



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

Radboud J. Duintjer Tebbens^{1,2}, Mark A. Pallansch³, Olen M. Kew³, Victor M. Cáceres⁴, Roland W. Sutter⁵, and Kimberly M. Thompson¹

¹ KidsRisk Project, Harvard School of Public Health, Boston, MA.

² Department of Mathematics, Delft University of Technology, Delft, the Netherlands.

³ Respiratory and Enteric Viruses Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.

⁴ Polio Eradication Branch, Global Immunization Division, National Immunization Program, Centers for Disease Control and Prevention, Atlanta, GA.

⁵ Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland.

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

disease outbreaks; disease transmission; models, statistical; poliomyelitis; poliovirus; risk assessment; vaccination

Abbreviations: IPV, inactivated polio vaccine; NID, National Immunization Day; OPV, oral polio vaccine.

Efforts following the 1988 World Health Assembly resolution to eradicate poliomyelitis 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 poliomyelitis eradication approaching (3), global, regional, and national decision-makers face important choices among strategies for managing future poliomyelitis risks, including whether to continue vaccination with any of the available vaccines (4). Apart from the relatively predictable occurrence of vaccine-associated paralytic poliomyelitis with the continued use of oral polio vaccine (OPV), cases of poliomyelitis could occur because of the unintentional re-

introduction 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 with neurovirulence and transmission characteristics similar to those of 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" (7, p. 42).

Several factors will influence the course of postcertification outbreaks (8). However, the absence of existing comprehensive dynamic models for poliomyelitis outbreaks

Correspondence to Dr. Kimberly M. Thompson, Harvard School of Public Health, 677 Huntington Avenue, 3rd Floor, Boston, MA 02115 (e-mail: kimt@hsph.harvard.edu).

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 actual future conditions by relying on average conditions, model users must recognize that deviations from assumed conditions can lead to substantially different outcomes.

In this paper, we describe and evaluate a mathematical model specifically designed to simulate the spread of polioviruses during an outbreak in a predefined population. We focus on controlled outbreaks and do not study the possibility of reestablished endemic transmission. This transmission model estimates the incidence of poliomyelitis 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 poliomyelitis outbreaks in the context of a larger effort to quantify the risks, costs, and benefits of future poliomyelitis risk management policies.

MATERIALS AND METHODS

Background on polioviruses and vaccines

Typically, infection with a poliovirus causes no clinical symptoms, but in approximately 1 out of 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, as well as 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 IPV (15). Trivalent OPV continues as the vaccine of choice of the Polio Eradication Initiative (12). 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 enhanced-potency IPV appear higher than those of trivalent OPV in many settings (18, 19).

Outbreaks of paralytic poliomyelitis 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 reintroduction of virus into a previously wild polio-free population or a single initiating infection with a vaccine-derived poliovirus.

Poliovirus importations only lead to an outbreak if the virus can establish effective person-to-person transmission and infect enough people to cause paralytic cases. In the initial stage, if carriers infect less than one new susceptible person on average during their infectious period, the outbreak will die out; but if this number (the “net reproductive number”) exceeds 1, 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 built on generic transmission models (21–23) and existing deterministic (13, 24–27) and stochastic (28–30) poliovirus transmission models to develop our poliomyelitis outbreak model, a deterministic, compartmental model that assumes continuously divisible populations in every compartment (complete details are provided in the technical appendix, which is posted on the *Journal's* website (<http://aje.oxfordjournals.org>) and is available on request from the authors). Each compartment represents the number of persons in one of 25 age groups with a given infection state (i.e., susceptible, latent, infectious, or removed/recovered) as a function of time. Mathematically, the model consists of a set of nonlinear ordinary differential equations (31), where the nonlinear 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, biologic variability implies that people have 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 assumed homogeneous mixing within (sub)populations, implying that an infected person instantly mingles within the entire (sub)population.

