

TECHNICAL APPENDIX TO: A Dynamic Model of Poliomyelitis Outbreaks: Learning from the Past to Help Inform the Future (KWI206) August 15 2005 (Corrected January 2006)

AUTHORS: Radboud J. Duintjer Tebbens,^{1,2} Mark A. Pallansch,³ Olen M. Kew,³ Victor M. Cáceres,⁴ Roland W. Sutter,⁵ and Kimberly M. Thompson¹

1. Kids Risk Project, Harvard School of Public Health, 677 Huntington Ave., 3rd Floor, Boston, MA 02115
2. Delft University of Technology, Dept. of Mathematics, Mekelweg 4, 2628 CD Delft, The Netherlands
3. Centers for Disease Control and Prevention, National Center for Infectious Diseases, Division of Viral and Rickettsial Diseases, Respiratory and Enteric Viruses Branch, Atlanta, GA, 30333
4. Centers for Disease Control and Prevention, National Immunization Program, Global Immunization Division, Polio Eradication Branch, Atlanta, GA, 30333
5. Immunization, Vaccines and Biologicals Department, World Health Organization, CH-1211 Geneva, Switzerland

1. 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.

2. 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 uninfected 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 (on 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 ≥ 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 (56)) 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

$S_a^s(t)$ = fully susceptibles in age group a and subpopulation s

$L_a^s(t)$ = “regular” latents in age group a and subpopulation s

$I_a^s(t)$ = “regular” infecteds (those that acquired infection as fully susceptibles) in age group a and subpopulation s

$PI_{i,a}^s(t)$ = partially infectibles of group i in age group a and subpopulation s

$LPI_{i,a}^s(t)$ = latent partially infectibles of group i in age group a and subpopulation s

$IPI_{i,a}^s(t)$ = infected partially infectibles of group i in age group a and subpopulation s

$R_a^s(t)$ = 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*]

$irateipv_a^s(t)$ = vaccination rate in age group a and subpopulation s , with eIPV, during the immunization response [*1/day*]

$irateopv_a^s(t)$ = vaccination rate in age group a and subpopulation s , with OPV, during the immunization response [*1/day*]

$secopvrate_a^s(t)$ = 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*]

ϵ_{opv3} = take rate of three doses of OPV by age 1 [*proportion*]

ϵ_{ipv3} = take rate of three doses of eIPV by age 1 [*proportion*]

ϵ_{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*]

ϵ_{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]

$incub$ = average duration of the incubation period between infection and onset of paralysis [days]

$pptoasymptus$ = 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

$R_0^{\text{seas}}(t)$ = basic reproductive number as a function of time, reflecting seasonal variations in transmissibility

ampl = amplitude of $R_0^{\text{seas}}(t)$, defined as maximum minus minimum value of R_0 in a year

pd = day of year on which $R_0^{\text{seas}}(t)$ reaches its maximum

covnid^i = coverage of i^{th} response NID round among its target group

duration^i = duration of i^{th} response round

A = last age group for which secondary OPV infection rate is at the maximum level

$\text{secrate}^{\text{rel}}$ = 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]

$\text{yrate}^{\text{routine}}$ = 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_{begin}^i = start of i^{th} response round [day]

t_{end}^i = end of i^{th} 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)

$$\begin{aligned}
 \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) \\
 &\quad - \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) \\
 &\quad - \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) \\
 &\quad - \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
 \end{aligned}$$

Differential equations for subsequent age groups (people older than 1; $age = 2, \dots, 25$):

