effects. We obtain a different ranking based on the mean elementary effects than the OWSA and DOE main effects, with H now the most important input, followed by δ and β. Figure 4 also reveals that for example the elementary effects of the

transmission coefficient β have a much greater standard deviation than those of the health cost H, although the mean elementary effects of those inputs are approximately equal. One interpretation of this is that the effect of H is more significant than that of β. In other words, the magnitude of the effect of β is dependent on where in the input space we investigate it, either because the relationship between β and the model output is non-linear and/or because β is involved in strong interactions, while H is not. The wedge in Figure 4 indicates where the mean is greater (outside the wedge) or smaller (inside the wedge) than twice the standard error of the mean (see appendix). The interpretation of an input lying outside the wedge is that its mean elementary effect is significantly non-zero. When an input lies inside the wedge, this indicates significant involvement of the input in curvature and/or interactions.

Figure 4: Mean and standard deviation of elementary effects using Morris' method with p=10, Δ=5/9 and r=100[12]



Case 3: Marginal distributions known and independence among model inputs

In the absence of further specification of input uncertainty, the methods in case 2 implicitly assume that each value in the uncertainty range is equally likely, which is equivalent to assuming independent, uniform distributions. Probabilistic sensitivity analysis methods sample input values according to the uncertainty distribution of the inputs and provide measures of importance that factor in this distribution. In this case, we assume that all inputs are independent (we assume dependence in the next case). For comparability with case 2, we first perform the probabilistic sensitivity analysis assuming uniform distributions. We then investigate how the results change when we take the distributions specified in Table 1.

Uniform marginals. Table 6 shows a number of probabilistic sensitivity measures in the event that the inputs are independent and uniform over their ranges. LRC tells us how much the

model changes per unit change of an input. It is comparable to the partial derivative in that it gives the slope of the model to an input, but LRC reflects the average slope over the entire input space rather than locally at one point of the input space. The differences between the partial derivatives from Table 1 and the LRCs from Table 6 illustrate that considering the entire input space matters. In contrast, we see that the magnitude of the PRCs changed little compared to the LRCs, indicating that interactions with other inputs do not impact the slope with respect to the inputs substantially. The degree of linearity, however, changes substantially if we consider all inputs, as indicated by the differences between PMC and PCC. PMC and RC suggest that the model responds most linearly and monotonously to β, δ and H, while the other inputs hardly correlate with the output. Note that in the DOE analysis, we identified β as an input expressing relatively strong non-linearities. However, a correlation of about 0.5 is not incompatible with this observation; we did find a clear, though non-linear response to β in the DOE analysis (see appendix).

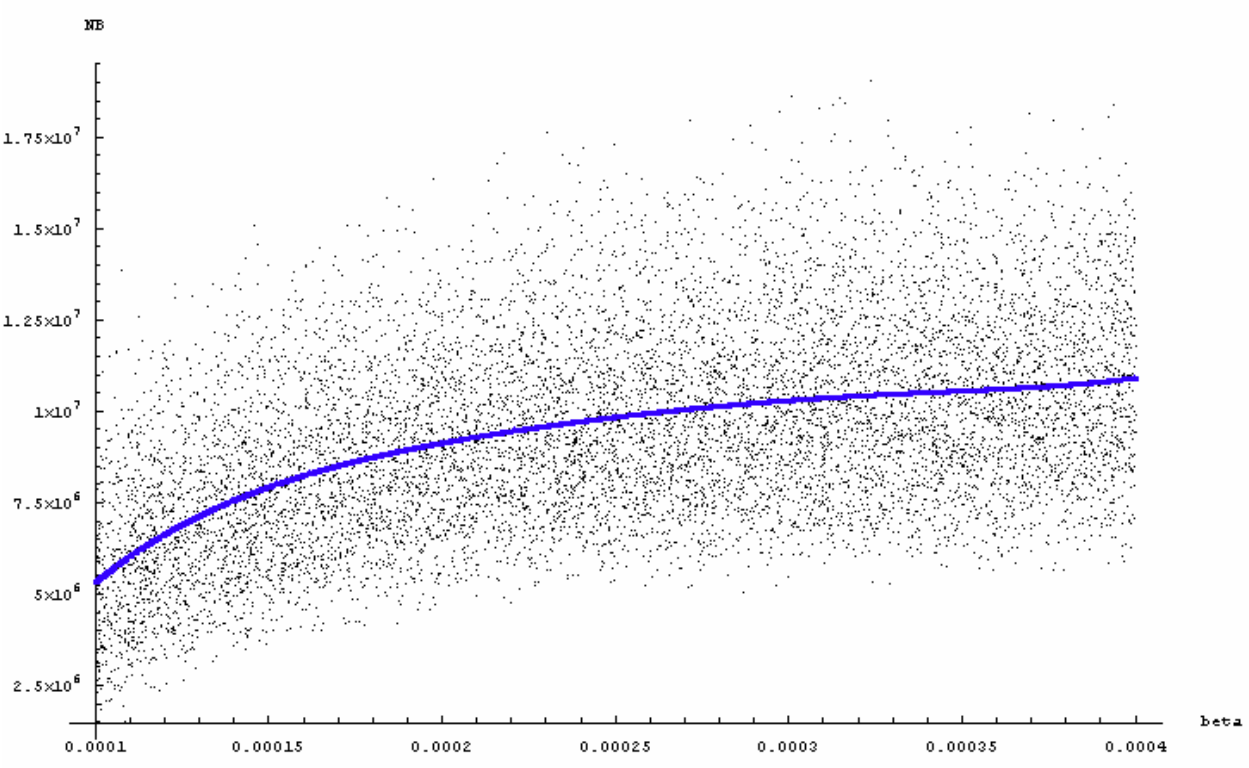
Table 6: Sensitivity analysis results assuming independent, uniform distributions over the ranges from Table 1; based on 10,000 samples.

Input	*LRC*	*PRC*	*PMC*	*RC*	*PCC*	*CR*	*LI*	*Rank*[*]
Recovery rate [γ]	-5.4×10^{4}	-5.5×10^{4}	-0.23	-0.22	-0.59	0.05	<0.01	4
Mortality/birth rate [μ]	4.9×10^{8}	5.0×10^{8}	0.10	0.10	0.29	0.01	<0.01	5
Transmission coefficient [β]	1.5×10^{10}	1.5×10^{10}	0.46	0.46	0.82	0.25	0.03	2
Vaccination coverage [vc]	2.2×10^{6}	2.0×10^{6}	0.06	0.05	0.15	0.01	<0.01	7
Vaccine take rate [tr]	3.6×10^{6}	3.7×10^{6}	0.05	0.05	0.17	<0.01	<0.01	8
Discount rate [δ]	-4.8×10^{7}	-4.7×10^{7}	-0.51	-0.50	-0.84	0.26	<0.01	3
Cost per immunized child [c]	-1.3×10^{5}	-1.4×10^{5}	-0.09	-0.09	-0.30	0.01	<0.01	6
Health cost per disease case [H]	1.1×10^{5}	1.1×10^{5}	0.60	0.60	0.87	0.35	<0.01	1

[*] Based on CR

CR = correlation ratio; LI = linearity index; LRC = linear regression coefficient; PCC = partial correlation coefficient; PMC = product moment correlation; PRC = partial regression coefficient; RC = rank correlation

Figure 5: Conditional expectation of the net benefit (NB) given the transmission coefficient (β). Assumes independent, uniform marginals; the dots show the sample of size and the line shows a polynomial fit of degree 5 on the first 5,000 samples representing the conditional expectation function (see appendix).



Finally, the CR provides an overall measure of the sensitivity of the model to each input. Figure 5 illustrates the conditional expectation of the model to the vaccination coverage *vc*. $CR(NB,\beta)$ equals the square of the PMC between the plotted line and the data points. The conditional expectation function represents the best regression of the model on the vaccination coverage and gives a graphical interpretation of the influence of β on the model. This function reveals a much sharper increase in the net benefit for values of β between approximately 0.0001 to 0.0002 than between 0.0002 and 0.0004. This is consistent with Figure 2 and Figure 3 but a much more general depiction of the relationship than we can obtain with MWSA or DOE.

When we rank the inputs according to the CR, we obtain a slightly different ranking than in the case 2 analyses, but H, β, and δ remain the 3 most important inputs. LI gives an indication of the degree of linearity of the conditional expectations (e.g., the function in Figure 5 for *vc*). If LI is close to 0, the conditional expectation function is almost linear, while an LI close to 1 indicates that the conditional expectation is non-linear. However, since LI is always smaller than CR, a small CR will always yield a small LI, and in those cases LI can conceal non-linearity of the conditional expectation (e.g., for *vc*). On the other hand, LI for H clearly indicates a high degree of linearity for the conditional expectation of the model on H.

Table 7 shows the ranking obtained according to the absolute values of selected sensitivity measures. All methods assume independent uniform marginals, either explicitly (i.e., the probabilistic measures discussed above) or implicitly by using only the uncertainty ranges and attributing equal likelihood to each point in them (i.e., the methods from case 2). To

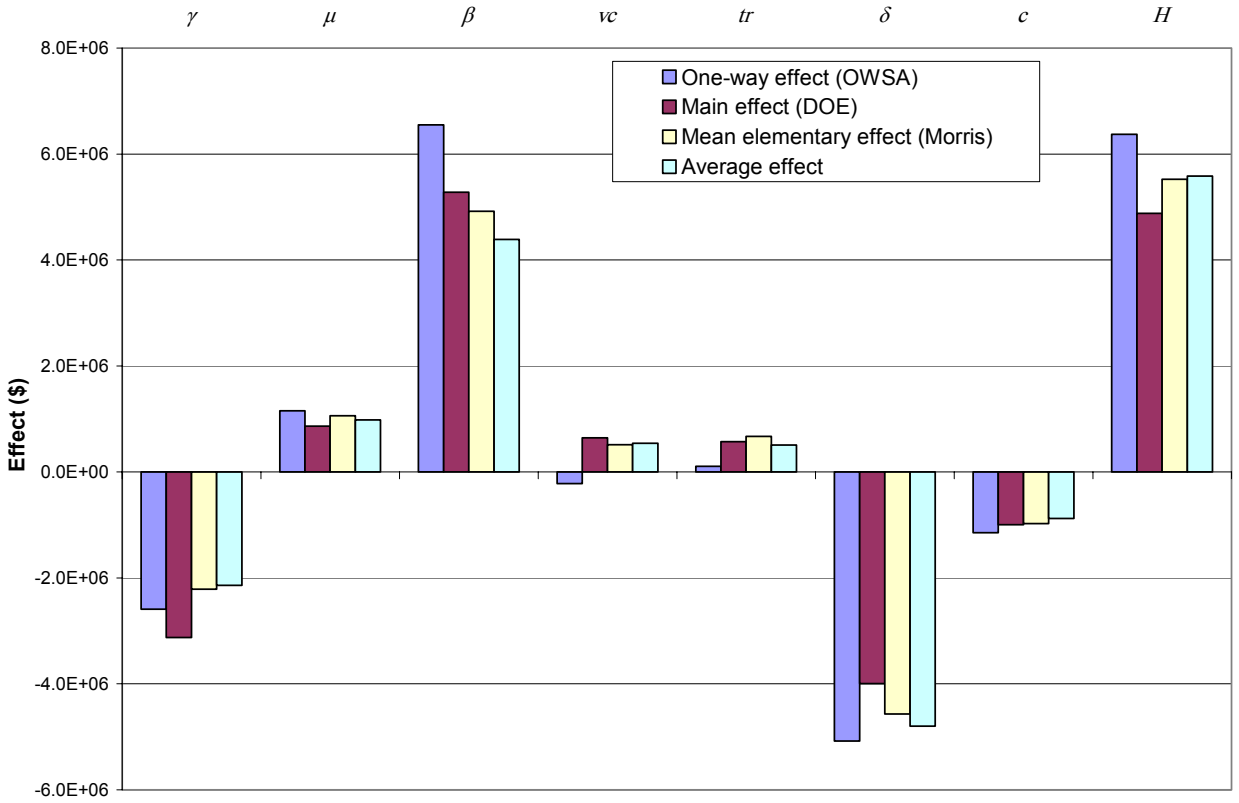
compare the probabilistic results with the case 2 results, we defined the average effect as LRC times (x_i^{max}-x_i^{min}), representing the effect of varying an output over its range averaged over the entire sample. In the case of independent, uniform marginals, this yields the same ranking as according to the PMC (see appendix). The one-way effect, main effect and mean elementary effect all approximate the average effect in some way, with increasing amount of consideration of interactions and curvature. Consequently, we see that Morris' elementary effects most closely reproduce the ranking obtained by average effects. Figure 6 illustrates this by showing the magnitudes of the effects. Morris' method is the only method that "correctly" identifies *H* as the most important input. Of the scaled measures, i.e., those whose units do not depend on the model units, the correlations (PMC, RC and PCC) all yield the same rankings as the average effect. However, they differ somewhat from the ranking obtained using the CR. The correlation measures focus on just one aspect of the relationship between an input and the output (i.e., degree of linear relationship or degree of monotone relationship), while CR summarizes the overall strength of the relationship between an input and the output, and the difference in rankings suggest that focusing on one aspect may not always be sufficient to identify the relative importance of inputs. As discussed, the partial derivate-based measures yield rankings completely different from the other measures as a result of their dependence on the input units.

Table 7: Comparison of the rankings of sensitivity analyses based on ranges or independent uniform distributions. Rankings are according to the absolute values of the selected measures.

Input	*Effect measures*				*Scaled measures*				*Partial derivatives*			
	One-way effect	Main effect[1]	Mean el. effect	Average effect[2]	PMC	RC	PCC	CR	PD[2]	Mean el. PD[3]	LRC	PRC
γ	4	4	4	4	4	4	4	4	8	8	8	8
μ	5	6	5	5	5	5	6	5	2	2	2	2
β	1	1	2	3	3	3	3	3	1	1	1	1
vc	7	7	8	7	7	8	8	7	4	5	5	5
tr	8	8	7	8	8	7	7	8	5	4	4	4
δ	3	3	3	2	2	2	2	2	3	3	3	3
c	6	5	6	6	6	6	5	6	6	6	6	6
H	2	2	1	1	1	1	1	1	7	7	7	7

[1] Main effect in the full factorial 2^8 design
[2] Defined as LRC times (x_i^{max}-x_i^{min})
[3] Partial derivative as the base case
[4] Defined as mean elementary effect divided by (x_i^{max}-x_i^{min}) (see appendix)
CR = correlation ratio; el. = elementary; LRC = linear regression coefficient; OWSA = one-way sensitivity analysis; PCC = partial correlation coefficient; PD = partial derivative; PMC = product moment correlation; PRC = partial regression coefficient; RC = rank correlation

Figure 6: Comparison of sensitivity analysis measures on uncertainty ranges or independent, uniform input distributions



Main effects based on the 2^8 full factorial design; mean elementary effect based on Morris' method with p=10, Δ=5/9 and r=100[12]; average effect defined as LRC times (x_i^{max}-x_i^{min}) based on 10,000 samples.

Table 8: Sensitivity analysis results assuming independence and distributions from Table 1; based on 10,000 samples.

Input	*LRC*	*PRC*	*PMC*	*RC*	*PCC*	*CR*	*LI*	*Rank**
Recovery rate [γ]	-6.8×10^4	-6.8×10^4	-0.16	-0.16	-0.61	0.03	<0.01	4
Mortality/birth rate [μ]	5.4×10^8	5.3×10^8	0.10	0.09	0.40	0.01	<0.01	5
Transmission coefficient [β]	1.7×10^{10}	1.7×10^{10}	0.51	0.50	0.92	0.28	0.03	2
Vaccination coverage [vc]	-1.4×10^5	-1.0×10^6	<0.01	<0.01	-0.07	<0.01	<0.01	7
Vaccine take rate [tr]	9.2×10^5	5.0×10^5	0.01	0.01	0.02	<0.01	<0.01	8
Discount rate [δ]	-5.0×10^7	-4.9×10^7	-0.45	-0.44	-0.90	0.21	<0.01	3
Cost per immunized child [c]	-1.4×10^5	-1.6×10^5	-0.09	-0.09	-0.43	0.01	<0.01	6
Health cost per disease case [H]	1.2×10^5	1.2×10^5	0.67	0.67	0.95	0.45	<0.01	1

* Based on CR

CR = correlation ratio; LI = linearity index; LRC = linear regression coefficient; PCC = partial correlation coefficient; PMC = product moment correlation; PRC = partial regression coefficient; RC = rank correlation

Non-uniform marginals. Table 8 shows the sensitivity measures when we assume the marginal input distributions from Table 1. Note the changes in magnitude of some of the sensitivity measures and ranking according to CR compared to Table 6, since we now sample different points in the input space with different probabilities, and the mass of each marginal distribution is generally concentrated around its corresponding base case value. Most notably, input *H* now appears by far the most important input according to CR. This reflects the important uncertainty we assumed for *H*, i.e., the distribution we chose for *H* has more spread than that of the other important inputs (δ and β). The regression coefficients also changed substantially (e.g., the LRC for *vc*) as a result of the different sampling distributions underlying Table 8.

Case 4: Marginal distributions known and dependence structure characterized

Table 9 shows the probabilistic sensitivity measures using the dependence structure from Figure 1 with the marginal distributions from Table 1. Clearly, the addition of a dependence structure affects the measures substantially compared to Table 8. Overall, we see that the influence of the vaccination coverage (*vc*) increased due to its correlations with *tr, c* and *H*. PMC and RC for *vc* are now clearly positive because of the (positive) correlation with *H* (which in turn positively correlates with the net benefit, as the previous simulations already showed). The fact that *vc* negatively correlates with the costs *c* only magnifies this trend, since lower vaccination costs and higher coverage both lead to greater benefits. Furthermore, the negative correlation between the vaccine take rate (*tr*) and *vc* changed the direction of the influence of *tr* from positive to negative PRC, PMC and RC between Table 9 and Table 8; larger values of *tr* correlate with smaller values of *vc*, which imply greater net benefits (i.e., since *vc* positively correlates with the net benefit). The negative correlation with γ reduces this effect, but given its low *CR* and the smaller magnitude of the correlation between γ and *tr*, the effect related to *vc* dominates.

Table 9: Sensitivity analysis results assuming marginal distributions from Table 1 and dependence structure in Figure 1; based on 10,000 samples.