We defined persons never exposed to live or killed polioviruses as “fully susceptibles.” Given that previously infected or successfully vaccinated persons can still acquire infections, we denoted them as “partially infectibles.” We distinguished three groups of partially infectibles: those recently infected with live poliovirus (i.e., OPV, vaccine-derived poliovirus, or wild poliovirus) (group 1), those historically infected with live poliovirus (group 2), and those only IPV-vaccinated (group 3). We considered only those persons who acquired an infection during the outbreak (the “removed”) as being fully protected from reinfection with the outbreak virus; they no longer participate in transmission during the outbreak after completing their infectious period. We assumed that no one began as uninfected prior to the outbreak, although we assumed that all partially infectibles and removeds remain fully immune to

TABLE 1. Generic model inputs* for a mathematical model designed to simulate the spread of polioviruses during a posteradication outbreak in a predefined population

Model input	Value	Range	Sources (ref. nos.)	Notes
Rate of paralytic poliomyelitis cases per infection for partially infectibles (proportion)	0			Assumes that persons in whom vaccine "took" or with previous natural infection (i.e., those who seroconverted) cannot get paralytic poliomyelitis
Average duration of latency period (days)	2	0.1–7	17, 28, 29, 49–51	Assumes equal duration for all groups of partially infectibles; another poliovirus transmission model uses 1 week (28), but in challenge studies (where the date of exposure is known)—as in those of Onorato et al. (17, figure 2) and Modlin et al. (49, figure 5) and those cited by Alexander et al. (50, figure 3)—the duration of the latency period, even for children vaccinated prior to challenge, appears short but greater than 0, confirming the estimate of Robertson (51, figure 1) and the estimate used in another poliovirus transmission model (29)
Average duration of infectious period for fully susceptibles (days)	35	20–50	13, 16, 50, 52–54	
Average duration of infectious period for partially infectibles (days)				
Group 1 (recent OPV† infection)	7	3–9	16, 17, 49	
Group 2 (historical OPV/wild infection)	9	7–13	50, 55	
Group 3 (IPV† only)	20	12–35	16, 17, 49	
Relative susceptibility of partially infectibles (proportion)				
Group 1 (recent OPV infection)	0.25	0.1–0.4	16, 17	See text for definition of this input; based on limited data from challenge studies
Group 2 (historical OPV/wild infection)	0.8	0.6–1.0		See text for definition of this input; based on judgment
Group 3 (IPV only)	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 (proportion)				
Group 1 (recent OPV infection)	0.1	0.05–0.25	16, 17	See text for definition of this input; based on limited data from challenge studies
Group 2 (historical OPV/wild infection)	0.5	0.3–0.7		See text for definition of this input; based on judgment
Group 3 (IPV only)	0.75	0.5–1.0	16, 17	See text for definition of this input; based on limited data from challenge studies
Rate of secondary OPV infection for children under age 5 years due to routine OPV immunization (1/year)	0.1	0–0.3	56	Base case estimate represents a loosely interpreted "average" of the three serotypes in the study by Chen et al. (56); upper end of range corresponds approximately to the type 2 rate (roughly derived from Chen et al. (56))
Rate of secondary OPV infection for last age group, as a proportion of the rate for children under age 5 years, for routine trivalent OPV immunization (rate declines linearly with age) (proportion)	0.3	0–1		Based on judgment
Average time from polio vaccine administration to individual immunity to infection and disease (days)				
Trivalent OPV	7	0–10		Neglects the difference between first and subsequent vaccine doses and the difference between time from vaccine administration to protection from infection and time from vaccine administration to protection from disease
Enhanced-potency IPV	7	0–10		Neglects the difference between first and subsequent vaccine doses; reflects duration to protection from disease rather than to infection
Average duration of incubation period (time from infection to onset of paralysis) (days)	10	0–20	13, 51, 57	Base case the same as in another poliovirus transmission model (13)

* Inputs and ranges represent averages over biologic variability; refer to the technical appendix (<http://aje.oxfordjournals.org>) for additional information on how we obtained and used inputs.

† OPV, oral polio vaccine; IPV, inactivated polio vaccine.

disease (i.e., they can become infected and participate in transmission but do not become paralyzed).

We solved the equations numerically in Mathematica (Wolfram Research, Inc., Champaign, Illinois) for the time period extending from the day of virus introduction through the subsequent 2 years, when the incidence approaches zero because of the increased population immunity resulting from natural infection and the mass immunization response or because of 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 multiway sensitivity analyses on key inputs.