$$\begin{aligned} \frac{dS_{age}^S(t)}{dt} &= (1/w_{age-1})S_{age-1}^S(t) \\ &\quad - \left\{ \frac{1}{w_{age}} + secopvrate_{age}^S(t) + irrateipv_{age}^S(t) + irrateopv_{age}^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_{age}^S(t) \\ \frac{dL_{age}^S(t)}{dt} &= (1/w_{age-1})L_{age-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] S_{age}^S(t) - \left\{ \frac{1}{w_{age}} + \alpha \right\} L_{age}^S(t) \\ \frac{dI_{age}^S(t)}{dt} &= (1/w_{age-1})I_{age-1}^S(t) + \alpha L_{age}^S(t) - \left\{ \frac{1}{w_{age}} + \gamma \right\} I_{age}^S(t) \\ \frac{dR_{age}^S(t)}{dt} &= (1/w_{age-1})R_{age-1}^S(t) + \gamma I_{age}^S(t) + \sum_{i=1}^3 [\gamma_i IPI_{i,age}^S(t)] - (1/w_{age})R_{age}^S(t) \\ \frac{dPI_{1,age}^S(t)}{dt} &= (1/w_{age-1})PI_{1,age-1}^S(t) + (secopvrate_{age}^S(t) + irrateopv_{age}^S(t)) \left(S_{age}^S(t) + s_2^{rel} PI_{age}^2(t) + s_3^{rel} PI_{age}^3(t) \right) \\ &\quad - \left\{ \frac{1}{w_{age}} + 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,age}^S(t) \\ \frac{dPI_{2,age}^S(t)}{dt} &= (1/w_{age-1})PI_{2,age-1}^S(t) - \left(\frac{1}{w_{age}} + s_2^{rel} secopvrate_{age}^S(t) + s_2^{rel} irrateopv_{age}^S(t) \right) PI_{2,age}^S(t) \\ &\quad - 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] PI_{2,age}^S(t) \\ \frac{dPI_{3,age}^S(t)}{dt} &= (1/w_{age-1})PI_{3,age-1}^S(t) + irrateipv_{age}^S(t) S_{age}^S(t) \\ &\quad - \left\{ \frac{1}{w_{age}} + s_3^{rel} secopvrate_{age}^S(t) + s_3^{rel} irrateopv_{age}^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,age}^S(t) \\ \frac{dLPI_{i,age}^S(t)}{dt} &= (1/w_{age-1})ILI_{i,age-1}^S(t) - \left(\frac{1}{w_{age}} + \alpha \right) LPI_{age,1}^S(t) \\ &\quad + 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,age}^S(t), \quad i = 1, 2, 3 \\ \frac{dIPI_{i,age}^S(t)}{dt} &= (1/w_{age-1})IPI_{i,age-1}^S(t) + \alpha LPI_{i,age}^S(t) - \left(\frac{1}{w_{age}} + \gamma_i \right) IPI_{i,age}^S(t), \quad i = 1, 2, 3 \end{aligned}$$

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:

$$Incsus_{age}^s(d) = \int_{t=d}^{d+1} \sum_{j=1}^n \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I_a^j(t) + \sum_{k=1}^3 i_k^{rel} IPI_{k,a}^j(t) \right) \right] S_{age}^s(t) dt$$

$$Incpi_{i,age}^s(d) = s_i^{rel} \int_{t=d}^{d+1} \sum_{j=1}^n \left[\beta_{sj}(t) \sum_{a=1}^{25} \left(I_a^j(t) + \sum_{k=1}^3 i_k^{rel} IPI_{k,a}^j(t) \right) \right] PI_{i,age}^s(t) dt, \quad i = 1, 2, 3$$

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

$$Incpp_{age}^s(w) = \sum_{d=7(w-1)}^{7w-1} \left[pptoasymptus \times Incsus_{age}^s(d - incub) + \sum_{i=1}^3 pptoasymppi_i \times Incpi_{i,age}^s(d - incub) \right]$$

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:

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

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 has 14,928,500 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:

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

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

Mass immunization and secondary OPV infection rates

If the i^{th} OPV (IPV) outbreak response round is held between t_{begin}^i and t_{end}^i , 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):

$$irrateopv_a^s(t) = -\frac{\text{Ln}(1 - covnid^i \times \varepsilon opv1)}{\text{duration}^i} \quad , t_{begin}^i \leq t - delayopv < t_{end}^i, \quad i = 1, \dots, \# \text{ of rounds}$$

$$irrateipv_a^s(t) = -\frac{\text{Ln}(1 - covnid^i \times \varepsilon ipv1)}{\text{duration}^i} \quad , t_{begin}^i \leq t - delayipv < t_{end}^i, \quad i = 1, \dots, \# \text{ of rounds}$$

and 0 elsewhere. With the exception of the Dutch outbreak, where we assume the secondary OPV infection rate equals a constant function ($= -\text{Ln}(1 - psec)/\text{response duration}$) 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:

$$sec\ opv\ ratenid_{age}^s(t) = 0, \quad t < t_{end}^i + delayopv + 1/\alpha, \quad i = 1, \dots, \# \text{ of rounds}, \text{ age} = 1, \dots, A$$

$$sec\ opv\ ratenid_{age}^s(t) = sec_0 \text{Exp}[\text{Ln}(0.5) \times (t - t_{end}^i - delayopv - 1/\alpha) / h], \quad t \geq t_{end}^i + delayopv + 1/\alpha, \quad i = 1, \dots, \# \text{ of rounds}, \text{ age} = 1, \dots, A$$

$delay_{opv} + 1/\alpha$ accounts for the delay between secondary OPV immunization and individual immunity and the latent period before vaccine recipients can infect others. We explain below how we use data from Cuba (59) to estimate sec_0 and h and that for a given half life h and a given proportion p_{sec} of susceptibles that eventually gets infected due to secondary OPV exposure after the outbreak response round, the formula for sec_0 is:

$$sec_0 = \frac{\text{Ln}(0.5)}{h} \text{Ln}(1 - p_{sec})$$

The function $secopvrate_{age}^s(t)$ 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 ($= -\text{Ln}(1 - y_{rate}^{routine})/365$) 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:

$$secopvrate_{age}^s(t) = secopvrate_1^s(t) \frac{(secrate^{rel} - 1) \times age + 25 - A \times secrate^{rel}}{25 - A}, \quad age = A + 1, \dots, 25$$

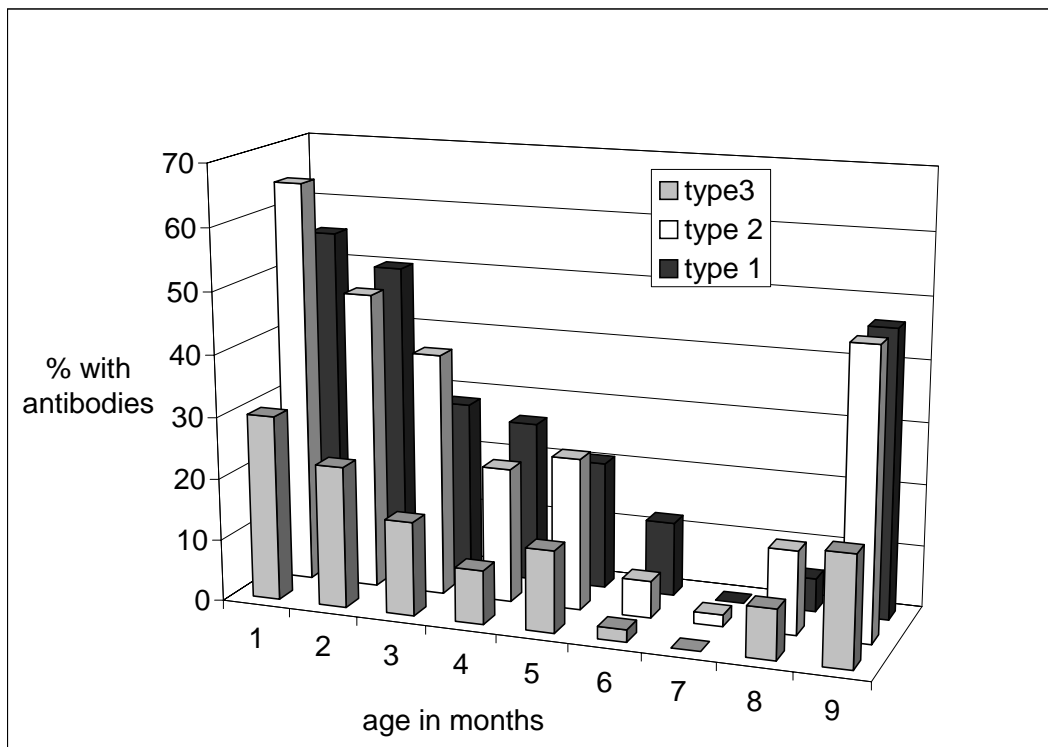
which corresponds to a linear decrease in the rate down to a proportion of $secrate^{rel}$ of the rate for children under A years of age in the last age group. In some instances, $secrate^{rel}$ and A may be defined separately for the response and routine immunization, in which case we apply the above 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 (59). 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, the study detected 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. (59))