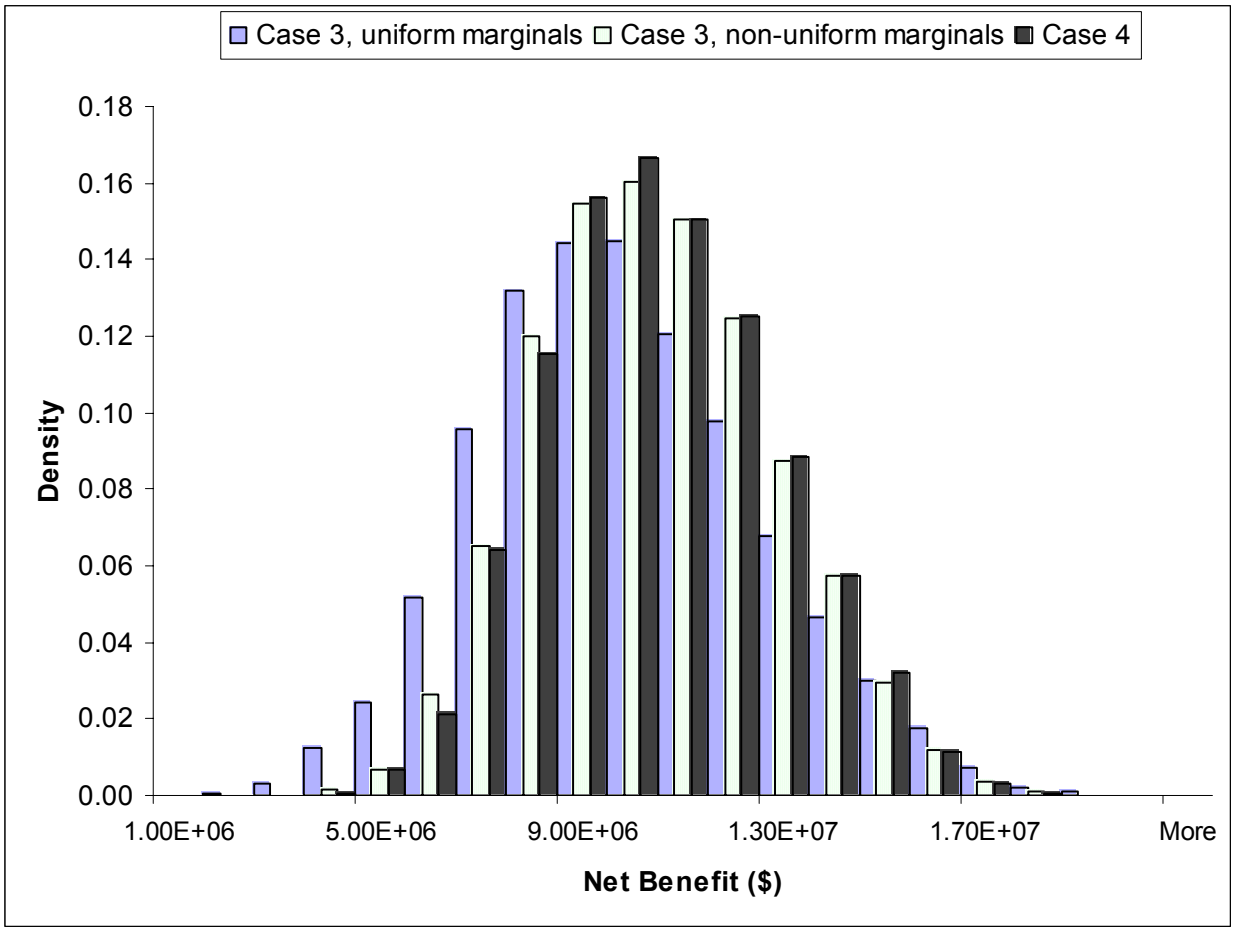
Input	*LRC*	*PRC*	*PMC*	*RC*	*PCC*	*CR*	*LI*	*Rank*[*]
Recovery rate [γ]	-4.9×10^{4}	-6.8×10^{4}	-0.12	-0.11	-0.61	0.01	<0.01	5
Mortality/birth rate [μ]	5.8×10^{8}	5.3×10^{8}	0.10	0.10	0.41	0.01	<0.01	6
Transmission coefficient [β]	1.7×10^{10}	1.7×10^{10}	0.51	0.49	0.93	0.29	0.03	2
Vaccination coverage [*vc*]	1.6×10^{7}	-1.1×10^{6}	0.24	0.24	-0.05	0.06	0.01	4
Vaccine take rate [*tr*]	-7.3×10^{6}	3.4×10^{5}	-0.07	-0.07	0.01	0.01	<0.01	8
Discount rate [δ]	-5.0×10^{7}	-5.0×10^{7}	-0.46	-0.46	-0.91	0.22	0.01	3
Cost per immunized child [*c*]	-1.2×10^{5}	-1.5×10^{5}	-0.08	-0.07	-0.28	0.01	<0.01	7
Health cost per disease case [*H*]	1.1×10^{5}	1.2×10^{5}	0.67	0.67	0.95	0.45	<0.01	1

[*] Based on CR

CR = correlation ratio; LI = linearity index; LRC = linear regression coefficient; PCC = partial correlation coefficient; PMC = product moment correlation; PRC = partial regression coefficient; RC = rank correlation

With the dependence structure and marginal distributions characterized, one can readily perform a full uncertainty analysis. Based on the same samples as generated Table 6, Table 8, and Table 9, Figure 7 shows the probability density functions of the output for the three different input uncertainty structures. In this model, moving first from uniform, independent marginals to independent non-uniform marginals and then to interdependent non-uniform marginals resulted in higher expected benefits and more certainty (i.e., lower standard deviation). However, this is not generally true and depends both on the nature of the model and on the nature of the uncertainty. Note that for all three cases, the expected net benefit ($9.5-10 million) is smaller than the expected net benefit at the base case ($11 million), as expected from the knowledge that in general $f(E(X)) \neq E(f(X))$. In this model, all three uncertainty characterizations lead to a high confidence in a positive net benefit of the vaccination program and therefore this hypothetical intervention would appear attractive either way. We emphasize that in specifying a dependence structure we assumed a given population, i.e., we focused on uncertainty rather than variability. In this case, the correlations do not lead to a substantial change in the probability distribution of the net benefit. However, if we consider populations in different settings (i.e., variability across populations), stronger correlation between the transmission coefficient, vaccination coverage, and take rates this would imply a much different distribution with a larger standard deviation and a possibility of negative net benefits, indicating that one decision for all populations may not be desirable.

Figure 7: Probability density function of the net benefit in case 3 and 4.



	Case 3 with uniform marginals	Case 3 with non-uniform marginals	Case 4, non-uniform marginals with dependence
Mean	9,415,359	9,897,268	9,951,444
Standard deviation	2,716,130	2,313,825	2,286,583

Cobwebs such as Figure 8 allow the model user to view a graphical representation of the relationship among inputs and the output. Each horizontal line consisting of piecewise straight segments represents one sample from the input distribution. The location where a line crosses each vertical axis reflects the value with respect to the input indicated above the axis. For the last axis, the location represents the resulting model output value (i.e., the net benefit). The pattern of these lines graphically illustrates the relationship among the variables (both inputs and output), including their correlation structure, the shape of the marginal distribution and functional relationship. Thus, cobwebs provide a means to graphically explore a multidimensional structure. Figure 8 shows a cobweb plot for the first 500 samples of the simulation in case 4 and illustrates the correlation among inputs and the resulting output (e.g., high values of *c* generally connect to low values of *vc*; see appendix). Figure 9 shows that the impact of an input on the output may depend on what region of the output distribution we focus on (note that the scales are in percentiles in this figure while we showed a cobweb on a natural

scale in Figure 8). For example, if an area of particular interest is where the net benefit is low, we see that the health cost per disease case (H) associated with low net benefits can take any value of its range (although generally H is low), while high net benefits almost exclusively occur when H is above its 50^{the} percentile. Similar local effects are less pronounced but still observable for δ and β, while the local effect for other inputs do not appear of influence. Applications exist that call for local probabilistic sensitivity methods rather than global methods[17] and Figure 9 illustrates that local analyses may yield different results.

Figure 8: Cobweb plot for simulation in case 4.

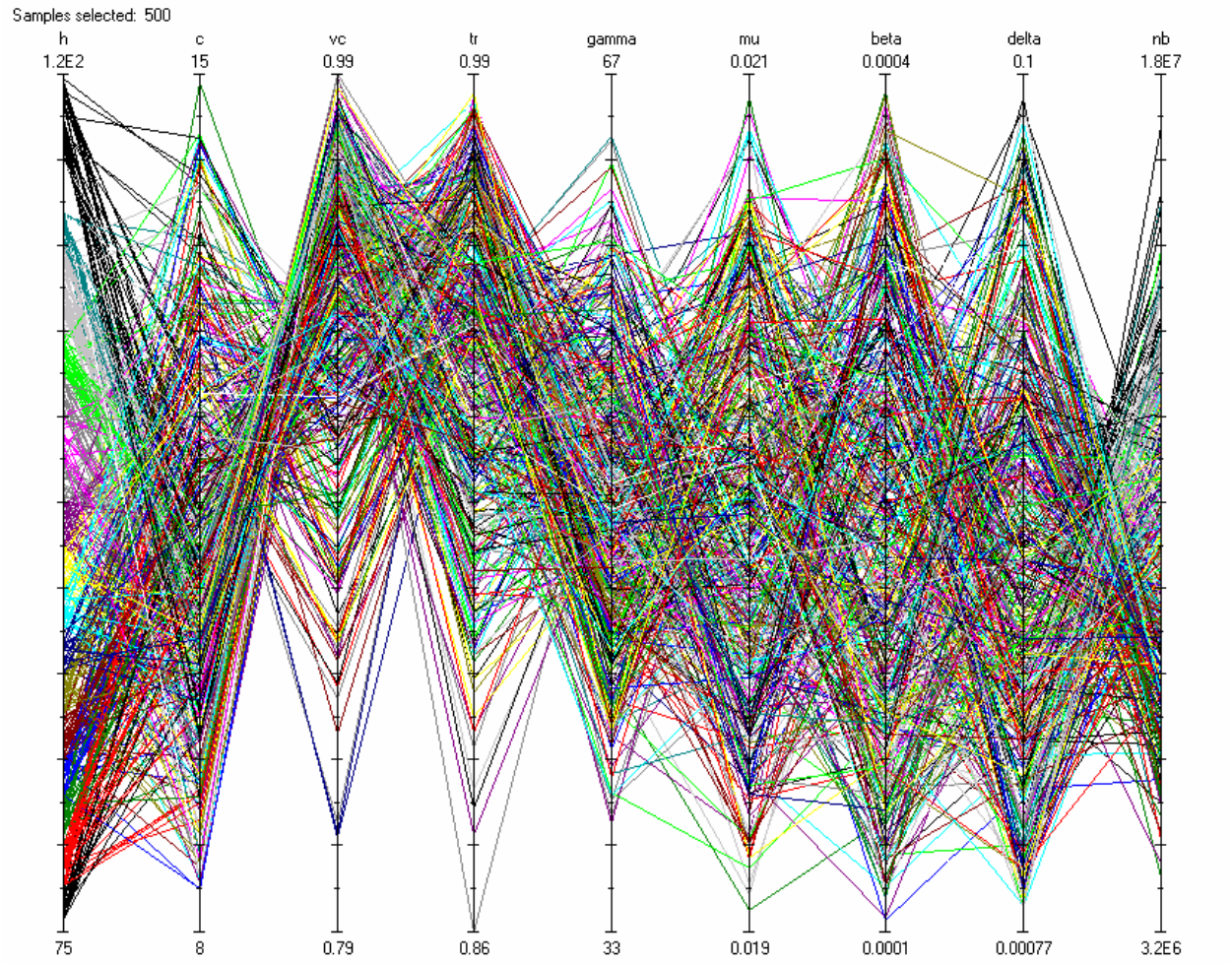
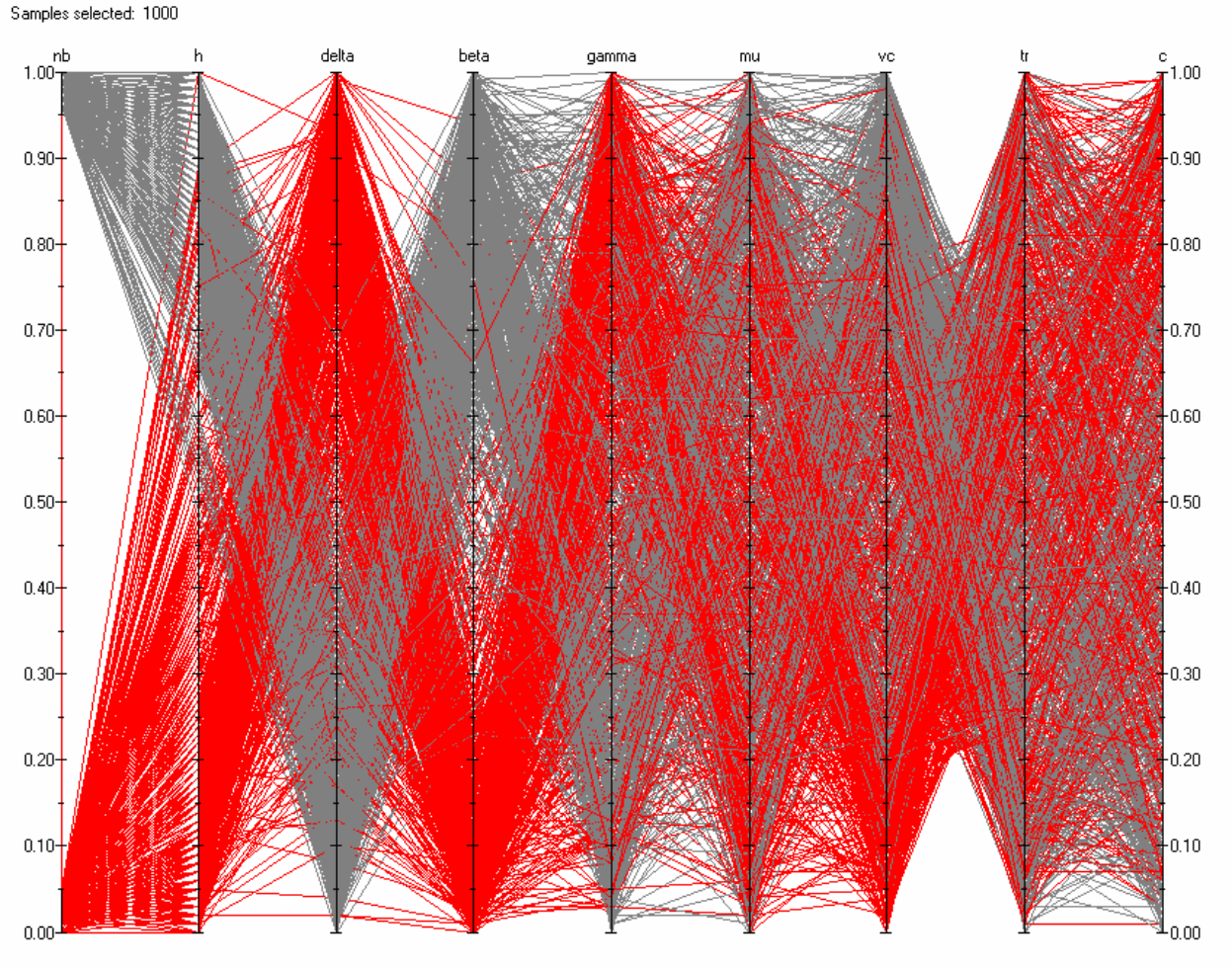


Figure 9: Local sensitivity of model to its inputs at the highest and lowest percentiles of the cumulative net benefit (sampled using uncertainty characterization from case 4).



DISCUSSION

We performed a number of sensitivity analysis methods on an existing economic evaluation model for vaccination against a hypothetical disease with the net benefit over a 10-year period as the outcome. We found that the magnitudes of the sensitivity measures and their rankings depend on methods of the sensitivity analysis and thus that the choice of method impact the insight from the analysis. In practice, the choice of sensitivity analysis method should depend on many factors, including:

- the type of characterization of the input uncertainty,
- the computational cost per model evaluation and number of uncertain inputs, and
- the desired type and accuracy of insights (e.g., effects of individual inputs, effects of individual inputs per unit change, interactions, curvature, or overall importance).

In most real-world models, dependence exists between model inputs. To perform a sensitivity analysis that truly quantifies the impact of uncertainty on the output, the analyst should start by seeking to characterize the input uncertainty in the most complete possible way, i.e., by specifying marginal distributions and a dependence structure. One can base these on data (i.e., from a clinical trial) or expert judgment if no data are available.[19] While the characterization and sampling of a dependence structure remains mathematically the most challenging part, dependence can have an important impact on the sensitivity analysis results. Dependence trees or correlation matrices rely on specification of (rank) correlations between pairs of inputs to build a joint distribution that satisfies the marginals and (rank) correlations. In this paper, we represented the dependence structure using a vine (Figure 1), which can characterize correlation involving more than two inputs using conditional rank correlation and whose specification is always consistent (i.e., one can sample the vine in Figure 1 for any combination of correlations).[13, 20] Bayesian belief nets provide a very intuitive way to characterize relationships between inputs and continue to grow in popularity. Evolving work to convert Bayesian belief nets to vines offers perspectives to sample from the dependence structure represented through Bayesian belief nets.[14] Uncertainty analysis software such as Unicorn™ is increasingly capable of sampling complicated dependence structure using intuitive graphical dependence structures.

While the analyst should always seek to characterize the uncertainty with a joint input distribution (case 4), in practice estimating or specifying dependence may not always be feasible and the analyst may need to contend with the assumption of independent inputs (case 3) or even only with ranges (case 2). However, there exists a choice element as well in the characterization of the uncertainty and the model users should weigh the costs and benefits of obtaining better uncertainty characterization of the inputs. Case 1 lacks the information to meet the sensitivity analysis goal of identifying inputs whose uncertainty most influence the output uncertainty since it assumes complete ignorance about the amount of uncertainty in each model input. Partial derivatives only allow for investigation of the effects of inputs per unit change. One cannot interpret the ranking obtained with partial derivatives as a measure of importance since it depends completely on the chosen input unit and does not relate to the uncertainty of inputs. With input uncertainty characterized by ranges, one could scale each input to the unit interval or by its standard deviation[16] such that comparison of partial derivatives (and if desired cross-derivatives to investigate interactions) becomes more meaningful. However, this method is very local and not generalizable to the entire input space unless the model is reasonably linear.

Table 10 shows the methods that we recommend in different situations, restricted to those methods discussed in this paper. OWSA always represents a good first step, but the analyst must

appreciate that this only provides a local importance ranking at the base case and neglects curvature and interactions. One could also perform OWSA as a first step in the case of probabilistic input by taking for example the mean of each input's distribution plus or minus two standard deviations as the range. We recommend the CR as the most general measure of the overall sensitivity of individual inputs. While this measure is less widely known and more difficult to compute than the PMC (also known as the standardized regression coefficient), the disadvantage of the PMC is that it focuses on the strength of linear relationship and may underestimate the importance of an input if for example the relationship is quadratic. RC quantifies the importance of any type of monotonic relationship, but even non-monotic relationships could contribute to uncertainty in the output, which only the CR would account for. With only ranges available, we still recommend using the CR or correlations obtained through a probabilistic sensitivity analysis with the ranges interpreted as independent, uniform distributions. Only in the event of very high computational costs do we recommend Morris' method to obtain an overall importance ranking. Due to its efficiency, one can apply this method even for many inputs and a computationally intensive model while still factoring in curvature and interactions.

We did not discuss probabilistic measures to quantify interactions, but in case of ranges two-level designs offer the possibility to quantify all or the most important interactions. In the event of a model with many inputs, one could first identify the most important inputs using Morris' method, CR, PMC, RC or even OWSA and then run a two-level design on those inputs to identify the most significant interactions. Well-known highly aliased multiple-level DOE designs also allow for investigation of curvature for up to 15 inputs[9] and DOE software such as Design-Ease™ includes these designs.

If the aim of the sensitivity analysis is to increase understanding and also investigate curvature in the model, we recommend considering all probabilistic sensitivity measure jointly. Conditional expectation plots and cobwebs can complement and help communicate the insights. Center-point designs or designs with more than 2 levels for some or all inputs offer alternative approaches among the methods discussed in this paper if the uncertainty characterization is in the form of ranges. However, for a computationally intensive model with many inputs, a comprehensive DOE analysis may be prohibitively expensive and MWSA may be the only feasible method. We note that one can also perform DOE even if the implicit assumption of independent, uniform marginals does not hold. In that case, one should interpret the results as an analysis of the relationships inherent in the model rather than a true sensitivity analysis, since it will not tell how the uncertainty in inputs contributes to uncertainty in the output.

Most methods presented here involve a substantial investment in both performing the sensitivity analysis and understanding the results. Such an investment is not justified if the model is very simple. For example, there is little use in running a large DOE design for a model like $y = ax_1 + bx_2 + cx_3x_4$ since we can readily calculate effects from the constants a, b and c. However, for more complicated models with no closed form such as the net benefit model analyzed in this paper, the added benefit of the investment in more sophisticated sensitivity analysis methods is a better understanding of the model behavior and the relative impact of the different input uncertainties. This can potentially change important and difficult decisions.