Model inputs

We based estimates for the model inputs on peer-reviewed studies, available unpublished data, or our own best judgments given the absence of other information. If more than one data set existed for an input, we used 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 based our estimates of R_0 on other studies that calculated R_0 from pre-vaccine-era data (20, 32), and we used an oscillating function to reflect seasonal variations in transmissibility (11). The estimates differed by population because of variations in contact rates and the survival of polioviruses in different settings.

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

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

Table 2 lists model inputs for the Albanian outbreak and the assumed initial population immunity profiles. The large, well-documented outbreak that occurred in Albania in 1996 (138 paralytic cases) involved almost the entire country (33). All virus isolates belonged to one lineage (34), strongly indicating that a single virus introduction led to the outbreak. Lacking conclusive information about the date of virus introduction, we assumed it had occurred approximately 2 months before the first paralytic case. The fact that

the index patient showed onset of paralysis within 2 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 circulating vaccine-derived poliovirus from Haiti in the spring of 2000 resulted in the first reported case in the Dominican Republic outbreak on July 12, 2000 (35–39). Authorities reported a total of 13 confirmed cases and 13 polio-compatible cases, with the last confirmed case showing paralysis onset on January 25, 2001. Reported cases occurred only in children under age 15 years, all scattered in low-coverage communities in 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 residents of the five provinces where the reported cases occurred. We made the key assumption that vaccine-derived polioviruses with the capacity to cause outbreaks possess the same transmissibility and neurovirulence characteristics as wild polioviruses, consistent with laboratory studies (35, 40, 41). We assumed that the introduction occurred during May 2000, based on extrapolation of the observed genetic changes in the VP1 region of the poliovirus genome among the outbreak isolates back to a common origin and assuming a constant mutation rate.

Finally, we modeled the large poliomyelitis outbreak that occurred in the Netherlands in 1992–1993, which affected almost exclusively members of specific religious communities (42–46). The Netherlands relies exclusively on IPV for routine immunization and consistently reaches approximately 97 percent coverage (42); however, substantial numbers of members of Orthodox Reformed churches refuse vaccination for religious reasons, leading to very low coverage in those subpopulations. The wild poliovirus type 3 outbreak in 1992–1993 resulted in 71 cases (61 paralytic cases, including two deaths) between September 17, 1992, and February 19, 1993 (42). Cases were distributed approximately evenly among age groups up to age 40 years, with three patients being older than 40. Since the approximately 300,000 members of religious communities in the Netherlands live in a socially and geographically close-knit network (42), we modeled the Dutch population as two subpopulations with distinct population immunity profiles. To estimate the transmission rates, we assumed that 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 poliomyelitis and the results of the simulation of the Albanian outbreak, with all inputs set at their base case values. Assuming that the virus introduction occurred in mid-February and that the virus survived the spring NID, we find

TABLE 2. Inputs for a model of the Albanian wild poliovirus importation outbreak that occurred in 1996*

Model input	Value	Range	Sources (ref. nos.)	Notes
No. of virus introductions (in random age groups)	1		33, 34	
Date of virus introduction	February 12, 1996	November 12, 1995–April 3, 1996		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 and 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 minus lowest)	14	10–20		Assumes considerable seasonal variation in Eastern Mediterranean Europe
Peak day of seasonal transmission	July 6, 1996	July 1–July 31, 1996		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		58	Equals size of Albanian population in 1996 (medium variant)
Birth rate (per day per total population)	0.000054		58	Annual births/(population × 365 days)
First day of spring NID‡				
Round 1	April 8, 1996		33	Estimated from Prevots et al. (33, figure 2)
Round 2	May 13, 1996		33	Estimated from Prevots et al. (33, figure 2)
First day of mass immunization response				
Round 1	October 7, 1996		33	
Round 2	November 10, 1996		33	
Age groups targeted by spring NID	0–4 years		33	
Age groups targeted by mass immunization response	0–49 years		33	
Duration of mass immunization rounds (days)	7		33	Exact dates for spring NID not given; this assumes the 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		59	Type 1 estimate

Table continues

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 cases 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 simulated cases vs. 25 reported cases).