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:

$$\begin{aligned} sec(t) &= 0, & t < 0 \\ sec(t) &= sec_0 e^{-kt}, & t \geq 0 \end{aligned}$$

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 $t_2=30$:

$$\begin{aligned} k &= \text{Ln} \left[\frac{\text{Ln}(1-ab1)}{\text{Ln}(1-ab2)} \right] / t_2 \\ sec_0 &= -k \text{Ln}(1-ab1) \end{aligned}$$

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. (59) , lines show the decay curve fits for type 1 (dashed), type 2 (dotted), and type 3 (solid)

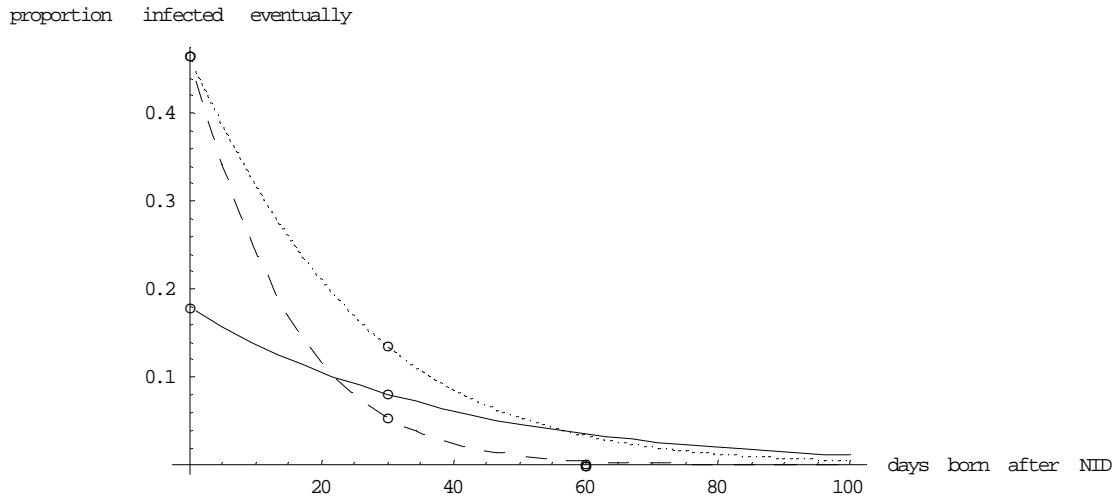


FIGURE A3. Decay curve fit for serotype average (line) and measured average (small circles show data from Ref. (59))