While we recommend methods depending on the computational cost of the model, we emphasize that the qualification of a "high" computational cost is relative to the stakes involved. A month of computer time is a high computational cost for a sensitivity analysis on a decision model between treating a single patient against a minor disease without permanent disabilities,

but may be justified for a sensitivity analysis of economic evaluation of a new HIV prevention strategy for developing countries, especially if the sensitivity might alter the decision. In other words, the analyst should consider the value of information of the sensitivity analysis in deciding whether the computational costs are acceptable compared to the expected benefits of performing a more sophisticated sensitivity analysis.[21]

The methods based on uncertainty ranges all yield as measures an effect, which provides some information about the robustness of the model since it is scaled in the units of the model output. However, particularly in the case of one-way sensitivity analysis, the analyst must not interpret the effects (or output ranges) as equivalents of a confidence interval. The analyst can only interpret effects as quantifications of the uncertainty attributable to inputs if the input uncertainty distributions are truly uniform and independent. The correlation ratio or other probabilistic measures do not provide metrics in terms of effects (except for the average effect). For investigation of the robustness of the model, the analyst should perform an uncertainty analysis rather than a sensitivity analysis.

The sensitivity analysis methods we discussed in this paper only represent a subset of all available methods[22] and model users may prefer to use alternative methods depending on the goals of the analysis or the nature of the model. Conceivably, the model user might want to perform several types of sensitivity analyses to investigate all aspects. The methods in this paper, varying from very simple and computationally inexpensive to more abstract and costly, underscore the feasibility of performing sensitivity analyses for models of varying degrees of complexity and can help model users and policy makers obtain insights into models. This underscores the well-recognized need to include sensitivity analyses in quantitative models supporting policy makers.[7, 16]

Table 10: Recommended sensitivity analysis methods among the methods presented in this article, for different types of models and desired insights.

Desired insights:	Few inputs, low computational cost per model run	Few inputs, high computational cost per model run	Many inputs, low computational cost per model run	Many inputs, high computational cost per model run
Ranking of individual inputs at base case	OWSA[1]	OWSA[1]	OWSA[1]	OWSA[1]
Overall ranking of individual inputs	CR, PMC, RC	Morris' method[2] CR, PMC, RC	CR, PMC, RC	Morris' method[3] CR, PMC, RC
Overall ranking of individual inputs and interactions[4]	2^k design[2]	Fraction of 2^k design[2]	Two-level design on most important inputs as identified by one of above methods[5]	Two-level design on most important inputs as identified by one of above methods[5]
Importance of curvature and/or increased understanding of the model	2^k design with center point, 3^k or mixed design (or more)[2] All probabilistic measures considered jointly, conditional expectation plots, cobwebs	Fraction of 2^k design with center point (or more)[2] All probabilistic measures considered jointly, conditional expectation plots, cobwebs	Fraction of 3^k or mixed design on most important inputs as identified by one of above methods[5] All probabilistic measures considered jointly, conditional expectation plots, cobwebs	MWSA for selected inputs[6]

[1] To obtain ranges in case of an uncertainty characterization using non-uniform distributions, one could use the mean plus and minus two standard deviations
[2] Applies only to uncertainty characterizations using ranges or independent, uniform distributions
[3] Would violate Morris' method's assumption of independent, uniform distributions in case of an uncertainty characterization using dependent or non-uniform distributions
[4] We did not discuss methods for this desired type of insight in the event of an uncertainty characterization in terms of non-uniform distributions
[5] May require a highly-aliased design if the prior analysis identified many inputs as important. Design-of-experiments software commonly includes two-level designs for up to 15 inputs.
[6] In case of uncertainty characterization using non-uniform or dependent input distributions, MWSA will not factor in this information
CR = correlation ratio; MWSA = multi-way sensitivity analysis; OWSA = one-way sensitivity analysis; PMC = product moment correlation; RC = rank correlation

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APPENDICES

Appendix A: The basic model
Appendix B: DOE: method description and supplemental results
Appendix C: Morris' method: sampling and supplemental results
Appendix D: Technical appendix

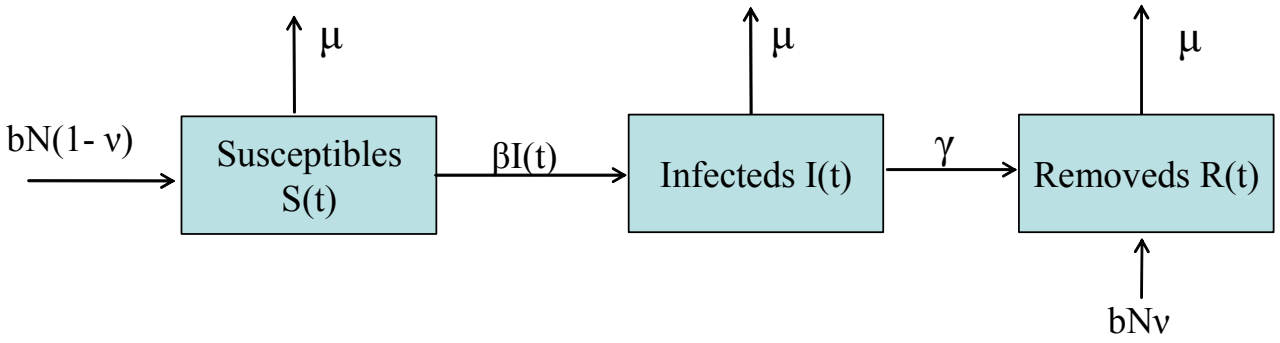
- Additional DOE results
- Impact of p and Δ in Morris' method
- Relationship between conditional and unconditional correlations
- Calculation of the probabilistic sensitivity measures
- Conditional expectation plots and Cobwebs

Appendix A: The basic model

The basic model on which we test the sensitivity analysis model draws from a generic dynamic economic evaluation model for a vaccination program against a hypothetical infectious disease[3] and consist of two parts. The first component of the model is a deterministic dynamic, population-based infectious disease transmission model that estimates the number of disease cases that the vaccination program would prevent. The second component uses that result and cost estimates to compute the cost-effectiveness ratio (CER), expressed as monetary units (e.g., dollars) per prevented disease case, or alternatively the net benefit (NB) in monetary units.

The transmission model stratifies members of a population according to their infection state. *Susceptibles* (*S*) did not yet experience an infection, *infecteds* (*I*) acquired an infection and can spread it to others, and *removeds* (*R*) recovered (or died) from an infection and presumably remain indefinitely protected from reinfection. Figure 10 shows a box diagram for this simple SIR model.[2, 3, 8]

Figure 10: Box model for the simple SIR model



A proportion ν of each birth cohort (bN) gets vaccinated at birth and becomes a removed, or immune individual. The remaining proportion $1-\nu$ that escapes vaccination (either because they receive no vaccine or because the vaccine does not take) stays susceptible. Susceptibles acquire infection at a rate $\beta I(t)$ proportional to the number of infecteds in the population, i.e., the higher the prevalence of infections, the higher the rate of infection. This property makes the system dynamic. Infecteds recover from the disease at a rate γ (equal to the reciprocal of the duration of infectiousness). Finally, each individual dies at a rate μ (the mortality rate). In our model, we assumed a stable population, so that $b = \mu$. The box diagram translates into a set of ordinary non-linear differential equations that describes the rates of change in the numbers of susceptible, infectious, and removed persons in the population. In our case, we consider one set of equations for a population with vaccination, and another for the same population without vaccination:

$$\frac{dS(t)}{dt} = \mu N(1-\nu) - \beta I(t) S(t) - \mu S(t)$$

$$\frac{dI(t)}{dt} = \beta I(t) S(t) - \gamma I(t) - \mu I(t) \qquad (9)$$

$$\frac{dR(t)}{dt} = \mu N\nu + \gamma I(t) - \mu R(t)$$

where:

$S(t)$ = number of susceptibles in the presence of vaccination,

$I(t)$ = number of infecteds in the presence of vaccination,
$R(t)$ = number of removeds in the presence of vaccination, and
N = population size,
μ = mortality rate = birth rate (assumed equal for susceptibles, infecteds and removeds),
γ = recovery rate (= 1/duration of infectiousness), and
β = transmission coefficient.
ν = vaccination efficacy (= vaccination coverage times vaccine take rate).

With no vaccination, ν equals 0 so that the equations reduce to:

$$\frac{dS^0(t)}{dt} = \mu N - \beta I^0(t) S^0(t) - \mu N$$
$$\frac{dI^0(t)}{dt} = \beta I^0(t) S^0(t) - \gamma I^0(t) - \mu I^0(t) \quad (10)$$
$$\frac{dR^0(t)}{dt} = \gamma I^0(t) - \mu R^0(t)$$

where:

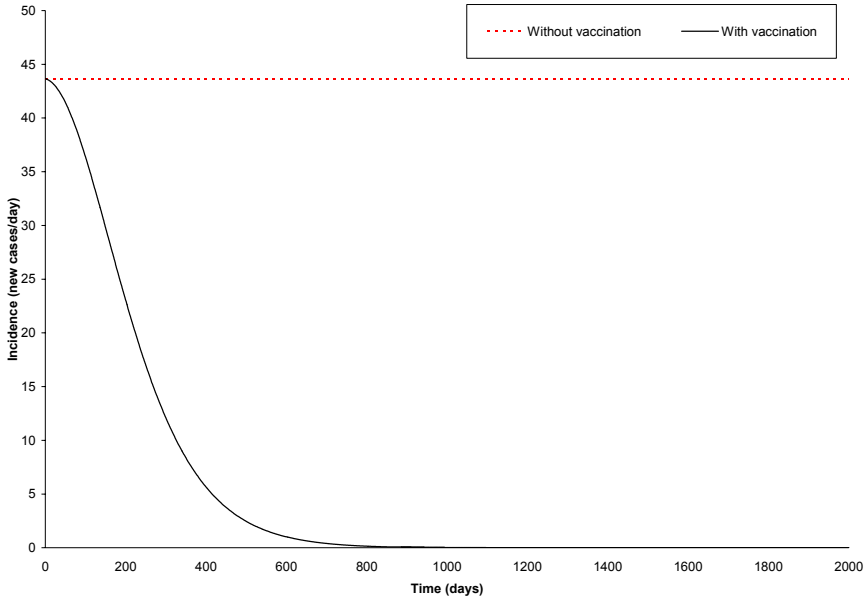
S^0(t) = number of susceptibles in the absence of vaccination,
I^0(t) = number of infecteds in the absence of vaccination,
R^0(t) = number of removeds in the absence of vaccination,

Due to the nonlinear term $\beta I(t)S(t)$, no closed form solution exists, but we can solve the equations numerically (see below). For given positive starting values, the solution always tends to an equilibrium solution, which in the absence of vaccination represents the *endemic equilibrium*. The endemic equilibrium corresponds to the solution of the set of equations (10) with all derivatives set to 0, or:

$$S^{eq} = \frac{(\mu + \gamma)}{\beta}$$
$$I^{eq} = \mu \frac{\beta N - (\mu + \gamma)}{\beta(\mu + \gamma)} \quad (11)$$
$$R^{eq} = \gamma \frac{\beta N - (\mu + \gamma)}{\beta(\mu + \gamma)}$$

The proposed net benefit model assumes that the disease is at endemic equilibrium at the outset (i.e., the causative agent spread freely for many years in the stable population), such that the set of solutions (11) represents the initial values for both sets of equations (9) and (10). Assuming that all infections lead to comparable clinical disease cases, the incidence, defined as the number of new cases of disease per time unit, equals $\beta I(t)S(t)$ with vaccination and the number of prevented disease cases per time unit equals $\beta(I^0(t)S^0(t) - I(t)S(t))$. Figure 11 shows the incidence over time with all inputs kept at their base case values (see Table 1) and the model starting at the endemic equilibrium.

Figure 11: Incidence from the dynamic model with all inputs at their base case values.[3] The initial values correspond to the endemic equilibrium.



The second component of the original model[3] computes the cost-effectiveness by comparing the discounted number of disease cases prevented by the vaccination program over a certain time period, say from $t = 0$ to T, with the discounted costs of the vaccination program during that period:

$$CER = \frac{\int_0^T C(t)e^{-\delta t}dt}{\int_0^T \beta\left(I^0(t)S^0(t) - I(t)S(t)\right)e^{-\delta t}dt} \tag{12}$$

where:

δ = discount rate, and

$C(t)$ = net costs of the vaccination program.

However, we switch to a net benefit formulation using input H that reflects the monetary equivalent of a prevented case, and furthermore split the vaccination efficacy into $v = vc \times tr$, where vc represents the vaccination coverage and tr the vaccine's take rate. In this way, the uncertainty in the vaccination efficacy splits into an uncontrollable uncertainty about the immunogenicity of the vaccine and a more controllable coverage uncertainty, which carries cost implications. Denoting the cost per immunized child by c, the net benefit model is:

$$NB = \sum_{t=0}^{T}\left[\beta(I^0(t)\times S^0(t) - I(t)\times S(t))\times H - c\times\mu\times vc\times N\right]\times e^{-\delta t}dt \tag{13}$$

We focus on solving the equations for $S(t)$ and $I(t)$ in the sets of equations (9) and (10), since we only need the term $\beta I(t)S(t)$ for the net benefit (i.e., the removeds $R(t)$ do not play a role in transmission and the solutions for $S^0(t)$ and $I^0(t)$ do not change from their initial equilibrium values). We denote the numerical solutions at time step j by S_j and I_j. For a given time step of τ

years and the initial values $S_0 = S^{eq}$ and $I_0 = I^{eq}$ (given in equations (11)), the solution for each subsequent step follows from the following backward difference equations:

$$\begin{aligned} S_j &= (\mu N(1-\nu) - \beta I_{j-1} S_{j-1} - \mu S_{j-1})\tau - S_{j-1} \\ I_j &= (\beta I_{j-1} S_{j-1} - \mu I_{j-1} - \gamma I_{j-1})\tau - I_{j-1} \end{aligned} \tag{14}$$

The solutions for susceptibles and infecteds without vaccination, $S^0(t)$ and $I^0(t)$, remain equal to the initial values at each time step since we assume that the model starts at the endemic equilibrium. The cumulative net benefit equals 0 at $j = 0$ and:

$$\begin{aligned} CNB_{j+1} &= CNB_j + \left[\left(I_j^0 S_j^0 - I_j S_j \right) \beta H - c\mu N v c \right] \tau e^{-\delta \tau j} \\ &= CNB_j + \left[\left(\frac{\mu(\beta N - \mu - \gamma)}{\beta^2} - I_j S_j \right) \beta H - c\mu N v c \right] \tau e^{-\delta \tau j} \end{aligned} \tag{15}$$

at subsequent time steps (i.e., the discrete equivalent of equation (13)). In practice, large τ leads to loss of precision and eventually unacceptable approximation of the solution (e.g., negative numbers), but if τ is very small the computational cost of each simulation becomes expensive. We use a time step of 1 day, or $\tau = 1/365$, such that the model output is $y = NB = CNB_T = CNB_{3650}$ for a 10-year time horizon.

Appendix B: Design-of-Experiments: method description and supplemental results

We limit this appendix to a discussion of basic concepts in design of experiments (DOE) and refer to existing text books for further details.[9, 10] Given the uncertainty ranges $[x_i^{min}, x_i^{max}]$ (i = 1,..,k), the 2^k full factorial design is the design that includes all 2^k possible combinations of the x_i^{max}'s and x_i^{min}'s. Each combination in the design corresponds to one run of the model at the given input levels, and yields one value for the output $y_j(x)$, or shortly y_j, where the index j denotes the run number and x is the corresponding corner of the input space. A 2^k design varies the endpoints in the hypercube that bounds the input space. A 3^k design explores the interior (medium level) points and provides more coverage of the input space. A fractional design attempts to capture the same effects as the full designs by suitable selection of a fraction of the extreme points, as illustrated in Figure 12. Obviously, as many selections exist which represent a fraction of the total, also many different fractional designs exist.

Figure 12: Illustration of a fractional factorial 2^{3-1} design (left), a full factorial 2^3 design (right) and a full factorial 3^3 design (right).

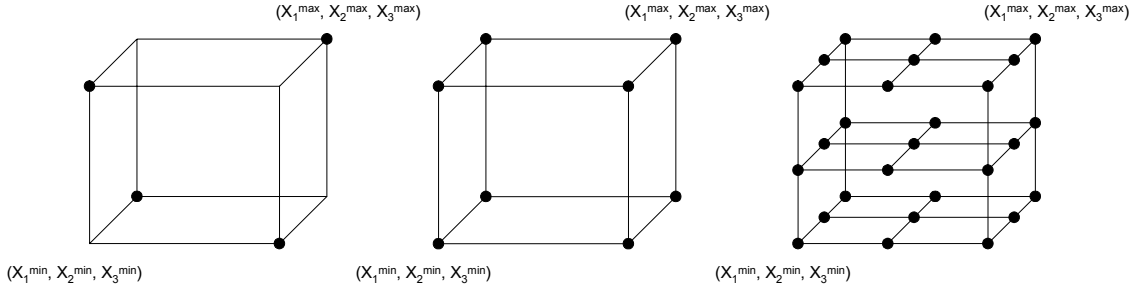


Table 11 illustrates the two-level full factorial design with an example involving 3 inputs. For brevity, in this table "+1" stands for the maximum value of the input of the corresponding column and "-1" for the minimum value.

Table 11: A 2^3 full factorial design

Run	x_1	x_2	x_3	x_1x_2	x_1x_3	x_2x_3	$x_1x_2x_3$	*Output*
1	-1	-1	-1	+1	+1	+1	-1	$y_1=y(x_1^{min}, x_2^{min}, x_3^{min})$
2	+1	-1	-1	-1	-1	+1	+1	$y_2=y(x_1^{max}, x_2^{min}, x_3^{min})$
3	-1	+1	-1	-1	+1	-1	+1	$y_3=y(x_1^{min}, x_2^{max}, x_3^{min})$
4	+1	+1	-1	+1	-1	-1	-1	$y_4=y(x_1^{max}, x_2^{max}, x_3^{min})$
5	-1	-1	+1	+1	-1	-1	+1	$y_5=y(x_1^{min}, x_2^{min}, x_3^{max})$
6	+1	-1	+1	-1	-1	-1	-1	$y_6=y(x_1^{max}, x_2^{min}, x_3^{max})$
7	-1	+1	+1	-1	+1	+1	-1	$y_7=y(x_1^{min}, x_2^{max}, x_3^{max})$
8	+1	+1	+1	+1	+1	+1	+1	$y_8=y(x_1^{max}, x_2^{max}, x_3^{max})$

The *main effect* $me(x_i)$ of an input x_i is defined as the average output of the model with $x_i = x_i^{max}$ minus the average output with $x_i = x_i^{min}$. So for the first input in this example, the main effect is:

$$me(x_1) = \frac{y_2 + y_4 + y_6 + y_8}{4} - \frac{y_1 + y_3 + y_5 + y_7}{4} \tag{16}$$

This corresponds exactly to the inner product of the column for input 1 (which we denote by a vector $\mathbf{x}_1$) and the last column (which we will denote by $\mathbf{y}$), divided by the number of "+1"s

in that column, or $\mathbf{x}_1^T\mathbf{y}/2^{k-1} = \mathbf{x}_1^T\mathbf{y}/4$. The two-way interaction between two inputs x_i and x_j is defined as half the difference between the main effect of x_i with $x_j = x_j^{max}$ and the main effect of x_i with $x_j = x_j^{min}$. In our example, the interaction between the first two inputs is:

$$\begin{aligned} int(x_1, x_2) &= \frac{me(x_1 \mid x_2 = x_2^{max}) - me(x_1 \mid x_2 = x_2^{min})}{2} \\ &= \frac{\left[\frac{1}{2}(y_4 + y_8) - \frac{1}{2}(y_3 + y_7)\right] - \left[\frac{1}{2}(y_2 + y_6) - \frac{1}{2}(y_1 + y_5)\right]}{2} \\ &= \frac{y_1 + y_4 + y_5 + y_8 - (y_2 + y_3 + y_6 + y_7)}{4} \end{aligned} \tag{17}$$

One can easily verify that $int(x_i,x_j) = int(x_j,x_i)$ and $int(x_i,x_j) = (\mathbf{x}_i\mathbf{x}_j)^T\mathbf{y}/4$, where the vector $\mathbf{x}_i\mathbf{x}_j$ is obtained through pairwise multiplication of the columns $\mathbf{x}_i$ and $\mathbf{x}_j$, as included in Table 11. Similarly the three-way interaction between x_i, x_j, and x_k equals $(\mathbf{x}_i\mathbf{x}_j\mathbf{x}_k)^T\mathbf{y}$, etc. Thus, we can easily compute all main effects and multi-way interactions using the design in Table 11.