Both the geographic distribution and the number of poliomyelitis cases due to circulating vaccine-derived polioviruses appeared much more limited in the Dominican

Republic outbreak than in the Albanian outbreak (although inadequate surveillance in the Dominican Republic prior to detection of the outbreak suggests the possibility of missed cases). The small number of cases and uncertainty about the true magnitude of the outbreak limited our ability to accurately define the outbreak population. The simulation results (shown in the technical appendix) contain some notable differences compared with the reported numbers of confirmed and polio-compatible cases (i.e., 31 of 46 cases occurred after the first NID in the model, but only five of 26 reported cases occurred after the first NID). Furthermore, the model predicts a much lower incidence in the first weeks

TABLE 2. Continued

Model input	Value	Range	Sources (ref. nos.)	Notes		
Proportion of susceptible children who will eventually get infected due to secondary OPV exposure from a mass immunization round (%)	46.4	20–60	59	Type 1 estimate		
Secondary OPV infection rate for last age group, as a proportion of the rate for children under age 5 years (rate declines linearly with age) (proportion)						
During spring NID	0.3					
During immunization response	1	0.3–1.0		Assumes that the rate of secondary infections was equal for all age groups because the response targeted adults as well		
Routine immunization coverage (≥ 3 doses) at time of outbreak (%)	90	80–98	33, 60	Assumes that the true coverage was lower than the official figure of $\geq 99.5\%$		
“Take” rate (%)						
For ≥ 3 doses of polio vaccine (routine immunization)	85	75–95	18	Type 1 trivalent OPV estimate; corresponds approximately to average of middle-income country estimates cited in the article by Patriarca et al. (18)		
For one dose of trivalent OPV (during response)	60	50–70	18	Type 1 estimate; corresponds approximately to average of middle-income country estimates derived from two-dose take rates cited in the article by Patriarca et al. (18)		
Rate of paralytic poliomyelitis cases per poliovirus infection for fully susceptibles (proportion)	1/100	1/200–1/50	11, 61	Type 1 estimate		
Initial population immunity profile (age or age group and %)						
Group 1 (recent live poliovirus infection§)			Group 2 (historical live poliovirus infection)			
<1 year: 76.5	1 year: 6.0	2 years: 6.2	<1 year: 0.0	1 year: 69.0	2 years: 70.8	Remaining percentages of each age group are fully susceptibles (i.e., we assume 0% in group 3 of inactivated polio vaccine 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, 58, 60, 62)
3 years: 6.4	4 years: 6.0	5–9 years: 6.6	3 years: 73.6	4 years: 69.0	5–9 years: 78.4	
10–14 years: 5.2	15–19 years: 5.4	20–24 years: 4.5	10–14 years: 64.8	15–19 years: 69.6	20–24 years: 60.5	
25–29 years: 5.0	30–34 years: 5.4	35–39 years: 5.7	25–29 years: 70.0	30–34 years: 79.6	35–39 years: 89.3	
40–44 years: 5.5	45–49 years: 5.3	>49 years: 4.0	40–44 years: 90.5	45–49 years: 91.7	>49 years: 95.0	

* Refer to the technical appendix (<http://aje.oxfordjournals.org>) for additional information on how we obtained and used inputs.

† R_0 , basic reproductive number (see text).

‡ NID, national immunization day; OPV, oral polio vaccine.

§ Live poliovirus infection indicates infection due to wild, oral poliovirus vaccine, or vaccine-derived poliovirus.

than was 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 R_0 and/or rate of paralytic cases per in-

fection for the strain of vaccine-derived virus in this outbreak as compared with wild polioviruses could explain the difference. Finally, the random path of the virus through this highly heterogeneous population (first in a small number of very low-coverage communities, where it caused the majority of cases, and then in the general population) ultimately