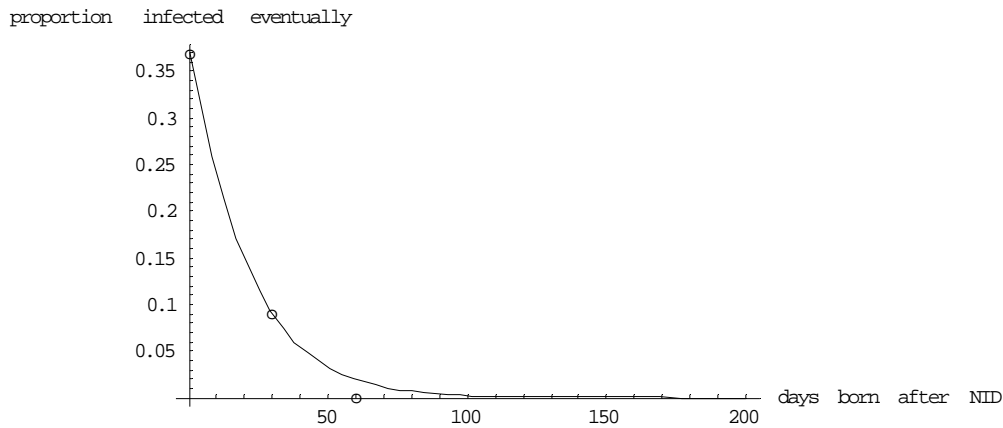


Table A1 shows the half lives and the daily secondary OPV infection rates during the NIDs (sec_0).

The half life equals $h = -\ln(1/2)/k$, so that $sec_0 = \ln(1/2) \times \ln(1-abI)/h$.

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

	type 1	type 2	type 3	average
Half life [<i>days</i>]	8.6	14.3	25.5	13.1
Infection rate during NID (<i>sec₀</i>) [<i>1/day</i>]	0.050	0.030	0.006	0.024

3. 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 $2 \times R_0^{\text{average}}$ 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 polioviruses.
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 remaining 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 $coverage \times single-dose\ take\ rate\ of\ OPV$ 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 $coverage \times two-dose\ take\ rate\ of\ eIPV$.

17. 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.
18. 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.
19. The secondary OPV infection rate does not depend on the intensity of immunization.
20. We neglect the presence of maternal antibodies in infants during the first six months of their lives.
21. The incubation period and delays between (OPV or IPV) immunization and individual immunity are constants and independent of age or group of infectibles.
22. 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.

4. 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 model 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.

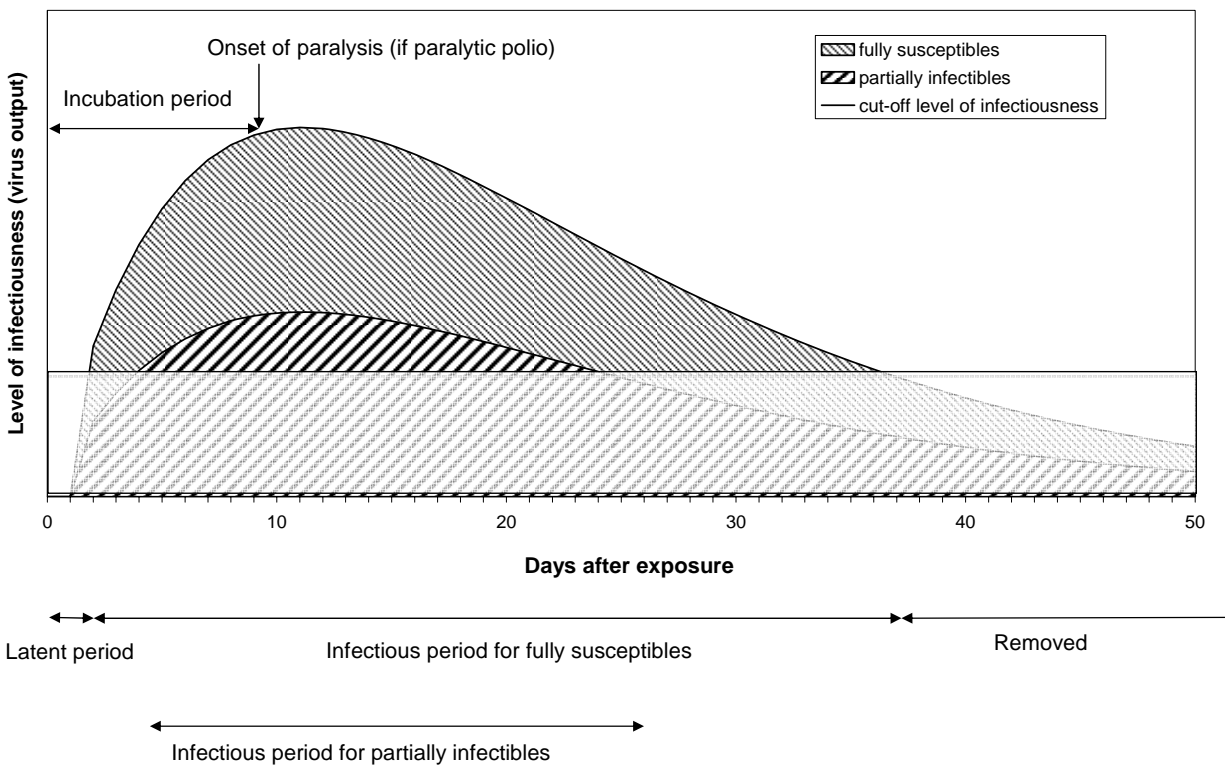
We base our estimates of the average R_0 on other studies that calculated R_0 from data from the pre-vaccine era under a number of assumptions (20, 32). The estimates differ by population because of variation in contact rates and the survival of polioviruses in different settings. Even for specific populations, 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 (50). 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 (50).