The full factorial design requires 2^k runs, which becomes problematic for large numbers of inputs and/or computationally expensive model evaluations. Using the concept of *aliasing*, one can reduce the number of runs at the cost of losing some of the ability of a design to fully explain the model. The idea is to consider only a fraction of the full factorial design by considering only those combinations of inputs that satisfy a given condition (commonly referred to as the *generator* of the design). For example, Table 12 shows the fractional 2^{3-1} design for which $\mathbf{x}_1\mathbf{x}_2\mathbf{x}_3=\mathbf{I}$, where $\mathbf{I}$ is a column with all ones and with appropriate dimension (4 in this case), and the multiplication is componentwise.

Table 12: A 2^{3-1} fractional factorial design with generator $x_1x_2x_3=I$

Run	x_1	x_2	x_3	x_1x_2	x_1x_3	x_2x_3	$x_1x_2x_3$	*Output*
2	+1	-1	-1	-1	-1	+1	+1	$y_2=y(x_1^{max}, x_2^{min}, x_3^{min})$
3	-1	+1	-1	-1	+1	-1	+1	$y_3=y(x_1^{min}, x_2^{max}, x_3^{min})$
5	-1	-1	+1	+1	-1	-1	+1	$y_5=y(x_1^{min}, x_2^{min}, x_3^{max})$
8	+1	+1	+1	+1	+1	+1	+1	$y_8=y(x_1^{max}, x_2^{max}, x_3^{max})$

We see that for example the column $\mathbf{x}_1$ equals the column $\mathbf{x}_2\mathbf{x}_3$. This follows from the condition $\mathbf{x}_1\mathbf{x}_2\mathbf{x}_3=\mathbf{I}$ as follows:

$$\begin{aligned} \mathbf{x}_1(\mathbf{x}_1\mathbf{x}_2\mathbf{x}_3) &= \mathbf{x}_1(\mathbf{I}) \\ (\mathbf{x}_1\mathbf{x}_1)\mathbf{x}_2\mathbf{x}_2 &= \mathbf{x}_1 \\ \mathbf{x}_2\mathbf{x}_3 &= \mathbf{x}_1 \end{aligned} \tag{18}$$

We used the fact that the square of two columns equals the identity column $\mathbf{I}$. We say that $\mathbf{x}_1$ is *aliased* with $\mathbf{x}_2\mathbf{x}_3$. From writing out the estimates for the main effect of x_1 and the interaction between x_2 and x_3 in the full factorial model and adding up the terms, it follows that the equality in equation (18) implies that:

$$\mathbf{x}_1^T\mathbf{y}/2 = (\mathbf{x}_2\mathbf{x}_3)^T\mathbf{y}/2 = me(x_1) + int(x_1, x_2), \tag{19}$$

where the denominator equals the number of "+1"s in the column of the fractional design. Assuming that higher order interactions are negligible compared to lower order interactions, we can approximate the main effect of $\mathbf{x}_1$ by the inner product $\mathbf{x}_1^T\mathbf{y}/2$ in the fractional design of Table 12, the advantage compared to the full factorial design being that we only need half as

many model evaluations. In models with more inputs, convenient fractional designs exist such that main effects and lower order interactions are always aliased with higher order terms, enabling approximation of the former.

Two-level designs are limited by the fact that they only evaluate the model at the corners of the input space, without consideration of the area in between. A *center point design* adds the model evaluation $y(\mathbf{x}^{center}) = y((x_i^{max} - x_i^{min})/2,...,(x_k^{max} - x_k^{min})/2)$ to the 2^k full factorial design. This allows for testing of the likelihood that the model is non-linear. Based on the 256 model evaluations, the factorial model would predict a center point value of $ 8.1 million (i.e., the mean of the 256 model evaluations), while the actual center point value is $11 million, indicating important curvature.

Given that the center point design indicates non-linearity in the model, we performed the highly-aliased Taguchi design[9] displayed in Table 13 to identify which inputs affect the model non-linearly. Like fractional factorial designs, Taguchi designs try to capture the input space with fewer points while still maintaining statistical efficiencies (some Taguchi designs are in fact fractional designs as well). The design is for 13 inputs but since we have only 8 inputs the last 5 have no impact. We used the insights from the Taguchi design (results shown in the technical appendix) in deciding to assign 3 levels for γ, μ, β and *vc* and two levels for *tr*, δ, *c* and *H*.

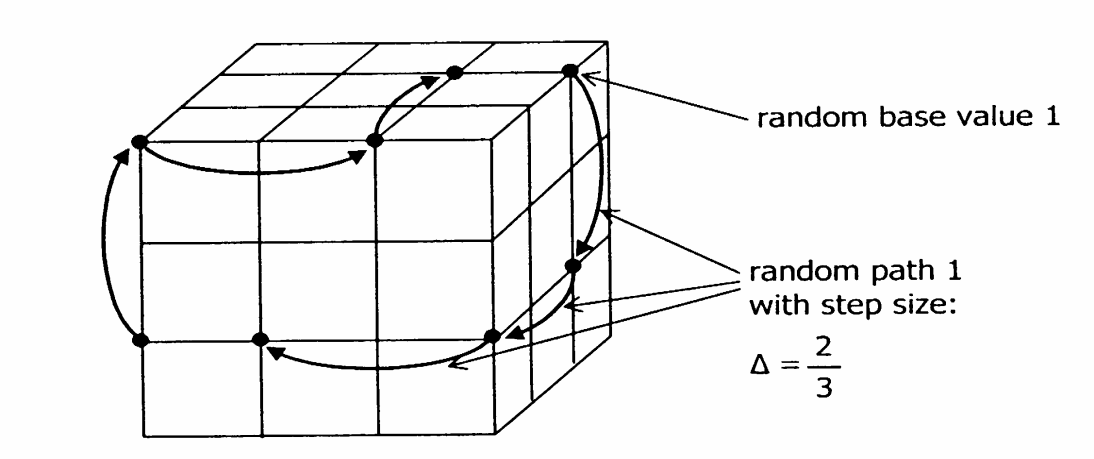
Table 13: The 3-level Taguchi design ("+1" indicates the upper end of the uncertainty range, "-1" the lower end, and "0" the midpoint).

Run	γ	μ	β	vc	tr	δ	c	H	y(x)=NB
1	-1	-1	-1	-1	-1	-1	-1	-1	7,530,473
2	-1	-1	-1	-1	0	0	0	0	7,611,434
3	-1	-1	-1	-1	+1	+1	+1	+1	7,368,962
4	-1	0	0	0	-1	-1	-1	0	12,809,623
5	-1	0	0	0	0	0	0	+1	14,220,484
6	-1	0	0	0	+1	+1	+1	-1	5,854,731
7	-1	+1	+1	+1	-1	-1	-1	+1	21,287,644
8	-1	+1	+1	+1	0	0	0	-1	8,876,448
9	-1	+1	+1	+1	+1	+1	+1	0	9,430,226
10	0	-1	0	+1	-1	0	+1	-1	5,981,449
11	0	-1	0	+1	0	+1	-1	0	7,705,823
12	0	-1	0	+1	+1	-1	0	+1	15,650,385
13	0	0	+1	-1	-1	0	+1	0	8,221,896
14	0	0	+1	-1	0	+1	-1	+1	10,206,408
15	0	0	+1	-1	+1	-1	0	-1	9,118,553
16	0	+1	-1	0	-1	0	+1	+1	6,812,890
17	0	+1	-1	0	0	+1	-1	-1	3,300,820
18	0	+1	-1	0	+1	-1	0	0	7,368,638
19	+1	-1	+1	0	-1	+1	0	-1	5,535,457
20	+1	-1	+1	0	0	-1	+1	0	12,300,237
21	+1	-1	+1	0	+1	0	-1	+1	13,337,683
22	+1	0	-1	+1	-1	+1	0	0	1,792,862
23	+1	0	-1	+1	0	-1	+1	+1	3,812,844
24	+1	0	-1	+1	+1	0	-1	-1	1,893,770
25	+1	+1	0	-1	-1	+1	0	+1	9,381,830
26	+1	+1	0	-1	0	-1	+1	-1	8,131,228
27	+1	+1	0	-1	+1	0	-1	0	9,863,758

Appendix C: Morris' method: sampling and supplemental results

Normally one requires two model runs (i.e., $y(x_1,\ldots x_i+\Delta(x_i^{max}- x_i^{min}),\ldots,x_k)$ and $y(\mathbf{x})$) to calculate one elementary effect (see equation (2)). However, the sampling algorithm of Morris' method is such that each next step evaluates the model at a point in the input space that differs by exactly $\Delta(x_i^{max}- x_i^{min})$ from the previous point in exactly one input. Thus, Morris' method uses each model evaluation in the calculation of two distinct elementary effects (except for the first and last evaluations which the method uses only once). Figure 13 gives an example of two random sampling paths through the input space. Each such path computes the k elementary effects (one for each input) using $k+1$ model evaluations.

Figure 13 : Illustration of Morris' method in a three dimensional region of interest



Morris (1991) describes in detail how to realize pseudo-random paths by performing a number of basic operations to a sampling matrix.[12] In the sampling scheme, taking an even number of levels p for each input and $\Delta=p/2(p-1)$ yields an even coverage of the input space. The number of possible elementary effects for given choice of p equals $p^k/2$. Thus, a larger p implies a better resolution of the input space but requires more random paths (greater r) to evaluate elementary effects over a large number of intervals in the range of each input.

In this paper, we defined the elementary effect as in equation (2). The mean elementary effects reflect the average amount of variation attributable to the entire uncertainty range (since we divide by Δ) and is the Morris equivalent of the main effect in DOE or the effects in OWSA. Alternatively, we can define the elementary effect as follows:

$$d_i(\mathbf{x}) = \frac{y(x_1,\ldots, x_i+\Delta(x_i^{max}-x_i^{min}),\ldots, x_k)-y(\mathbf{x})}{\Delta(x_i^{max}-x_i^{min})} \tag{20}$$

In that case, the elementary effect is unit-dependent and approximates a partial derivative rather than an effect. Table 14 compares the "elementary partial derivatives" as defined by equation (20) with the other partial derivative based measures. This illustrates the difference between local evaluation of the partial derivatives locally (i.e., at the base case) and approximation in different points of the input space, although the ranking changed only between *vc* and *tr*.

Table 14: Comparison of local partial derivatives and approximation of "elementary partially derivates" defined by (20) using Morris' method.

Input	*Partial derivative at base case*[1]	*LRC*[2]	*PRC*[2]	*Morris' mean elementary partial derivatives*[3]
Recovery rate [γ]	-64,681	-56,482	-54,831	-66,141
Mortality/birth rate [μ]	571,861,004	436,475,764	503,275,559	446,835,644
Transmission coefficient [β]	15,150,852,947	15,255,158,289	14,846,121,190	15,078,498,472
Vaccination coverage [vc]	-1,207,193	2,479,088	2,220,113	2,163,049
Vaccine take rate [tr]	712,488	3,707,127	3,555,006	3,136,654
Discount rate [δ]	-56,286,032	-46,275,262	-46,694,683	-43,655,107
Costs per immunized child [c]	-163,922	-119,880	-139,531	-142,463
Health costs per disease case [H]	127,488	109,890	110,135	100,771

[1] Using $\varepsilon = 10^{-7}$ in equation (1)
[2] Linear/partial regression coefficients assume independent, uniform marginals and use 10,000 samples
[3] Uses $p = 10$, $\Delta = 5/9$ and $r = 100$ and calculates elementary partial derivatives using equation (20)
LRC = linear regression coefficient; PRC = partial regression coefficient

Appendix D: Technical appendix

Statistical interpretation of DOE analysis and additional results

One can view the main effects and interactions as coefficients in a linear regression model on the response y (after scaling each input's range to the interval [-1,1]):

$$y(\mathbf{x}) = intercept + \sum_{i=1}^{k}[\frac{me(x_i)}{2}x_i] + \sum_{i=1}^{k}\sum_{j=i+1}^{k}[\frac{int(x_i,x_j)}{2}x_i x_j] + \ldots + \frac{int(x_1,x_2,\ldots,x_k)}{2}x_1 x_2 \ldots x_k \qquad (21)$$

If we include all inputs, the model will have a perfect fit to the data since the model is deterministic. But if we only include significant terms (meaning terms with large coefficients, i.e. large effects) in the regression and consider the other terms as error (random noise from a standard normal distribution), we can calculate the residuals and evaluate the fit of that regression model to the run results of the design using common statistical tests in an analysis of variance. For example, a model F-value (= model mean square (= sum of squares divided by model degrees of freedom) divided by residual mean square) much greater than one indicates that the variance of the model is much larger than that of the error terms, i.e., that the terms in the model are significant. The regression model with all 20 most important effects from Table 5 in the full factorial design has a model F-value of ~850, with a probability of obtaining a larger F-value due to random noise of less than 0.01%, indicating that none of the effects included may be regarded as noise. For the regression model based on the 20 most important effects, Figure 14 shows the normal plot of the residuals. If the residuals are close to the line, the errors (i.e., the excluded effects) are close to normally distributed (i.e., one could view them as random noise).

In the center point design, when we compare the variance of the curvature to that of the background noise in a regression based on the 20 most important effects from Table 5, we obtain an F-value of about ~23.5 and a probability of obtaining a larger F-value due to noise of less than 0.01%, confirming our observation that curvature is significant.

Figure 14: Normal plot of residuals based on a regression model including the 20 most important effects from Table 5 in the full factorial two-level design.

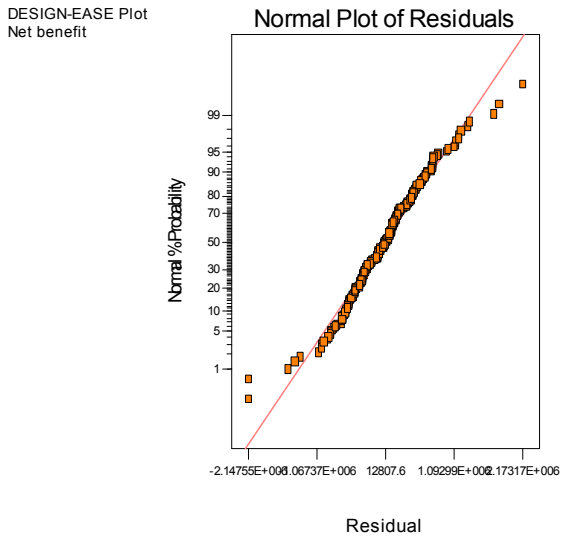
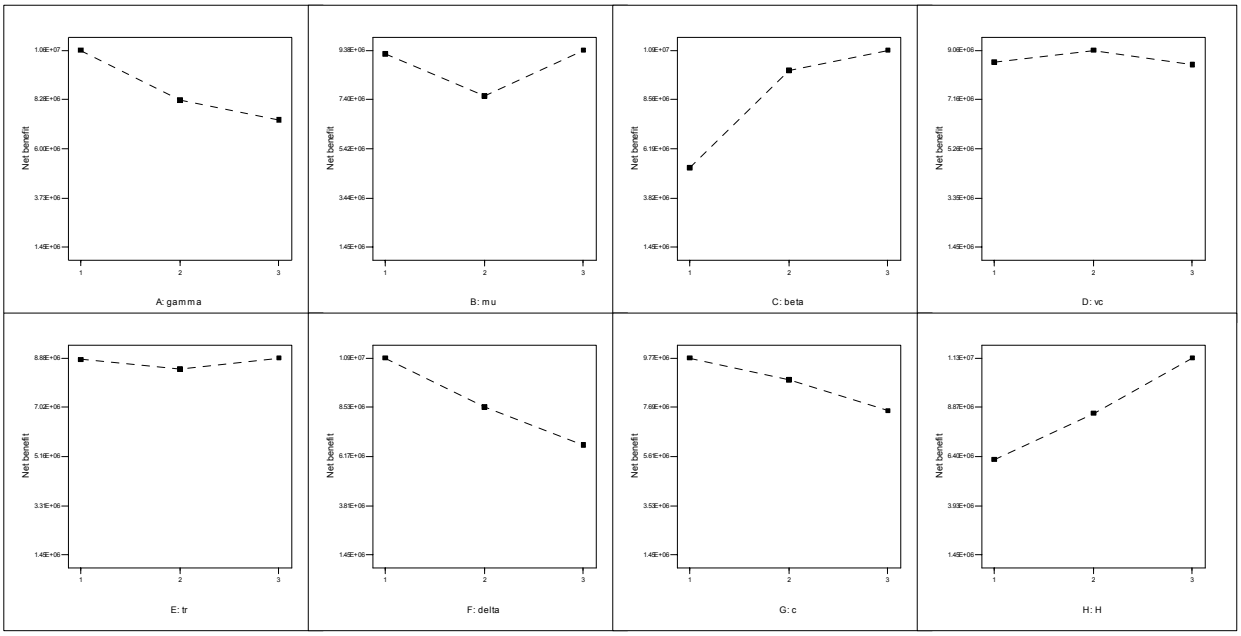


Figure 15 shows the effect plots for the 8 inputs in the Taguchi design. The data points for each input reflect the averages over the other input values. Based on these visual representations of the nature of the relationship between inputs and the model (i.e., linear or non-linear), we assigned three levels to γ, μ, β and *vc*, while we assigned two levels for *tr*, δ, *c* and *H*. However, we emphasize that the highly-aliased structure of the Taguchi design may either have masked or exaggerated non-linearities.

Figure 15: Effect plots for the 8 inputs in the Taguchi design.



Assuming that the choice of levels based on the Taguchi design is appropriate, the mixed full factorial $2^4 3^4$ should be capable of building an adequate regression model of the net benefit model, taking into account both the interactions and curvature to some extent, by including significant cross- and quadratic terms. DOE analysis software (such as Design-Ease™ used here) provides tools that facilitate building and analyzing such a regression model. Conceivably, in the event of a computationally expensive model, one could perform a probabilistic sensitivity using as output the regression model to obtain approximations of model runs at low computational cost but satisfactory accuracy. However, building a model of the model lies beyond the scope of this paper. We merely show the normal plot for such a model without going into further details (Figure 16). Figure 17 illustrates a complicated interaction between γ and β, whose apparent involvement in higher order interactions yields differences between the left and right graph.

Figure 16: Normal plot of residuals in a model based on the most significant terms (509 linear and quadratic terms including 117 main effects and interactions) in the $2^4 3^4$ mixed design.