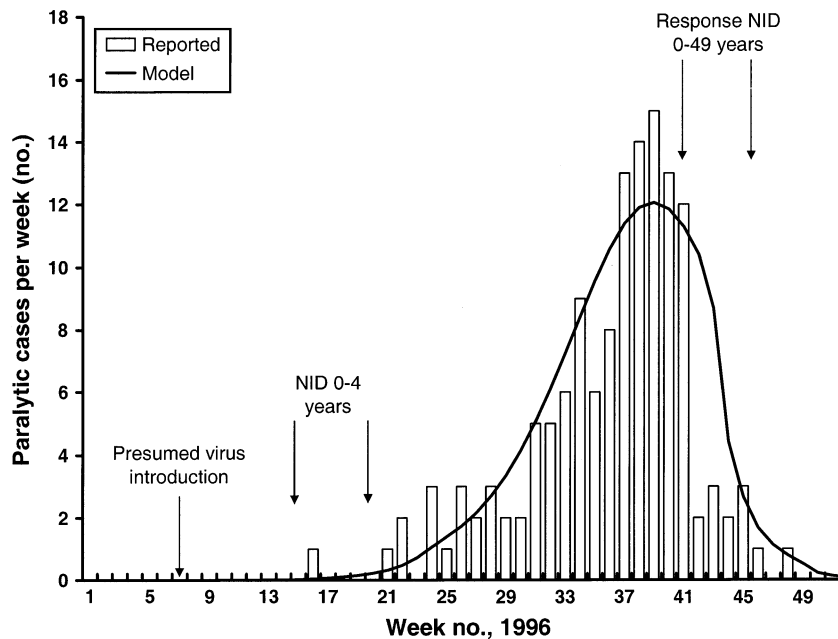


FIGURE 1. Weekly incidence of paralytic poliomyelitis in the 1996 outbreak in Albania, as reported by Prevots et al. (33), and modeled results. NID, National Immunization Day.

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 (see technical appendix), we again found heterogeneity in the population to be 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 existed about their size and vaccination status. As with the reported numbers, cases in the religious subpopulation dominate the simulated model incidence, while the high levels of population immunity and the low contact rate between the two subpopulations prevent any substantial outbreak in the general population. Unlike the simulations of the other two 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 total of 59 model-predicted poliomyelitis cases up to week 60 (last reported case) compares well with the 71 reported cases.

Sensitivity analysis

Using the 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 shown in tables 1 and 2 for the Albanian outbreak and similar ranges for the other two outbreaks (see tables in technical appendix). The sensitivity analyses identified several key uncertain inputs, including the duration of in-

fectiousness, 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 the peak day of seasonal transmission both interacted importantly with each other, with R_0 , and with its amplitude, and in some instances we observed nonmonotonic 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, on the basis of insights from our extensive synthesis of the literature and experience from modeling three historical outbreaks, that poliovirus transmission models provide helpful tools for studying potential outbreaks after eradication. We offer a generic prospective model that we believe might help in assessing 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 in past outbreaks the date of virus introduction often remained unknown and the time to 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 to the time of the outbreak, independent of the vaccine used. We also implicitly assume unlimited access to vaccine for response, presumably either from ongoing production or from a stockpile. With specific guidelines for the strategy for responding to poliomyelitis 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 vaccination for response 2, with either monovalent OPV or trivalent OPV as the vaccine used for immunization response.

DISCUSSION

We developed a dynamic disease transmission model aimed at simulating the spread of poliovirus infection after reintroduction of virus 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 same numbers as those reported, although 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 epidemiologic data with plausible model input values, but inadequate data about heterogeneity in the Dominican Republic population made modeling that outbreak more difficult. On the basis of review and synthesis of the literature and our experience from modeling these outbreaks, we identified and estimated inputs for a prospective model for poliomyelitis outbreaks. We hope the prospective model will serve as a useful tool in exploring future policies related to management of poliomyelitis risks (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 provide better focus for 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 in which

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 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 would occur with more heterogeneous mixing (47). The model does not incorporate the influence of heterogeneous mixing between age groups, partly because of difficulties in obtaining such data. Although heterogeneous mixing between age groups possibly played a role in the Dominican Republic outbreak, where all reported cases occurred in children (35), the age distribution in the other two outbreaks does not suggest more transmission among children than among adults (33, 42). 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 (48). Inclusion of 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 poliomyelitis 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 will perform 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 therefore 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 (47) and use appropriate inputs to prospectively model particular (i.e., "non-average") scenarios of interest.