Excretion rate from regression curve				Proportion of excretors stopping to excrete during given week				Length of excretion (midpoint)×frequency			
Day*	Wild, cross-sectional	Wild, longitudinal	Sabin, longitudinal	Week*	Wild, cross-sectional	Wild, longitudinal	Sabin, longitudinal	Midpoint of interval (day*)	Wild, cross-sectional	Wild, longitudinal	Sabin, longitudinal
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 subtract 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 (50):

- 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 sensitive 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 (53). Therefore, the averages in the table may be underestimates. Adding 8 days to the means in table A2 for the time between the end of the latent period and onset of paralysis yields an estimate of 31.5 days for the infectious period of wild poliovirus infections

For one of the original, longitudinal studies (52), 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 (54). 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 7 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 (55).

Duration of the infectious period for IPV vaccinees. Onorato et 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 ($i=1, 2, \text{ or } 3$) 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 (49). 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. We 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 ($i=1, 2, \text{ or } 3$) 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*

	<i>Previously eIPV- vaccinated</i>	<i>Previously tOPV- vaccinated</i>
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 (TCID₅₀) 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-vaccinees, 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) (42). 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 (45), 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 communities 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 diphtheria-tetanus-pertussis vaccine (DTP3) remains almost constant beyond 2004 (Lara Wolfson, World Health Organization, personal communication, 2004). Based on the current small difference between DTP3 coverage and coverage with 3 or more doses of tOPV (64), 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 (65). 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 infection. 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, 58, 60, 62)

[‡]Assumes no one is in partial infectivity group 3 (IPV-only). Sources include population data, vaccination coverage and vaccination history (35, 39, 58, 60, 64) and unpublished data on vaccination coverage (Pedreira MC, Pan American Health Organization, personal communication, 2003)

[§]Assumes 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 (42, 43, 46, 58, 60)

[#]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 6 weeks before the base case value, upper end is 2 weeks before the first reported case
Mean R_0^\dagger 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		(64)	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 from (35, Fig.1)
First day of mass immunization response round 3	04/29/'01		(35)	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		(59)	Type 1 estimate
Proportion of susceptible children who will eventually get infected due to secondary OPV [†] exposure from a mass immunization round [%]	41.2%	20%-60%	(59)	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%	(60)	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 estimates derived from 2-dose cited in (18)
Rate of paralytic polio cases per poliovirus infection for fully susceptibles [proportion]	1/100	1/200-1/50	(11, 61)	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^\dagger 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		(58)	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		(46)	
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		(58)	Annual births/(population x 365)
First day of immunization response	09/22/'92		(42)	
Age groups targeted by immunization response	all ages	0-15 yrs.- 0-45 yrs.	(42)	Although the main focus of immunization may have been children at some stage, this restriction was dropped after the occurrence of 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%	(45)	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 (45) 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%	(59)	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%	(43, 46)		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%	(42, 60)		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, 44)		A Dutch study showed only 77.1% of children had antibodies to type 3 poliovirus before administration of the 4 th doses of IPV around 1980 (cited in 44); 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-weighted 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, 63)		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 = basic 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

5. 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, 42)).