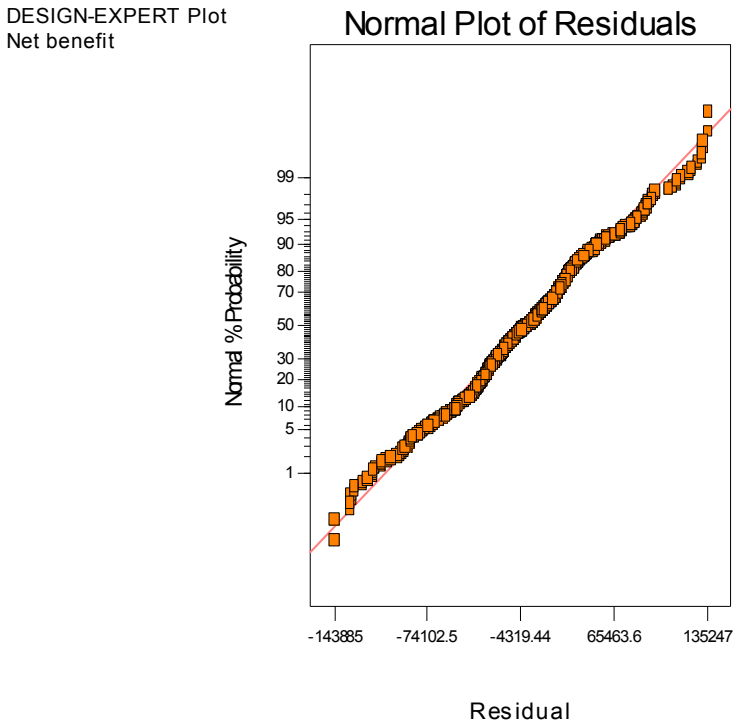
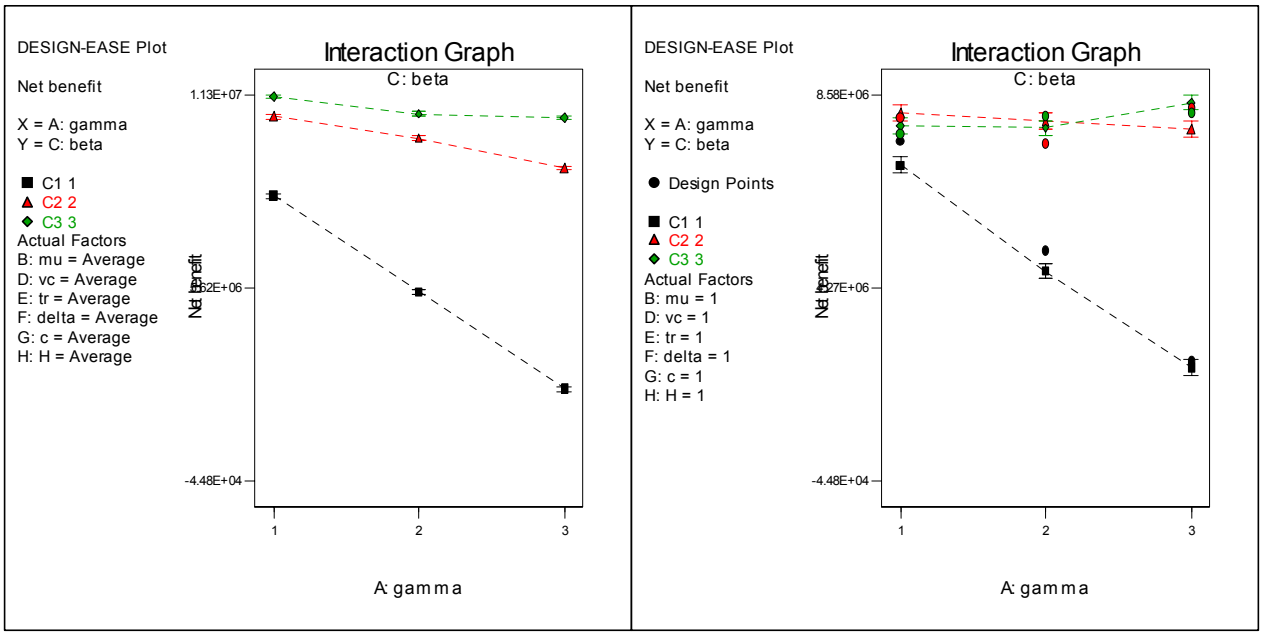


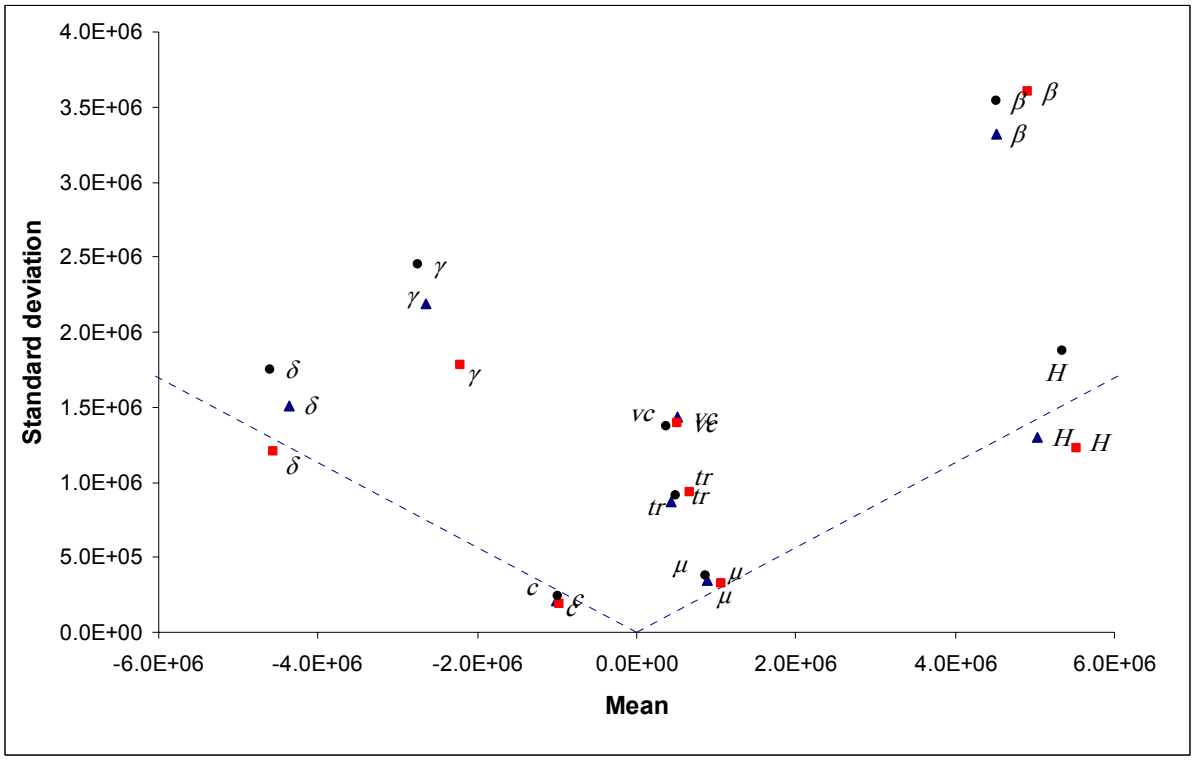
Figure 17: Interaction between the recovery rate (gamma) and the transmission coefficient (β) with all inputs held at their maximum value (right graph) and average over the other inputs (left graph)



Impact of p and Δ in Morris' method

Figure 18 illustrates the impact of different choices of p and Δ and gives an idea of the convergence of the means and standard deviations with respect to r. The standard error of the mean (SEM_i) of the distributions F_i of the elementary effects equals $\sigma_i/\sqrt{r}$, where σ_i denotes the standard deviation of the r elementary effects.[12] If the mean of the elementary effects exceeds $\pm 2SEM_i$, the "one might interpret this, approximately, as significant evidence that the expectation of F_i is non-zero." [12, p. 165] The wedge in Figure 4 and Figure 18 equals the line where $d_i(\mathbf{x}) = \pm 2SEM_i = \pm 2\sigma_i/\sqrt{r}$.

Figure 18: Convergence and impact of p, Δ on the elementary effects. The (blue) triangles and (red) squares represent two different simulations with $p = 10$, Δ=5/9 and r=50, while the (black) dots represent one simulation with $p = 4$, Δ=2/3 and r=50.



Relationship between conditional and unconditional correlations

Denoting the partial correlation between two random variables X_1 and X_2 out of the set $\{X_1,...,X_n\}$ shortly as PCC(1,2;3,...,n), the following recursive formula describes the relationship between partial correlations:[23]

$$PCC(1,2;3,...,n) = \frac{PCC(1,2;3,..,n-1) - PCC(1,n;3,...n-1)\,PCC(2,n;3,...n-1)}{\sqrt{(1-PCC(1,n;3,..,n-1)^2)(1-PCC(2,n;3,..,n-1)^2)}} \tag{22}$$

Thus, we have for the inputs H, c and vc in the vine (Figure 1):

$$\begin{aligned} PCC(H,vc;c) &= \frac{PCC(H,vc;\varnothing) - PCC(H,c;\varnothing)\,PCC(vc,c;\varnothing)}{\sqrt{(1-PCC(H,c;\varnothing)^2)((1-PCC(vc,c;\varnothing)^2)}} \\ &= \frac{PMC(H,vc) - PMC(H,c)\,PMC(vc,c)}{\sqrt{(1-PMC(H,c)^2)((1-PMC(vc,c)^2)}} \end{aligned} \tag{23}$$

where $\varnothing$ denotes the empty set. Our goal is to choose a $PCC(H,vc;c)$ such that $PMC(H,vc) = 0.3$ while we keep $PMC(H,c) = 0$ and $PMC(vc,c) = -0.8$. Thus simply solve $PCC(H,vc;c)$ out of equation (23), yielding a solution of $PCC(H,vc;c) = 0.5$. However, the vine specification uses conditional (rank) correlations and not partial (product moment) correlations, which are in general not equal unless the $X_1,...,X_n$ follow a joint normal distribution. Fortunately, the PCC

provides a good approximation of the conditional rank correlation. The rank correlation matrix below based on a sample from the vine in Figure 1 shows that $RC(H,vc) \sim 0.3$:

Table 15: Rank correlation matrix based on 10,000 samples, marginal distributions from Table 1 and vine in Figure 1 using the diagonal band copula.

Input	H	c	vc	tr	γ	μ	β	δ
H	1.00	0.00	0.28	-0.13	0.05	0.00	-0.01	-0.01
c	0.00	1.00	-0.80	0.42	-0.12	0.01	0.00	0.02
vc	0.28	-0.80	1.00	-0.50	0.15	0.00	0.01	-0.02
tr	-0.13	0.42	-0.50	1.00	-0.30	0.00	-0.01	0.00
γ	0.05	-0.12	0.15	-0.30	1.00	0.00	0.01	-0.01
μ	0.00	0.01	0.00	0.00	0.00	1.00	0.01	-0.01
β	-0.01	0.00	0.01	-0.01	0.01	0.01	1.00	0.00
δ	-0.01	0.02	-0.02	0.00	-0.01	-0.01	0.00	1.00

Calculation of the probabilistic sensitivity measures

As there is no general sensitivity measure that would capture all information on impact of input factors on model output, analysts should combine various measures to obtain a broader image of interactions between different modes. This appendix focuses on describing so-called variance-based methods for probabilistic sensitivity analysis to assess complex relationships in a given model.

List of symbols

Y - model output as a random variable $Y = Y(\mathbf{X}) = Y(X_1,...,X_k)$
y^j - j^{th} realization of random variable Y
x_i^j - j^{th} realization of random variable X_i
n - the total number of realizations of random variable X_i
$\mathbf{x}$ - matrix of realizations of $\mathbf{X}$
$\mathbf{x}_{\sim i}$ - matrix of realizations of $\mathbf{X}$, except the realization of X_i
μ_i - the mean value of random variable X_i (μ_y is the mean of Y)
σ_{X_i} - the standard deviation of variable X_i (σ_y is the mean of Y)
$Cov(X_i, Y)$ - the covariance of random variables X_i and Y ($=E(X_i Y)-E(X_i)E(Y)$)
$Var(X_i)$ - the variance of random variable X_i

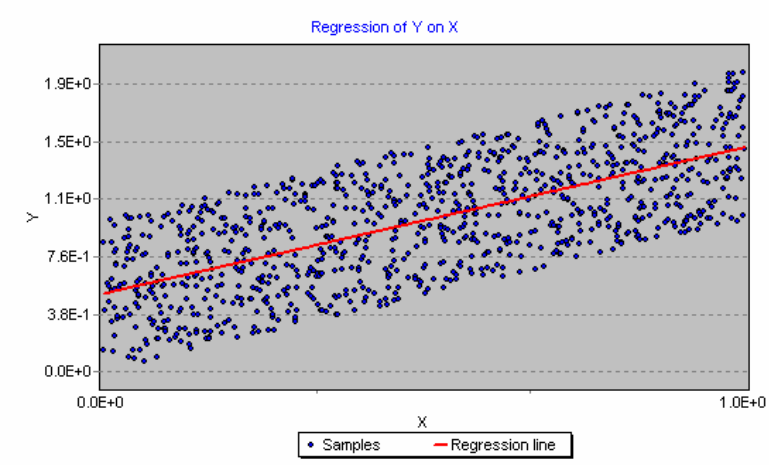
The **linear regression coefficient** (LRC) of input X_i on Y is the slope a of a line obtained using linear least squares fitting of $Y = aX_i+b$. We computed LRC using the following formula for a that minimizes the sum of square differences between y^j and ax_i^j-b (where b is the intercept):

$$LRC(Y, X_i) = a = \frac{Cov(Y, X_i)}{Var(X_i)} = \frac{\sum_{j=1}^{n}(x_i^j - \mu_i)(y^j - \mu_y)}{\sum_{j=1}^{n}(x_i^j - \mu_i)} \quad (24)$$

The regression coefficient tells by how much Y would increase if X_i increases by one unit. If the slope is zero, the line is flat, so there is no relationship between the inputs (see Figure 19). Note that it follows from equations (24) and (3) that the standardized regression coefficient[16] for an input equals the product moment correlation between the model output and that input:

$$LRC(Y, X_i)\frac{\sigma_{X_i}}{\sigma_Y} = \frac{Cov(Y, X_i)}{\sigma_{X_i}^2}\frac{\sigma_{X_i}}{\sigma_Y} = \frac{Cov(Y, X_i)}{\sigma_{X_i}\sigma_Y} = PMC(Y, X_i) \tag{25}$$

Figure 19: Example of a linear regression line with slope *a*.



The regression coefficient is closely related to the notion of the **product moment correlation** PMC(Y,X_i) since

$$LRC(Y, X_i)LRC(X_i, Y) = \frac{Cov^2(X_i, Y)}{Var(X_i)Var(Y)} = PMC^2(X_i, Y) \tag{26}$$

Thus, we can calculate PMC from the LRCs using equation (4). If X_i, i=1,..,k have independent, uniform distributions on [x_i^{max}, x_i^{min}], then the rankings obtained based on PMC and the "average effect" are equal: for all i=1,...,k, we have for the average effect:

$$LRC(Y, X_i)(x_i^{max} - x_i^{min}) = LRC(Y, X_i)\sigma_{X_i} 2\sqrt{3} = PMC(Y, X_i)(2\sqrt{3}\sigma_Y) \tag{27}$$

Thus, the average effect equals $2\sigma_Y\sqrt{3}$ times PMC for each input. Since the rank remains invariant under multiplication by a constant, both measures yield the same rank.

Partial correlation coefficients (PCCs) examine the correlations between two inputs jointly considering some or all inputs at once. The calculation of the partial correlation involves computing the cofactor matrix of the product moment correlation matrix R. Considering a sample from the k+1-variate distribution for $\{X_1,.. ,X_k, Y\}$, R consists of the PMCs for each pair of inputs:

$$R=\begin{pmatrix} PMC(X_1, X_1) & \cdots & PMC(X_1, X_k) & PMC(X_1, Y) \\ \vdots & \ddots & \vdots & \vdots \\ PMC(X_k, X_1) & \cdots & PMC(X_k, X_k) & PMC(X_k, Y) \\ PMC(Y, X_1) & \cdots & PMC(X_k, Y) & PMC(Y, Y) \end{pmatrix} \tag{28}$$

The element $C_{i,j}$ of the cofactor matrix is the determinant of matrix R with removed i^{th} row and j^{th} column and multiplied by -1^{i+j}. The partial correlation between X_i and Y equals:

$$PCC(Y, X_i) = -\frac{C_{i,k+1}}{\sqrt{C_{i,i}C_{k+1,k+1}}} \tag{29}$$

The **partial regression coefficient (PRC)** between Y and X_i equals:

$$PRC(Y, X_i) = -\frac{\sigma_Y}{\sigma_{X_i}}\frac{C_{i,k+1}}{C_{k+1,k+1}} \tag{30}$$

The notion of **correlation ratio** comes from regression analysis interested in studying functional relationships between dependent random variables. The correlation ratio belongs to a family of global quantitative measures of importance of input factors on a given model; it is a variance-based non-parametric method closely related to Sobol indices and measures the relative importance of the analyis-of-variance (ANOVA) components.[24] Sobol's method relies on decomposing the model function $Y(\mathbf{X})$, into summands of increasing dimensionality

$$Y(\mathbf{X}) = Y_0 + \sum_{i=1}^{k} Y_i(X_i) + \sum_{1\le i<j\le k}^{k} Y_{ij}(X_i, X_j) + \ldots + Y_{1,\ldots,k}(X_1, \ldots, X_k) \tag{31}$$

where $Y_0 = \int Y(\mathbf{x})d\mathbf{x}$ denotes the expectation of $Y(\mathbf{X})$. The variance of Y equals:

$$Var(Y) = \int \ldots \int Y^2(\mathbf{x})d\mathbf{x} - Y_0^2 \tag{32}$$

One can show that

$$Y_i(X_i) = \int \ldots \int Y(\mathbf{x})d\mathbf{x}_{\sim i} - Y_0 = E(Y|\ X_i) - Y_0 \tag{33}$$

Hence, the partial variance of $Y_i(X_i)$ is

$$\begin{aligned} Var(Y_i(X_i)) &= Var(E(Y|\ X_i) - Y_0) = Var(E(Y|\ X_i)) \\ &= E(E^2(Y|\ X_i) - E^2(E(Y|\ X_i)) = \int\left[\int \ldots \int Y(\mathbf{x})d\mathbf{x}_{\sim i}\right]^2 dx_i - Y_0^2 \end{aligned} \tag{34}$$

We can define the partial variance $Var(Y_{i_1,\ldots,i_t}(X_{i_1}, \ldots, X_{i_t}))$, $1 \le t \le k$, analogously. The Sobol t^{th} order sensitivity index $X_{i_1}, \ldots, X_{i_t}$ is

$$S_{i_1,\ldots,i_t} = \frac{Var(Y_{i_1,\ldots,i_t}(X_{i_1}, \ldots, X_{i_t}))}{Var(Y)} \tag{35}$$

The first order Sobol indices, already used by Pearson at the turn of the twentieth century, are of special importance to us. Since $Var(Y) = E(Var(Y|X_i)) + Var(E(Y|X_i))$, a small expected variance reduction of Y from conditioning on X_i implies a large $Var(E(Y|X_i))$. Thus, when normalized, $Var(E(Y|X_i))$ represents a useful sensitivity measure. Most often this quantity is referred to as the correlation ratio.

One can show that the correlation ratio of Y on X_i equals:[20]

$$CR(Y, X_i) = PMC^2(Y, E(Y|\ X_i)) = \max_{f;\sigma^2_{f(X)}<\infty} PMC^2(Y,\ f(X_i)) \tag{36}$$

and that:

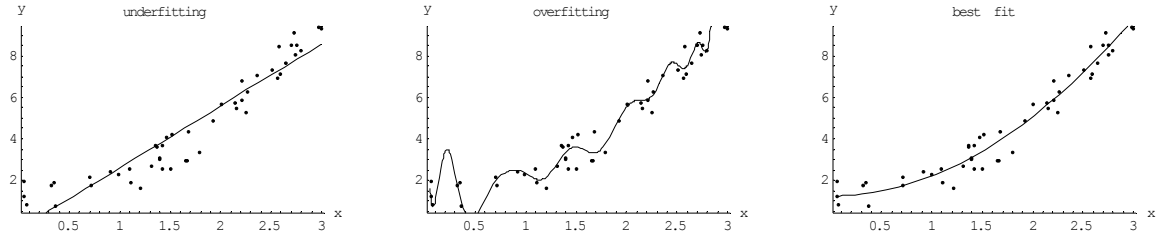
$$\operatorname{argmax}_{f;\sigma^2_{f(X)}<\infty} PMC^2(Y,\ f(X_i)) = \operatorname{argmin}_{f;\sigma^2_{f(X)}<\infty} E(Y-\ f(X_i))^2 \tag{37}$$

In other words, the conditional expectation of Y to X_i is equal to the function f (with finite variance) that maximizes the squared (product moment) correlation (SQC) between Y and $f(X_i)$. Furthermore, the function that maximizes this SQC equals the best fit between Y and X_i in least-square sense. In our situation, we have a finite sample of y^j's and x_i^j's (j=1,...,*sample size* n) and our approach is to approximate $f = E(Y|X_i)$ by a polynomial in X_i of degree D. Given that in practice, minimizing the least-squares is a faster optimization problem than maximizing the SQC, we proceed with the minimization problem to find f for given y^j's and x_i^j's (using standard least-square fitting routines in Mathematica™). Thus, the coefficients $c_1,...,c_D$ of the best-fitting D-th degree polynomial satisfy the following minimization problem:

$$\min_{c_0,...,c_D} \sum_{j=1}^{n} \left(\sum_{d=0}^{D} c_d (x_i^j)^d - y^j \right)^2 \tag{38}$$

Once we find the coefficients of f, the SQC between the y^j's and $f(x_i^j)$'s is our CR estimate for input i. Note that if we use $D = 1$, we will get $CR(Y,X_i) = PMC(Y,X_i)$, which, unless $E(Y|X_i)$ is truly linear, represents a situation of underfitting. On the other extreme, if we use $d = n$, the polynomial with the least square distance to the n data points will go through each data point and $CR(Y,X_i) = 1$ (unless replicates of x_i^j's exists with different y^j's), which represents a situation of overfitting unless Y depends only on X_i (see Figure 20). The challenge in finding an approximation of $E(Y|X_i)$ based on a finite sample is to avoid both underfitting and overfitting. In this appendix, we describe two methods that deal with this problem in different ways. The results are based on the case 4 sample of size 10,000 for the situation of non-uniform marginals with the vine dependence structure. In both methods, we divide the sample into 2 samples of size 5,000 and refer to the first half-sample as the test sample and to the second half-sample as the independent sample.