TABLE 3. Inputs for a prospective model* designed to simulate the spread of polioviruses during a posteradication outbreak in a predefined population

Model input	Value	Range/alternative values	Sources (ref. nos.)	Notes
<i>Independent of income level and decisions</i>				
Average rate of paralytic poliomyelitis cases per infection for fully susceptibles (proportion)	1/200	1/1,000–1/100	9, 11–13, 61, 63	Range reflects variation among serotypes
Time from administration of monovalent OPV† to individual immunity to infection and disease (days)	7	0–10		Assumes that the delays are equal for the trivalent vaccine and the monovalent vaccine
No. of virus introductions	1	10, 100		
Half-life of secondary OPV infection rate after the response (days)	13.1	8.6–25.5	59	Serotype average
Detection trigger for acute flaccid paralysis surveillance (no. of paralytic cases)	1	1–5		Judgment
Detection trigger for passive surveillance (no. of paralytic cases)	5	5–15		Judgment
Detection trigger for environmental surveillance, all income levels (no. of infections)	5,000	1,000–10,000		Assumption
<i>Dependent on outbreak response decisions</i>				
Time between detection and responses 1 and 2, respectively‡ (days)	45, 70	30–210	8, 20, 42	Judgment; assumes that response time will decrease sharply postcertification in comparison with the study by Fine et al. (8, table 1, p. 50), where average was ~120 days in 17 recent outbreaks; neglects discrepancy between wild poliovirus (93 days) and outbreaks of circulating vaccine-derived poliovirus (212 days) in Fine et al. (8, table 1, p. 50); upper end of range corresponds to approximate average of the outbreaks of circulating vaccine-derived poliovirus
Target age groups	All age groups born since OPV cessation	Include cohorts born up to 15 years prior to OPV cessation	20	Assumes that 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
No. of rounds in responses 1 and 2, respectively	3, 2			Assumption
Achieved coverage (%)	90	80–99		Judgment
Maximum age (years) at which children experience full secondary OPV infection rate from mass immunization response (denoted by A below)	Oldest targeted age group	5–99		Assumption
Secondary OPV infection rate for last age group due to mass immunization response, as a proportion of the rate for children under age A	0.3	0–1		Judgment; rate declines linearly with increasing age
<i>Dependent on income level</i>				
Proportion of susceptible children who will eventually become infected due to secondary OPV exposure from a response immunization round				
Low-income country	0.60	0.4–0.8	59	Judgment based on available data from Cuba (59) and assumption that secondary OPV exposure is substantially greater in low-income settings
LMI† country	0.37	0.2–0.5	59	Judgment based on available data from Cuba (59); value of 0.37 corresponds to the average proportion secondarily infected across serotypes; range reflects serotype variability
UMI† country	0.30	0.15–0.5	59	Judgment based on available data from Cuba (59) and assumption that secondary OPV exposure is somewhat lower in UMI settings

Table continues

TABLE 3. Continued

Model input	Value	Range/alternative values	Sources (ref. nos.)	Notes
High-income country	0.20	0.1–0.3	59	Judgment based on available data from Cuba (59) and assumption that secondary OPV exposure is substantially lower in high-income settings
R_0 § of the outbreak virus				
Low-income country	10, 13	8, 16	20, 32	Consider two base case values to reflect large uncertainty and variability
LMI country	8, 11	6, 14	20, 32	Consider two base case values to reflect large uncertainty and variability
UMI country	6, 9	4, 12	20, 32	Consider two base case values to reflect large uncertainty and variability
High-income country	4, 6	2, 9	20, 32	Consider two base case values to reflect large uncertainty and variability
Size of the outbreak population	Variable			Conduct analyses for different population sizes (e.g., 500,000, 5 million, 10 million, 50 million, 100 million)
Birth rate (per day per total population)	Variable		58	Linear interpolation between pentannual averages of medium variant estimates (of births/population × 365) over income level
Age breakdown of the population	Variable		58	Linear interpolation between pentannual averages of medium variant estimates over income level
Routine immunization coverage (%)				
Low-income country	68	50–80	Lara Wolfson, WHO†, PC†, 2004; 64, 65	Average WHO-projected DTP3† coverage for 2004 and beyond for low-income countries (2002 World Bank stratification)
LMI country	90	75–95	Lara Wolfson, WHO, PC, 2004; 64, 65	Average WHO-projected DTP3 coverage for 2004 and beyond for LMI countries (2002 World Bank stratification)
UMI country	92	90–100	Lara Wolfson, WHO, PC, 2004; 64, 65	Average WHO-projected DTP3 coverage for 2004 and beyond for UMI countries (2002 World Bank stratification)
High-income country	94	90–100	Lara Wolfson, WHO, PC, 2004; 64, 65	Average WHO-projected DTP3 coverage for 2004 and beyond for high-income countries (2002 World Bank stratification)
“Take” rate for three doses of trivalent OPV (%)				
Low-income country	71	40–98	18	Base case estimate corresponds approximately to unweighted average of studies in income level cited in the article by Patriarca et al. (18, table 1, p. 929), averaged over the three serotypes; range reflects variation among cited studies and the three serotypes
LMI country, UMI country	85	60–100	18	Base case estimate corresponds approximately to unweighted average among studies cited in the article by Patriarca et al. (18, table 1, p. 929) in given income levels, averaged over the three serotypes; range reflects variation among cited studies and the three serotypes; “LMI country” and “UMI country” were lumped together because of limited results (four data sets) for UMI countries, with somewhat lower rates than the LMI countries
High-income country	95	85–100	12, 18	Base case estimate corresponds approximately to unweighted average of studies cited in the article by Patriarca et al. (18, table 1, p. 929), averaged over the three serotypes; range reflects variation among cited studies and the three serotypes

Table continues

TABLE 3. Continued

Model input	Value	Range/alternative values	Sources (ref. nos.)	Notes
"Take" rate for three doses of enhanced-potency IPV† (%) Low-income country, LMI country, UMI country	95	65–100	19	Assumes that seroconversion rates are similar when used in combination vaccines; base case estimate corresponds approximately to unweighted average of studies in income level cited in the article by Sutter et al. (19, table 2, p. 35), averaged over the three serotypes; range reflects variation among cited studies and the three serotypes; we lumped low-income country, LMI country, and UMI country together because differences between income levels in the article by Sutter et al. (19, table 2, p. 35) were small
High-income country	99	95–100	15, 19	Assumes that seroconversion rates are similar when used in combination vaccines; seroconversion estimates cited by Plotkin and Vidor (15) are almost all close to 100%
"Take" rate per single dose¶ of trivalent OPV (during response) (%) Low-income country	45	13–65	18	Base case estimate corresponds approximately to unweighted average among studies cited in the article by Patriarca et al. (18, table 1, p. 929) in given income levels, averaged over the three serotypes; range reflects maximum variation among cited studies and the three serotypes
LMI country, UMI country	65	35–80	18	Base case estimate corresponds approximately to unweighted average among studies cited in the article by Patriarca et al. (18, table 1, p. 929) in given income levels, averaged over the three serotypes; range reflects maximum variation among cited studies and the three serotypes; LMI country and UMI country were lumped together because of limited results (four data sets) for UMI countries, with somewhat lower rates than the LMI countries
High-income country	78	40–95	66	Base case corresponds to average of three serotypes and ranges to maximum variation among serotypes in cited studies
"Take" rate per single dose of monovalent OPV (during response) (%) Low-income country	76	52–93	67	Base case estimate corresponds approximately to average of three serotypes of Uganda and India studies in the article by Cáceres and Sutter (67, table 3, p. 536); range reflects largest range in same table
LMI country, UMI country, high-income country	91	67–100	67	Base case estimate corresponds approximately to average of three serotypes of all studies except Uganda and India studies in the article by Cáceres and Sutter (67, table 3, p. 536); range reflects largest range in same table
<i>Inputs related to population immunity profile at time of certification#</i>				
Proportion with recent OPV infection if SIAs† continue until certification, ages 0–4 years (low-income country, LMI country, UMI country)	0.95	0.90–1.00		Judgment; this input represents the proportion of children under age 5 years that seroconverted due to primary or secondary trivalent OPV infection during recent SIAs
Proportion with historical OPV infection if SIAs continue until certification, ages 0–4 years (low-income country, LMI country, UMI country)	0.005 × age (in years)	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 (low-income country, LMI country, UMI country)				
Ages 5–19 years	0.97	0.95–1.00		Judgment; assumes no influence of SIA policy until certification on immunity in persons over age 5 years
Ages ≥20 years	0.99	0.95–1.00		Judgment; assumes very good immunity due to frequent exposure to SIAs and/or endemic wild polioviruses

Table continues

TABLE 3. Continued

Model input	Value	Range/alternative values	Sources (ref. nos.)	Notes
Total proportion of partially infectibles if SIAs were discontinued 10 years prior to certification, ages ≥ 20 years (low-income country, LMI country, UMI country)	0.99	0.95–1.00		Judgment; estimate equal to previous input because both reflect age cohorts born at a time when SIAs were still being conducted and/or wild viruses still circulated
Proportion of partially infectibles (i.e., historical OPV/wild) (high-income country)				
Ages 10–49 years	0.95	0.90–1.00		Judgment; assumes that high-income countries switched from trivalent OPV to enhanced-potency IPV on average 10 years prior to certification of global poliomyelitis eradication
Ages ≥ 50 years	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 biologic variability; refer to the technical appendix (<http://aje.oxfordjournals.org>) for additional information on how we obtained and used inputs.