Figure 20: Example of underfitting (left figure; degree 1), overfitting (middle figure; degree 40) and the best fit (right figure; degree 2) of *x* on *y*.



Method 1 for estimation of the correlation ratio: Early stopping

The method of early stopping is popular in neural networks-based methods for fitting a function to data, and commonly refers to the test sample as the training set while referring to the independent sample as the validation set.[25] The idea is that over time (i.e., as the neural network gets closer to the correct solution for the training set), the mean squared error (MSE) for

the training set decreases, while the MSE for the validation set initially decreases, but at some point starts to increase again as the algorithm starts to overfit to the training set. The algorithm then simply stops as the MSE in the validation set is at its lowest. In our case, we should expect the SQC for the test sample to continue to increase as we increase the degree of the polynomial, while the SQC for the independent sample should reach a maximum for some degree before the effect overfitting reduces the SQC again. The degree of the best polynomial fit should coincide with the degree for which the SQC with respect to the independent sample is highest. Figure 21 shows the SQCs as a function of the degree for the 8 inputs. We see that the SQCs for the test sample (dashed lines) do not increase as nicely as we might expect, which relates to the fact that the fitting routine cannot always find the global optimum. In the case of γ and *H*, we even observe substantial drops in the SQC as we get to high degrees. Remarkably, the test-sample SQC for γ and β are most often lower than their independent-sample SQCs. For degree one this is consistent with the product moment correlations (0.010 (test sample) vs. 0.018 (independent sample for γ and 0.251 (test sample) vs. 0254 (independent sample) for β), but the fact that this persist for higher degrees is a somewhat surprising artifact of the sample (although the differences in SQCs are not large). The SQCs for the independent sample (solid lines) all appear to reach a maximum for a low degree polynomial, with the exception of *tr* which reaches the maximum at degree 49. Table 16 shows the results with the early stopping method, with either the first 5,000 or the second 5,000 samples as the test sample. The CR estimates remained relatively unvaried, improving our confidence in them. However, the degrees that lead to the lowest independent-sample MSEs varied. Possibly, the higher-degree polynomials effectively could be well-approximated by the lower degree polynomials (i.e., because the low-degree terms dominate). The largest discrepancies occur for the input *tr*, for which Figure 22 shows the polynomial approximations of the conditional expectation. This illustrates that the greatest difference between the two polynomial fits occur around the edges of the range of *tr*, although the effect is large enough to have some impact on the estimate of the CR for *tr* in Table 16.

Figure 21: Squared correlations (SQCs) between the best polynomial fit of the net benefit to the 8 inputs for the test sample (dotted line) and the independent sample (solid line) as a function of the degree of the polynomial. The test sample SQC does not increase monotonically with the degree due to the inability of the solver to always find the global optimum.

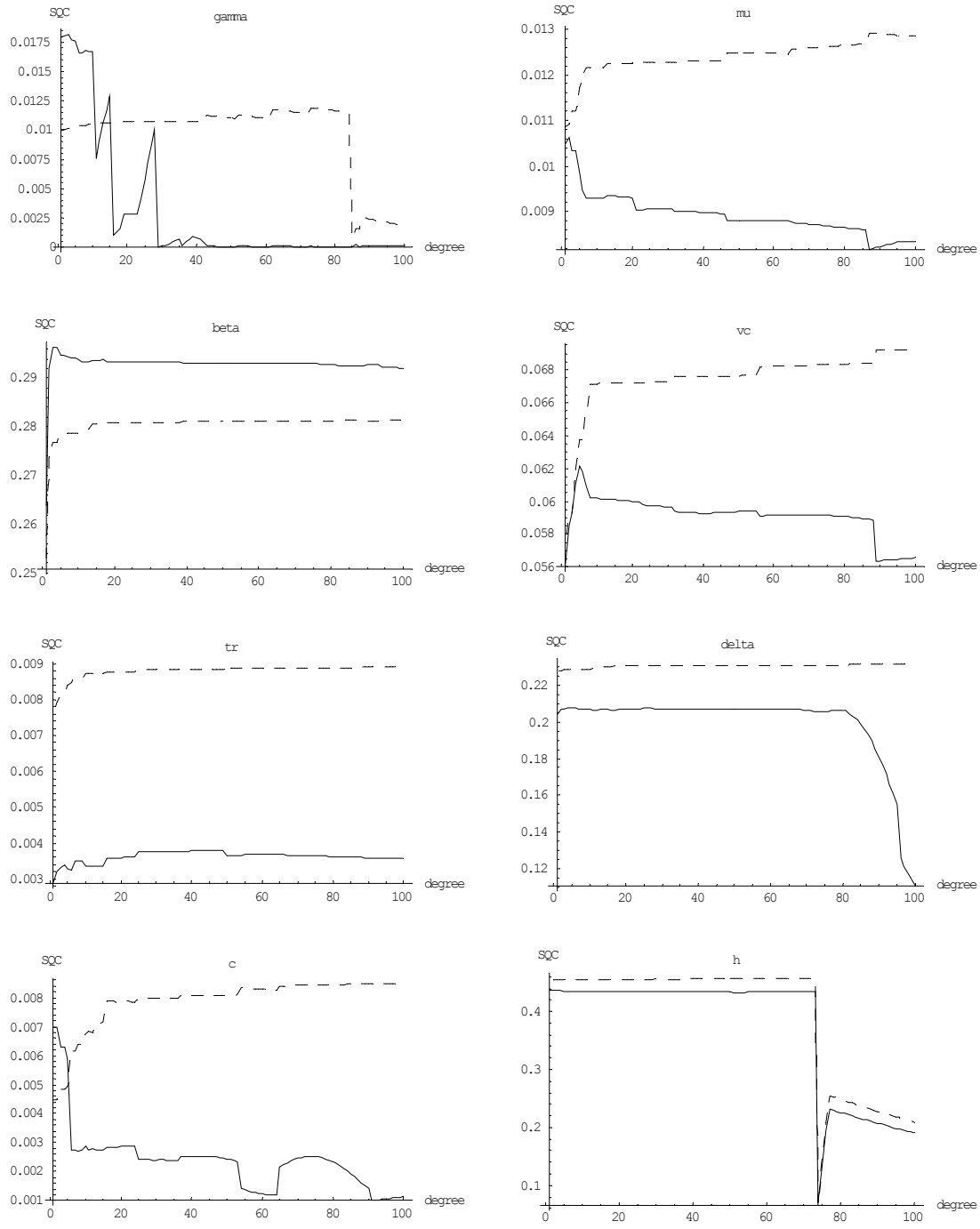
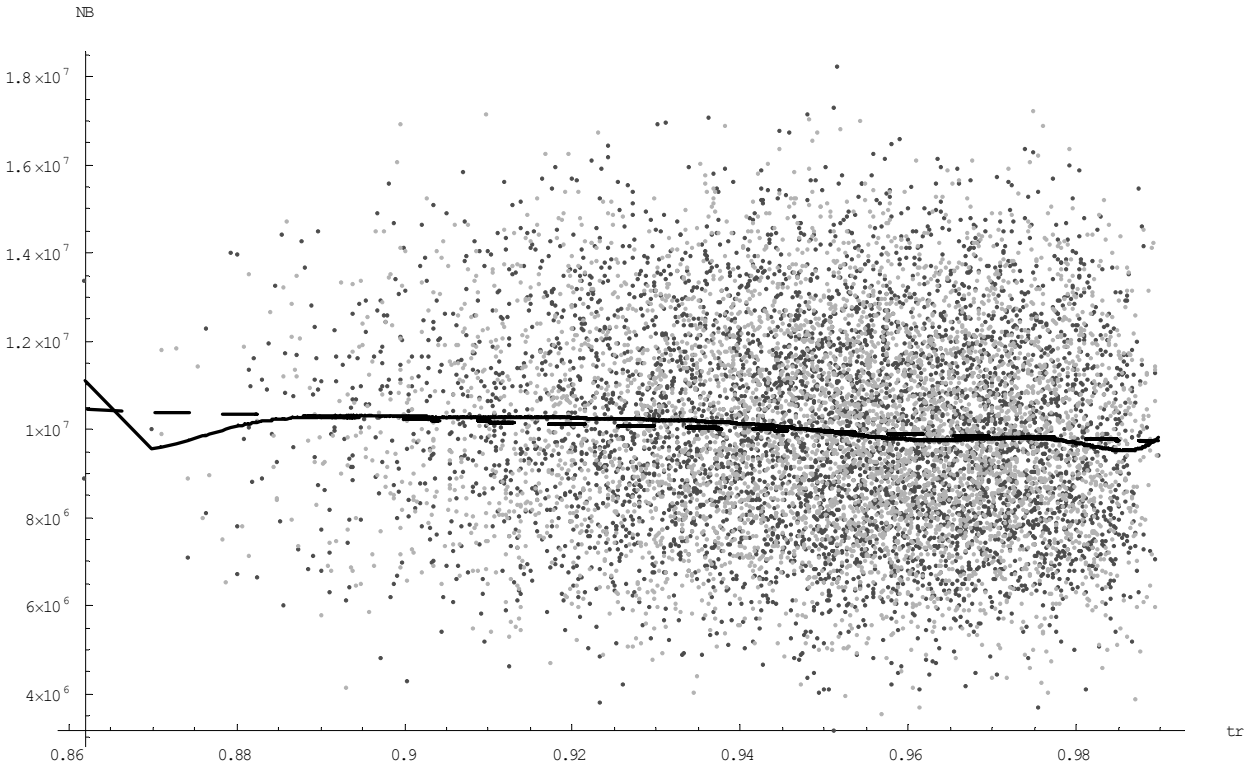


Table 16: Estimates of the correlation ratios using the early stopping method (tested up to degree 100)

Input	Test sample: first 5,000 samples; independent sample: second 5,000 samples		Test sample: second 5,000 samples; independent sample: first 5,000 samples	
	Degree for which least-square fit to test sample maximizes the independent-sample-SQC	Full-sample SQC based on polynomial of given degree (fitted to the test sample)	Degree for which least-square fit to test sample maximizes the independent-sample-SQC	Full-sample SQC based on polynomial of given degree (fitted to the test sample)
gamma	3	0.0138	3	0.0138
mu	2	0.0108	5	0.0108
beta	3	0.2863	6	0.2865
vc	5	0.0629	7	0.0631
tr	49	0.0061	1	0.0050
delta	4	0.2180	2	0.2178
c	2	0.0057	1	0.0057
h	3	0.4451	3	0.4451

SQC = squared (product moment) correlation (between the y^j's and $f(x_i^j$'s))

Figure 22: Best polynomial fits for the take rate (*tr*) with the first (solid line) or second (dashed line) 5,000 samples takes as the test sample; data points show first (black dots) and second (gray dots) 5,000 samples (*NB* = net benefit).



Method 2 for estimation of the correlation ratio: Hypothesis testing

For this method, we divide both the test sample and the independent sample further into 10 subsamples of size 500 each. The main idea is to generate SQCs for each subsample (given a

fixed polynomial degree) and then to compare the 10 SQCs obtained using the subsamples from the test sample with the 10 SQCs obtained using the subsamples from the independent sample, where for all SQCs we use a polynomial fitted to the entire test sample (i.e., of size 5,000). We can then test the null-hypothesis that the 10 test-sample-SQCs have the same distribution as the10 independent-sample-SQCs against the alternative hypothesis that the distribution of the test-sample-SQCs is "greater" than that of the independent-sample-SQCs. If we can reject the null-hypothesis in favor of the alternative hypothesis, we have significant evidence for overfitting and reject the corresponding SQC. The CR estimate will then correspond to the greatest of the SQCs that we do not reject at a certain confidence level. To test the hypothesis, we use the non-parametric Wilcoxon rank sum test statistic.[26] This test first merges the set of the 20 test-sample-SQCs and independent-sample SQCs into one ranked sets. The sum of the ranks of the 10 test-sample-SQCs then provides information about the likelihood that both have identical distributions, based on the distribution of the sum of ranks that one would obtain if the null-hypothesis were true (shown in Figure 23). We would expect a high sum of the ranks (i.e., a sum of ranks in the tail of the distribution in Figure 23) for the test-sample-SQCs in a situation of overfitting.

Figure 23: Probability density function of the Wilcoxon statistic of the sum of the ranks of two sets of 10 variables from the same distribution

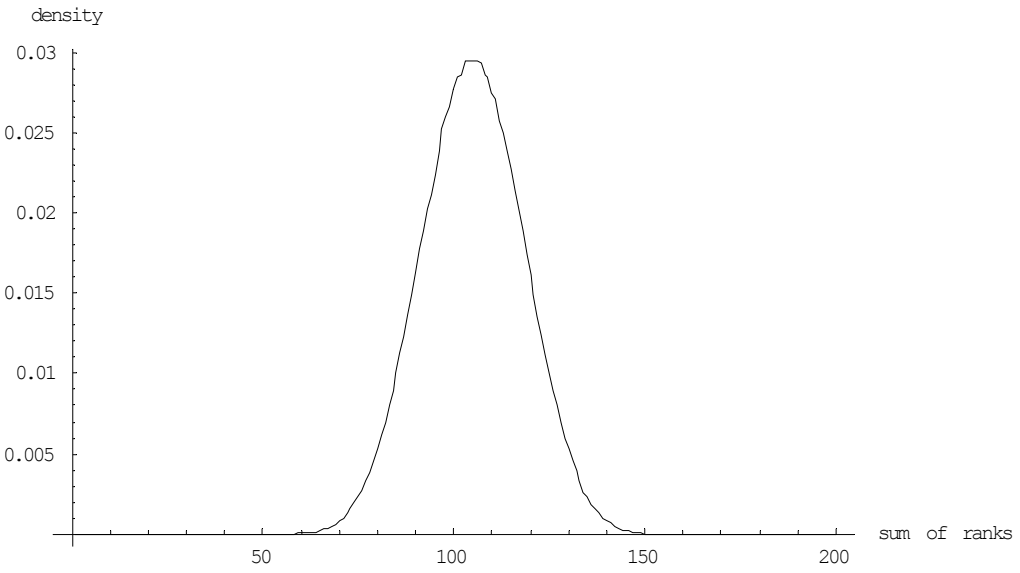


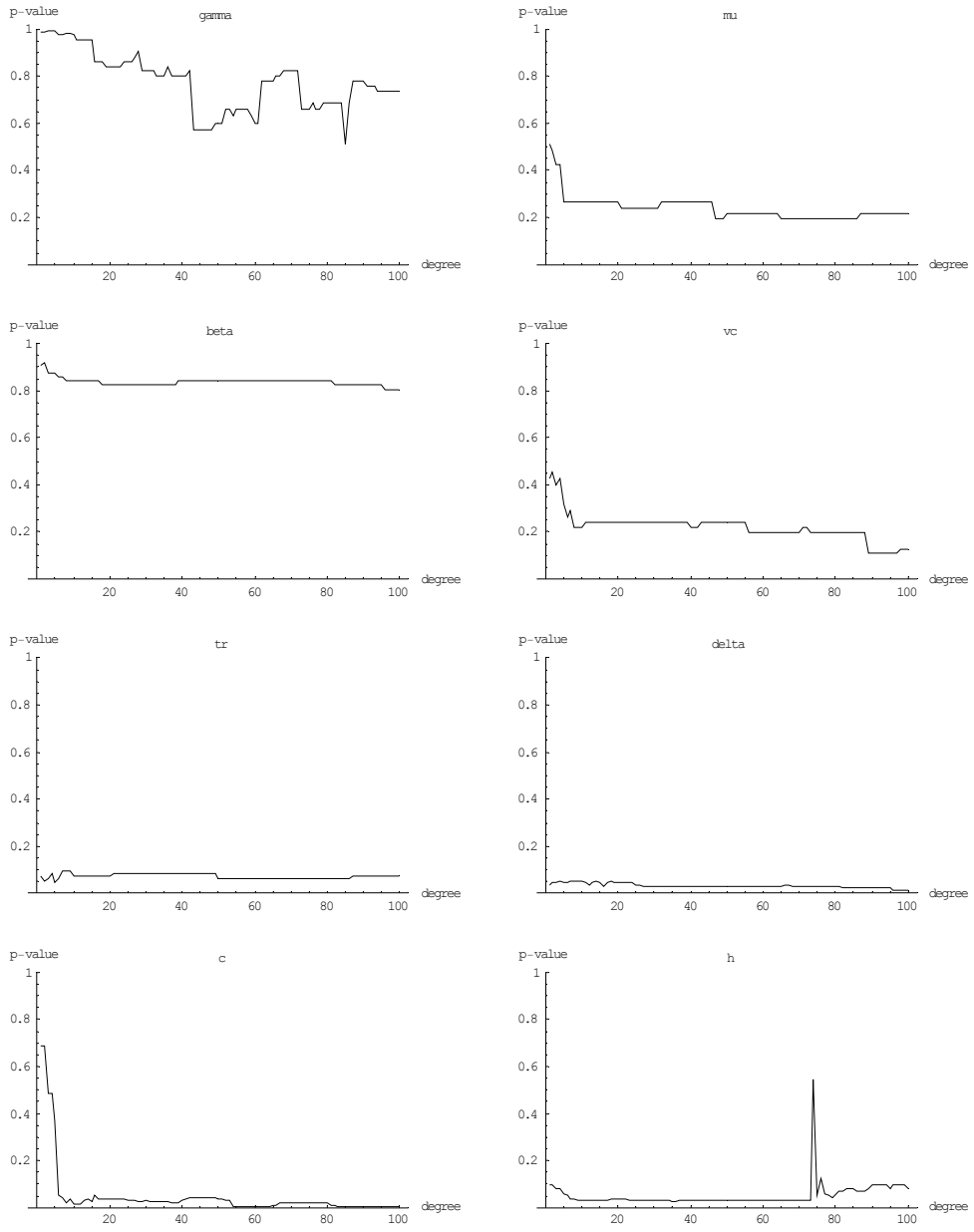
Figure 24 shows the p-values of the Wilcoxon statistic as a function of the degree of the polynomial. A low p-value implies a low probability of obtaining a rank sum test higher than observed due to randomness if the null-hypothesis that the SQCs of the test sample and the independent sample have equal distribution holds and would lead to rejection of this hypothesis in favor of the alternative hypothesis that the test sample has a "greater" distribution. In other words, a low p-value suggests overfitting. Figure 24 shows very different patterns for each input, with γ and β showing no statistical evidence for overfitting (consistent with Figure 21). For μ, *vc,* and *c*, increasing the degree appears likely to lead to overfitting, while for *tr* and δ overfitting may occur even for low degrees. If we reject SQCs at a significance level of 0.05, we

obtain the CR estimates in Table 17. The table also shows the results if we consider the first 5,000 samples the independent sample and the last 5,000 samples the test sample. For input γ and the second 5,000 samples consider the test sample, we reject all estimates, although after degree 88 we obtain p-values greater than 0.05 due to local solutions of the least-square fitting routine that perform poorly on both the test and independent sample. The rejection of low-degree fits is not surprising given that the product moment correlation for γ is much greater based on the independent sample than based on the test sample (as discussed in context of the early stopping method). The "optimal" degree depends both on whether we reject polynomial fits due to overfitting and on how well a fit on the test sample performs on the entire sample. Both the nature of the data sets and the fact that the fitting algorithm does not always find the global optimum can lead to an optimal degree below 100 even if we never reject a polynomial for overfitting (e.g., for γ and β). Note that for γ we obtain very different results depending on the choice of the test sample, which is consistent with its behavior in Figure 21 and Figure 24.

In conclusion, we observed that the choice of test sample (first vs. second 5,000 samples) appears of greater influence on the CR estimates than the choice of method (early stopping vs. hypothesis testing). Both methods calculate CR based on the full-sample-SQC between output and a polynomial of the input fitted only to the test sample. The only difference between the two methods is the stopping criterion, with the hypothesis testing methods explicitly looking for statistical evidence of overfitting based on comparison of test sample and independent sample results, while the early stopping method assumes that a decreasing SQC on the independent sample indicates overfitting without further regard of the test sample. However, the hypothesis testing method requires defining a significance level that represents a threshold for overfitting, but it is not clear what would be the most appropriate choice. If we set the significance level at 10%, we would reject all SQCs for tr and δ. On the contrary, with a significance level of 5%, we effectively reject many SQCs not because of overfitting but because the full-sample SQC stops improving. For input β, we never obtain a p-value lower than 0.8, but the full-sample SQCs stop increasing after degree 17. This means that we continue increasing the degree in search for evidence of overfitting without actually increasing the full-sample-SQC, thus possibly adding unnecessary computer time. Given that both methods yield similar results, performing the early stopping method until the first degree for which the independent-sample SQC is lower than the previous degree may be satisfactory for a rapid and reasonably accurate estimate of the CR. However, it can occur that the SQC starts to decrease for one or two degrees but then increases towards the real maximum (e.g., tr in Figure 21), in which case the rapid procedure would yield an underfit (but not an overfit). Regardless of the criteria for deciding up to which degree to calculate SQCs, unlike the hypothesis testing method the early stopping method does not require calculating additional SQCs for (20) subsamples. However, we note that the hypothesis testing method is able to find higher SQCs without statistical evidence that these represent overfitting (as shown in Table 17 for a 5% significance level). In case the CR-estimate differ (much) depending on the choice of test sample (i.e., first vs. second half-sample), the smaller of the two appears most appropriate in the early stopping method based on Figure 22 (i.e., the irregular behavior around the edges is likely a result of the small number of samples there rather than a true phenomenon of the model). For the hypothesis testing approach, it appears more appropriate to use the greater estimate given the possibility that an atypical sample leads only to accepting of a poor fit (as was the case with γ if we considered the second 5,000 samples the test sample). With both methods, we recommend cross-validation through reversal of the test and independent sample. We generated the results presented in this paper using the early stopping

method, checking the trend in the independent sample SQCs up to degree 100 (in all cases, the downward trend started well before degree 100).

Figure 24: P-values* for each input as a function of the degree of the polynomial fitted to the test sample.



*(the p-value represents the probability that the 10 squared correlations on the test sample have a higher rank sum than observed based on the Wilcoxon rank sum test statistic assuming that the squared correlations of the test sample and the independent sample have identical distributions)

Table 17: Estimates of the correlation ratios using the hypothesis testing method at a significance level of 5% (tested up to degree 100)

Input	Test sample: first 5,000 samples; independent sample: second 5,000 samples		Test sample: second 5,000 samples; independent sample: first 5,000 samples	
	Degree for which least-square fit to test sample maximizes the full-sample-SQC, if not rejected for overfitting	Full-sample SQC based on polynomial of given degree (fitted to the test sample)	Degree for which least-square fit to test sample maximizes the full-sample-SQC, if not rejected for overfitting	Full-sample SQC based on polynomial of given degree (fitted to the test sample)
gamma	3	0.0138	88	0.0032
mu	5	0.0108	5	0.0108
beta	17	0.2870	16	0.2869
vc	71	0.0637	7	0.0631
tr	45	0.0061	4	0.0055
delta	18	0.2188	38	0.2186
c	2	0.0057	2	0.0057
h	3	0.4451	63	0.4452

SQC = squared (product moment) correlation (between the y^j's and $f(x_i^j$'s))

Conditional expectation plots and cobwebs

Figure 25, Figure 26 and Figure 27 show the conditional expectation for all inputs in the case 3 analysis with uniform and non-uniform marginals and for the case 4 analysis, respectively. We generated the results using the early stopping method, checking the trend in the independent sample SQCs up to degree 100 (in all cases, the downward trend started well before degree 100). For each choice of the test sample (i.e., first or second half-sample), we kept the maximum SQC, and then proceeded with the polynomial that lead to the smallest of the two SQCs as the polynomial that approximates the conditional expectation. For all cases, we can immediately see that the conditional expectations with respect to H, β and γ correlate most strongly with the net benefit. Except for β, most conditional expectation functions appear fairly linear in all cases, consistent with the linearity indices in Table 6, Table 8 and Table 9. While the location of the data points is the only striking visual difference between the two case 3 figures (Figure 25 and Figure 26), the conditional expectation plots changed more by going from independence to the case with dependence (Figure 26 vs. Figure 27) then by changing the input distributions. Most notable, increasing vaccination coverage (*vc*) beyond 0.95 appears to have more benefit if we do consider dependence.

To graphically see sensitivities on a cobweb, it is convenient to view variables on a percentile scale (i.e., such that the highest X% of the samples also occupy the highest X% of the vertical lines) and to place the input of interest first. For example, Figure 28 shows the impact of *H*. The importance is apparent from the fact that regardless of values of the other inputs, the highest 10% of *H*-values (the red lines) lead to large benefits in general and vice versa. In contrast, Figure 29 illustrates the lack of importance of the take rate *tr*.

Figure 25: Conditional expectation and samples with independent, uniform marginals (based on 10,000 samples and polynomial of degree determined using early stopping tested up to degree 100).

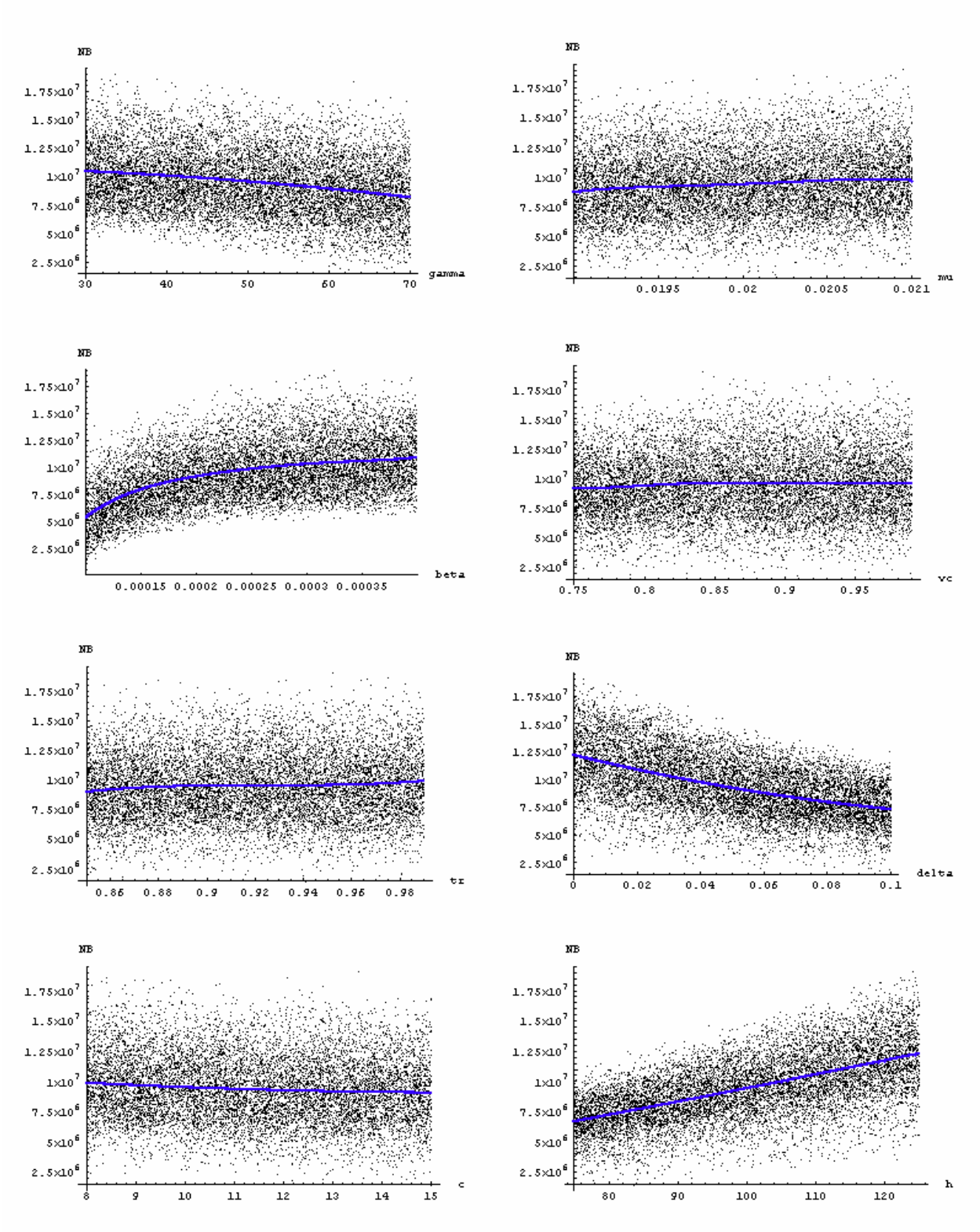


Figure 26: Conditional expectation and samples with independent, non-uniform marginals (based on 10,000 samples and polynomial of degree determined using early stopping tested up to degree 100).

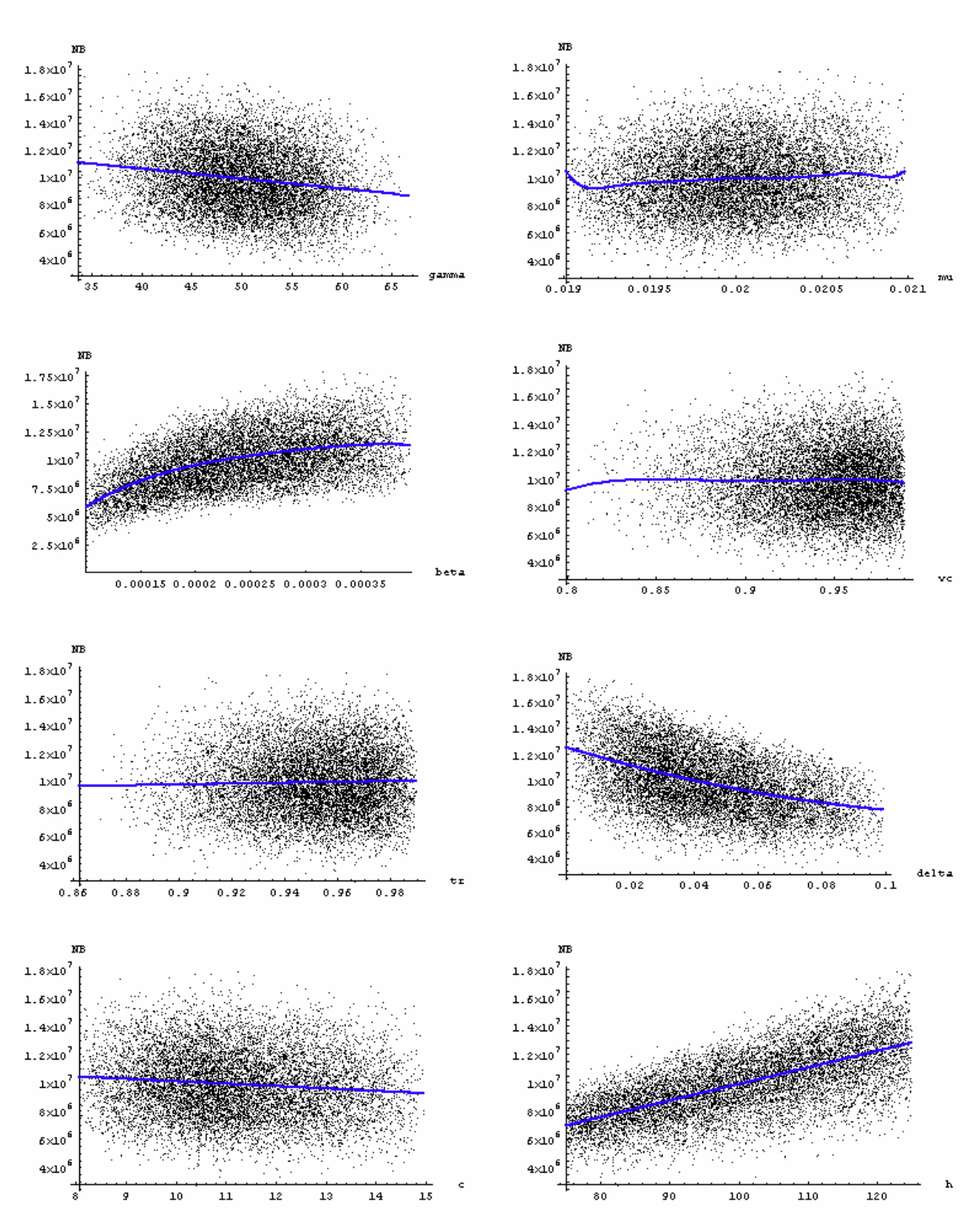


Figure 27: Conditional expectation and samples with non-uniform marginals and the vine dependence structure (based on 10,000 samples and polynomial of degree determined using early stopping tested up to degree 100).

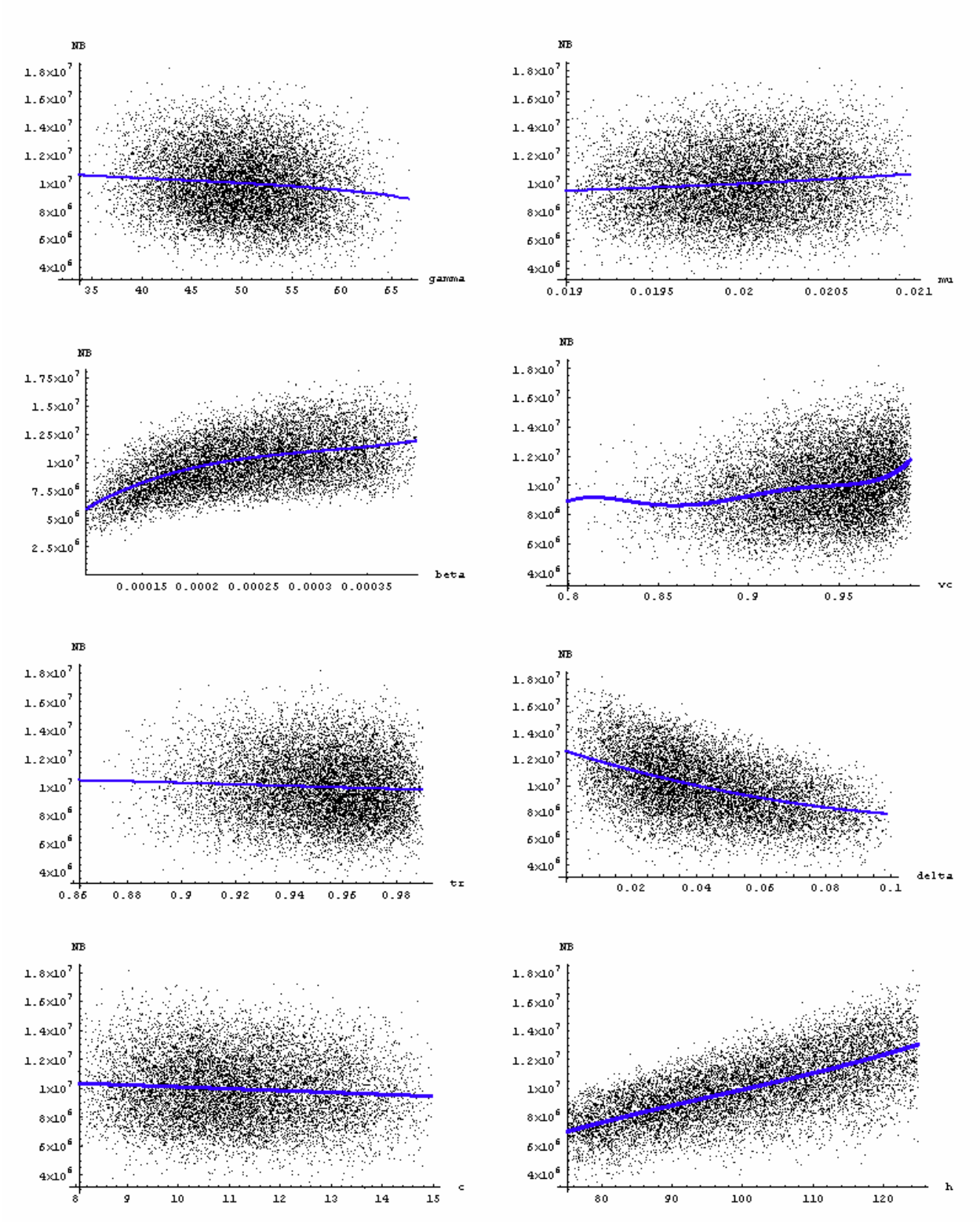


Figure 28: Graphical illustration of the importance of H using cobwebs.