† OPV, oral polio vaccine; LMI, lower middle-income; UMI, upper middle-income; WHO, World Health Organization; PC, personal communication; DTP3, diphtheria-tetanus-pertussis vaccine (≥ 3 doses); IPV, inactivated polio vaccine; SIAs, supplemental immunization activities.

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

§ R_0 , basic reproductive number (see text).

¶ Rather than the use of observed single-dose take rates, these estimates reflect the average take rate of the first two doses, so that the cumulative effect of two rounds of mass immunization 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 routine immunization coverage and on the secondary OPV infection inputs from this table; the technical appendix (<http://aje.oxfordjournals.org>) explains the use of these inputs and displays the initial population immunity profiles at the time of certification.

In the context of prospective modeling, the times between virus introduction and detection and between detection and response emerge as critical inputs (8) for characterizing the

impact of potential responses. The quality of surveillance clearly influences the timeliness of detection; therefore, when using prospective models, investigators will need to

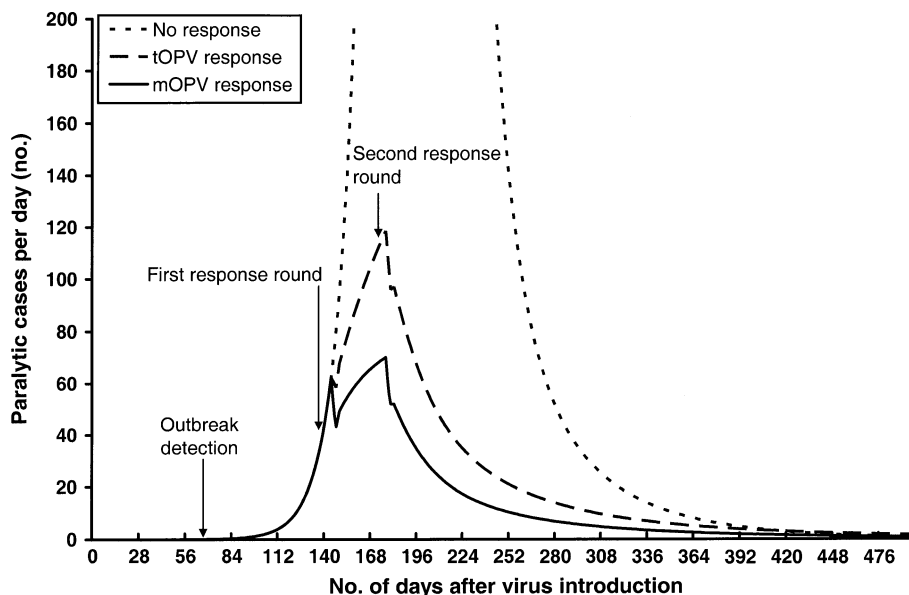


FIGURE 2. Example of a prospectively modeled outbreak occurring after cessation of poliomyelitis vaccination in a hypothetical country. This model assumes a low-income country with $R_0 = 13$ and a population of 100 million 5 years after cessation of all polio immunizations and 10 years after stopping supplemental immunization activities. Detection occurs as soon as the cumulative incidence reaches one 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 under age 5 years in 3 days. The “no response” curve reaches a peak of over 1,700 cases on day 197. tOPV, trivalent oral polio vaccine; mOPV, monovalent oral polio vaccine.

carefully consider future changes in the surveillance network. This model can estimate the length of time until a threshold number of paralytic poliomyelitis cases or infections occurs and model any appropriate dependence on the type and quality of surveillance. Clearly, when developing response policies, investigators 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 predefined 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 (42), and inadequate supplies could similarly affect 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 susceptible persons 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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