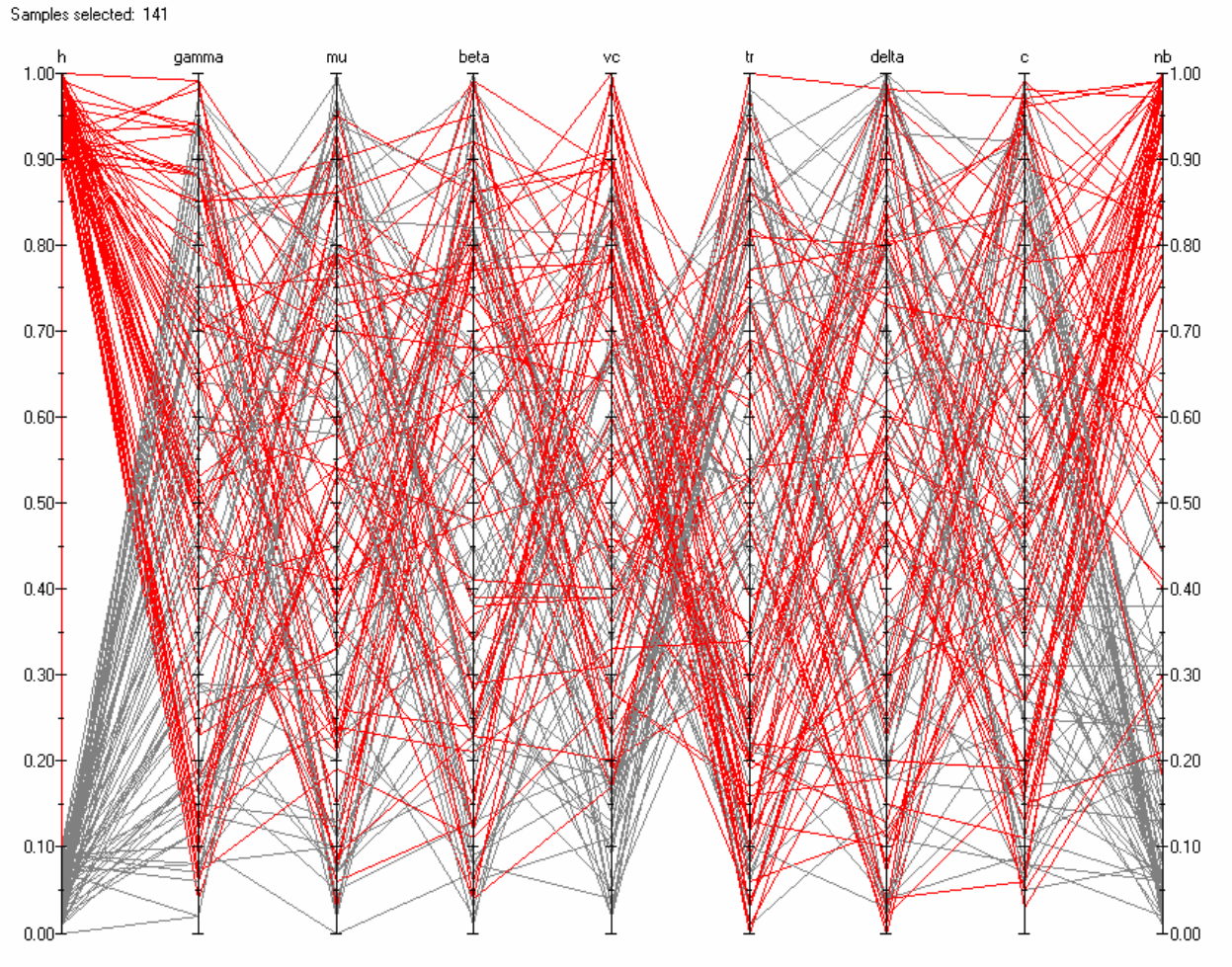
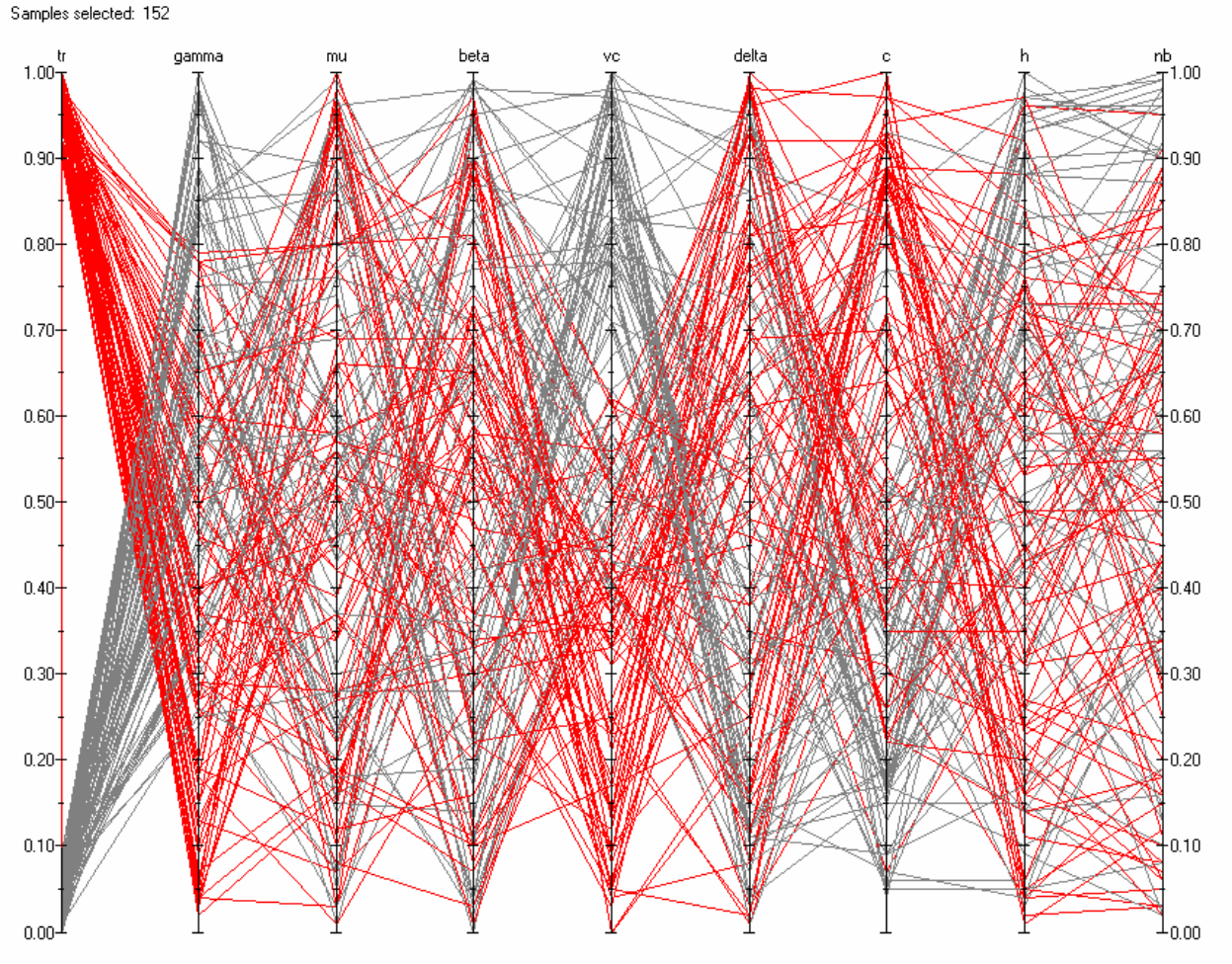


Figure 29: Graphical illustration of the lack of importance of *tr* using cobwebs.



Implications for the decision model of polio risk management policies after eradication

This paper investigates the impact and implications of different sensitivity analysis approaches. By performing the analyses on a dynamic economic evaluation model, we hope to provide a helpful reference to the clinical community and to obtain more insights into the choice of a method for the decision model for polio risk management policies after global eradication.[27-30]

The polio decision model has many inputs that we would identify as uncertain and that potentially have a great impact on the results, including but not limited to the exponential decay in the risk of circulating vaccine-derived polioviruses, the transmissibility of polioviruses in different settings, the size or structure of outbreak populations, the future costs of the inactivated polio vaccine, the threshold of detection of virus reintroductions, the likely time from outbreak detection to response, the other characteristics of the outbreak response, the population immunity at T_0, the relative infectiousness and susceptibility of different types of partially infectibles and their durations of infectiousness, the true prevalence of currently excreting long-term excretors of vaccine-derived polioviruses in different income levels, the frequency of release of poliovirus from a laboratory or vaccine manufacturing site, the frequency of intentional poliovirus releases,

the conditional probability of an outbreak given a release, the size of the vaccine stockpile and the rates of vaccine-associated paralytic polio associated with monovalent oral polio vaccines.

The model also requires substantial computational effort, even to evaluate a single decision option, since we must run the outbreak simulation many times to capture rare events and we need to consider a long time horizon. This places us in a situation reflected in the last column of Table 10; many inputs and a very high computational cost per model run. Like the dynamic economic evaluation model presented in this paper, the polio model also contains a (large) dynamic component and costs over time with additional complexity in the form the outbreak risk simulation and income level stratification. To further complicate matters, our model does not yield just one output of interest but an estimate of expected cases and expected costs for every decision option and income level (as a function of different time periods). For practical purposes, it is thus necessary to focus the sensitivity analysis on one or a few outputs that inform particular key decisions, such as for example the incremental net benefit of switching to inactivated polio vaccine vs. stopping polio vaccinations altogether in upper-middle income countries. This would still require assumptions about the policies for stockpile and response, surveillance, containment, and management of long-term excretors, since these decisions interact with the vaccination decision. One could even model the other decisions as uncertain inputs and investigate their importance compared the other uncertain inputs, which would require estimating probabilities for each option. Henceforth, we assume that we would identify one output of primary interest (if we have several, we could repeat the sensitivity analysis), but we still remain in the last column of Table 10.

Currently, we obtained ranges for most of the uncertain inputs and these underwent or will undergo peer review. However, it is obviously preferable to estimate uncertainty distributions for each input to correctly estimate their contribution to the output uncertainty. With very limited data available for each input, expert elicitation on at least selected inputs would improve the informative capacity of the polio decision model through a probabilistic sensitivity analysis and eventually an uncertainty analysis. During our work on the polio decision model, by far the most debated input has been the transmissibility (R_0) for wild and vaccine-derived polioviruses, followed by the relative infectiousness of partially infectibles. Contingent on experts' willingness to participate, structured expert judgment would summarize their different opinions into one consensus distribution (with experts weighed according to their performance using calibration questions) and provide traceability of the distributions.[19] The expert judgment could also elicit information about dependencies among the inputs by querying on conditional probabilities. For example, since high R_0's generally correlate with low income settings, which in turn correlate with poor surveillance, we might enforce a positive correlation between R_0 and the threshold of detection of virus reintroductions. By stratifying the world into income levels we already partly accounted for this variability, but even within income levels correlations exist that could impact the results since in the case of polio risky conditions often coincide.

With or without input distributions characterized, given the size of the model, OWSA offers a useful first step to get a sense of the relative importance of inputs at the base case. If any inputs clearly have little influence, one could eliminate them from further analysis after verifying that non-linearities and interactions did not mask their low OWSA effects in a MWSA specifically designed for that purpose (or even by analyzing the model equations). If the uncertainty characterization remains limited to ranges, the next step would be to perform Morris' method to reduce the set of inputs to a more manageable number and then perform a large DOE

analysis on the highest ranking inputs, as suggested in Table 10. The number of inputs for the DOE should depend both on the absolute values of the mean elementary effects and on the computational cost of model runs. If the computational cost even to obtain only the one selected output is very high, we must either use a highly-aliased design (at the expense of losing some of the ability to measure all effects and potentially missing important interactions) or include fewer inputs in the DOE analysis.

If we do succeed in obtaining (non-uniform) input distributions, Morris' method would violate the assumption of independent, non-uniform marginal distributions. However, the great advantage of Morris' method is that it enables a quick selection of important vs. unimportant inputs while still considering curvature and interactions. CR, PMC or RC would not achieve an equally statistically efficient coverage of the input space in the same number of runs. Thus, an investment into extending Morris' sampling scheme to sample from non-uniform distributions may be worthwhile. The simplest approach would be to attribute weights to each of the p-1 sub-intervals according to their distributions, or alternatively to take p-1 sub-intervals of non-equal size for each input and adapt Δ accordingly. Factoring in dependence would be more challenging. The adapted version of Morris' method would still only serve the purpose of excluding non-important inputs from further analysis; eventually we would like to obtain CR estimates. The benefit of first eliminating inputs for the probabilistic sensitivity analysis using Morris' method comes from obtaining better coverage of the input space. Thus, we would require less model evaluations for the probabilistic sensitivity to achieve statistical convergence of the results compare to a probabilistic sensitivity analysis on all inputs. For the polio decision model, this two-step approach might prove time saving without loosing statistical power of the analysis for the inputs that matter most.

Finally, an alternative approach in the event we succeed in obtaining input distributions would be to first build a regression model of the polio decision model using an appropriate design with as many runs and inputs as feasible, without consideration of the input distributions. This regression model would not include inputs that Morris' method or OWSA identified as unimportant. Once we built a satisfactory regression model, we can use that model to approximate as many model runs as we want at very low computational cost to perform the full probabilistic analysis. This approach appears very elegant as it would allow us to factor in any input uncertainty characterization while avoiding the high computational cost of the model. The major challenge would be to construct a design (probably mixed and highly-aliased) with sufficient coverage of the input space to obtain a satisfactory regression model of the model.

SAMENVATTING

Dit proefschrift presenteert de onderdelen van een beslissingsanalysemodel voor strategieën ter beheersing van polio risico's na wereldwijde uitroeiing van het virus. Het model beoogt de ondersteuning van beslissingen op globaal, regionaal en nationaal niveau middels verstrekking van kwantitatieve informatie, te verkrijgen met wiskundige methoden, over de kosten en baten van verschillende strategieën. Alhoewel gevallen van polio door natuurlijke oorzaak in grote delen van de wereld al lang niet meer voorkomen, blijven er risico's bestaan dat poliovirussen zelfs na wereldwijde uitroeiing opnieuw geïntroduceerd worden. Mogelijke wegen van herintroductie zijn onder meer mutatie van overgebleven, levende vaccinvirussen naar een vorm die epidemieën kan veroorzaken, ontsnapping van het natuurlijke virus uit een laboratorium of vaccinproductiefaciliteit of een bioterrostische aanslag met het poliovirus. De epidemie die Nederland trof in 1992 toont aan dat in het geval van herintroductie het virus wel degelijk aanzienlijke schade kan aanrichten, zelfs in de meest ontwikkelde landen. Eventuele stopzetting van polio inentingen (met één van de twee beschikbare vaccins, het orale poliovaccin (OPV) of het geïnactiveerde poliovaccin (IPV)) na uitroeiing zou bij een herintroductie in de toekomst bovendien drastische gevolgen kunnen hebben door toegenomen ontvankelijkheid voor het virus in de bevolking. Gezien de in hoge mate onzekere kosten en baten van de verschillende strategieën is het belang van kwantitieve informatie ter ondersteuning van het beslissingsproces groot.

Hoofdstuk 2 somt de verschillende opties die landen na uitroeiing zullen hebben op. De Wereldgezondheidsorganisatie zal binnen enkele jaren resoluties en aanbevelingen voorstellen aan de Wereldgezondheidsvergadering (WHA) voor het "post-uitroeiingstijdperk". Na goedkeuring door de WHA zullen deze aanbevelingen van grote invloed zijn op de beslissingen van alle landen, maar uiteindelijk zullen de nationale overheden besluiten welk poliobeleid ze zullen voeren. De verzameling van logischerwijs beschikbare opties voor supplementaire vaccinatieactiviteiten, epidemiebestrijding, vaccinreserves, polio surveillance, beveiliging van virussen in laboratoria of IPV-productiefaciliteiten en beheersing van het risico van herintroducties via chronisch besmette patiënten hangt af van het gekozen routinematige inentingsbeleid. Dit kan bestaan uit inenting met OPV, inenting met IPV óf stopzetting van alle routinematige poliovaccinatie (gesynchroniseerd met andere landen of volgens een onafhankelijke tijdsplanning). Gezien de verschillen in volksgezondheidsbegroting, hygiëne, vaccinatiedekking, effectiviteit van de vaccins en andere factoren zullen verschillende landen mogelijk verschillende voorkeuren hebben. Teneinde deze variabiliteit enigermate in het model mee te nemen verdelen we de landen van de wereld volgens de inkomstenniveaus van de Wereldbank en hebben veel variabelen in het model waarden die afhangen van het inkomstenniveau.

Iedere beslissing impliceert vaste kosten (alhoewel deze kunnen veranderen als een functie van de tijd) voor aankoop en toediening van vaccins, surveillance en andere programmatische activiteiten. Hoofdstuk 3 vat de beschikbare kostengegevens samen teneinde deze kosten te schatten. Naast de vaste kosten zullen autoriteiten in het geval van een epidemie hoogstwaarschijnlijk kosten maken voor een grootschalige bestrijdingscampagne met een

poliovaccin. Deze kosten hangen af van de eigenschappen van de epidemie en van de bestrijdingsstrategie.

De beslissingen hebben ook invloed op het niveau van immuniteit in de bevolking (veranderend als een functie van de tijd), hetgeen één van de factoren is die mede bepaalt of een epidemie kan ontaarden. Hoofdstuk 4 bespreekt de factoren die de kans op polio na wereldwijde uitroeiing beïnvloeden en bevat kwantitatieve schattingen voor de risico's als functie van het beleid, het inkomstenniveau en de tijd. We beschrijven de risico's door middel van Poisson frequenties en simuleren het aantal epidemieën in elk jaar door steekproeven te nemen uit de Poissonverdeling met de voor een gegeven scenario relevante frequentie.

Als in de simulatie een epidemie begint in de context van een gegeven verzameling van beslissingen, van een gegeven jaar en van een gegeven inkomstenniveau, dan zal een dynamisch epidemiemodel de omvang van een epidemie in de betreffende situatie schatten. Hoofdstuk 5 beschrijft dit deterministische model alsmede de resultaten van drie testsimulaties van gerapporteerde polio epidemieën in Albanië in 1996, in de Dominikeinse Republiek in 2000-2001 en in Nederland in 1992-1993. Op basis van literatuuronderzoek en onze ervaring met het modelleren van deze epidemieën verstrekken we de beste schattingen van variabelen voor een model toegespitst op het analyseren van de omvang en het verloop van toekomstige epidemieën. Tevens presenteren we resultaten van dit prospectieve model. De omvang van een epidemie hangt af van een groot aantal factoren, zoals onder meer het immuniteitsprofiel in een bevolking (en daardoor dus de tijd sinds stopzetting van routinematige (OPV) inenting, mits van toepassing), de hygiënische en andere omstandigheden in het land van de epidemie, de kwaliteit van polio surveillance en de tijd tussen detectie van het virus en aanvang van een bestrijdingscampagne.

De resultaten van het allesomvattende model zullen bestaan uit de kosten en het aantal poliogevallen voor iedere permutatie van de beslissingsopties. De beslissingsanalyse is een "levend model" dat blijft evolueren naar aanleiding van huidige gebeurtenissen (zo verbeteren nieuwe detecties van gemuteerd OPV virus bijvoorbeeld ons inzicht in het risico op en de aard van epidemieën veroorzaakt door een dergelijk virus) en verdere verfijning van het model (zoals bijvoorbeeld verandering van de huidige variabelen met betrekking tot epidemiebestrijding, die gezien het ontbreken van richtlijnen hierover nog voorlopige waarden bevatten). Aangezien de resultaten van de onderdelen over risico's en kosten en het dynamische model afhangen van variabelen met soms zeer onzekere waarden zullen ook de uiteindelijke uitkomsten van het model functies zijn van deze onzekere variabelen. We kunnen nog geen onzekerheids- of gevoeligheidsanalyse uitvoeren op het allesomvattende model voordat erover consensus is verschaft. Omwille van de omvang en implicaties van het model zal het echter wel essentieel zijn een toepasselijke methode te kiezen om de onzekerheid te behandelen. Met dat vooruitzicht hebben we verschillende methoden getest op een eenvoudiger dynamisch beslissingsmodel voor een inentingsprogramma tegen een denkbeeldige besmettelijke ziekte.

Hoofdstuk 6 beschrijft dit eenvoudigere model alsmede de methoden voor en resultaten van het uitvoeren van een selectie uit de beschikbare gevoeligdsheidsmethoden, waaronder "one-way" gevoeligheidsanalyse, "multi-way" gevoeligheidsanalyse, experimentele ontwerpen ("design-of-experiments"), Morris' methode en berekening van lokale partiële afgeleiden en probabilistische gevoeligheidsmaten. Hoewel het hoofdstuk zich toespitst op gevoeligheidsmethoden laten we zien dat de noodzakelijke steekproef voor de probabilistische gevoeligheidsanalyse voldoende is om tevens een onzekerheidsanalyse uit te voeren. Dit hoofdstuk dient zowel ter demonstratie van het gebruik van deze methoden in een

volksgezondheidscontext als ook ter onderzoeking van de voor- en nadelen van kanditaat-methoden voor het beslissingsmodel voor polio. Hoofdstuk 6 bespreekt daarom ook de keuze van een gevoeligheidsmethode voor het allesomvattende beslissingsmodel voor polio op basis van de opgedane ervaring. We benadrukken de noodzaak van formele expertmeningen voor toekomstige verfijningen van het beslissingsmodel teneinde de onzekerheid op de best mogelijke manier weer te geven.

CURRICULUM VITAE

Radboud Jacobus Duintjer Tebbens was born on May 3rd, 1976 in The Hague in the Netherlands but moved to Luxembourg with his family at six years of age. There, he received his European Baccaluareate from the European School in 1994. In 2002, he graduated as a Master in Applied Mathematics at Delft University of Technology after having conducted much of his graduation project at the Harvard School of Public Health (HSPH) in Boston. His Master's thesis work involving a retrospective cost-effectiveness analysis of polio vaccinations in the United States led him to return to Boston to continue working on polio, but this time on a global and prospective model, with Prof. Kimberly Thompson at the Department of Health Policy and Management at HSPH and in close cooperation with collaborators from the US Centers for Disease Control and Prevention. In January 2004, he officially made this work part of his Ph.D. under the supervision of Prof. Roger Cooke at the Delft Institute of Applied Mathematics' group of Operations Research and Risk Analysis. Since then, he has divided his time between Delft, where he worked primarily on the sensitivity analyses, and Boston, where he continued to work on all components of the model for polio risk management policies after global eradication.