	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	113	154	155	
Relative difference*	0.38	0.00	0.12	0.12	0.95
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	40	11	32	46	
Relative difference*	0.30	-1.00	0.19	0.43	1.02
The Netherlands, reported	38	1	71	71	
The Netherlands, model at base case	39	0.7	59	60	
Relative difference*	0.03	-0.43	-0.20	-0.18	0.62

* (model-reported)/reported

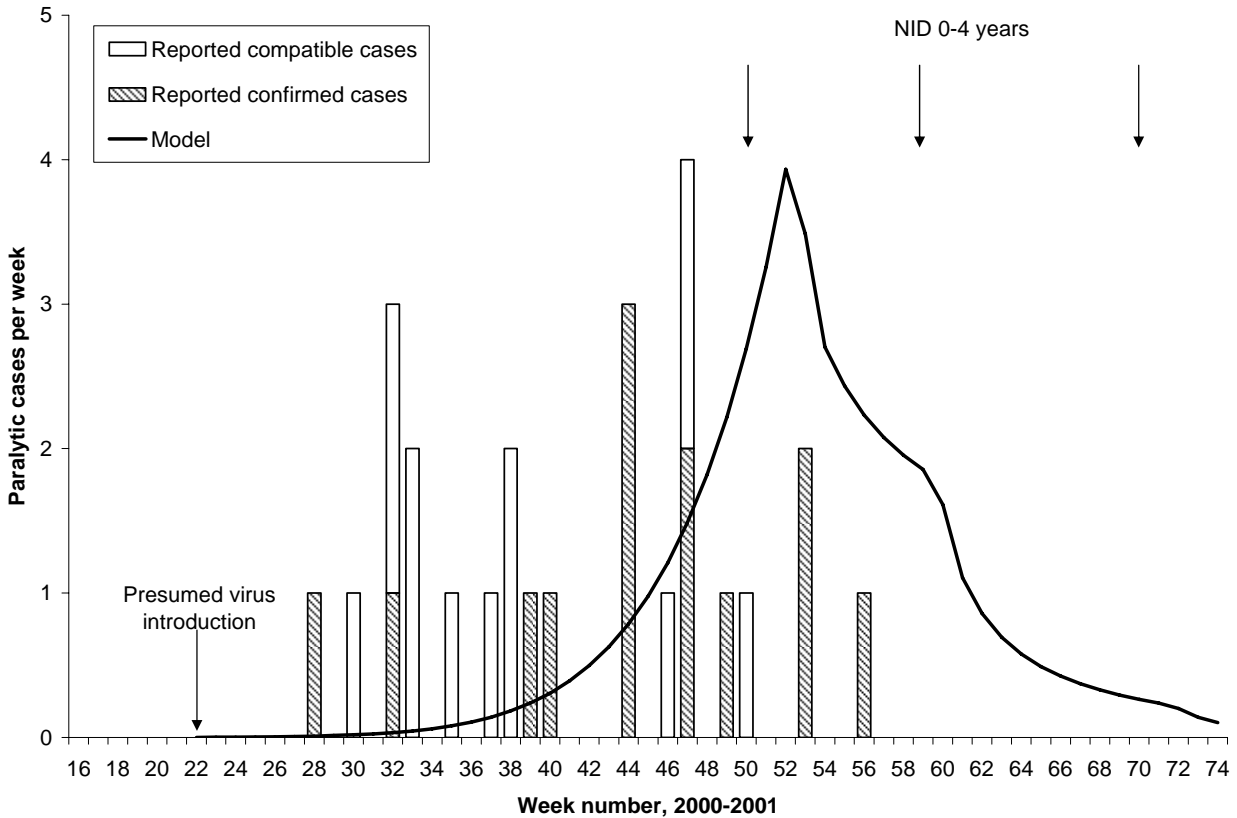
Notes about the Albania outbreak simulation

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, 61). 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 (“2.46 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. (42)

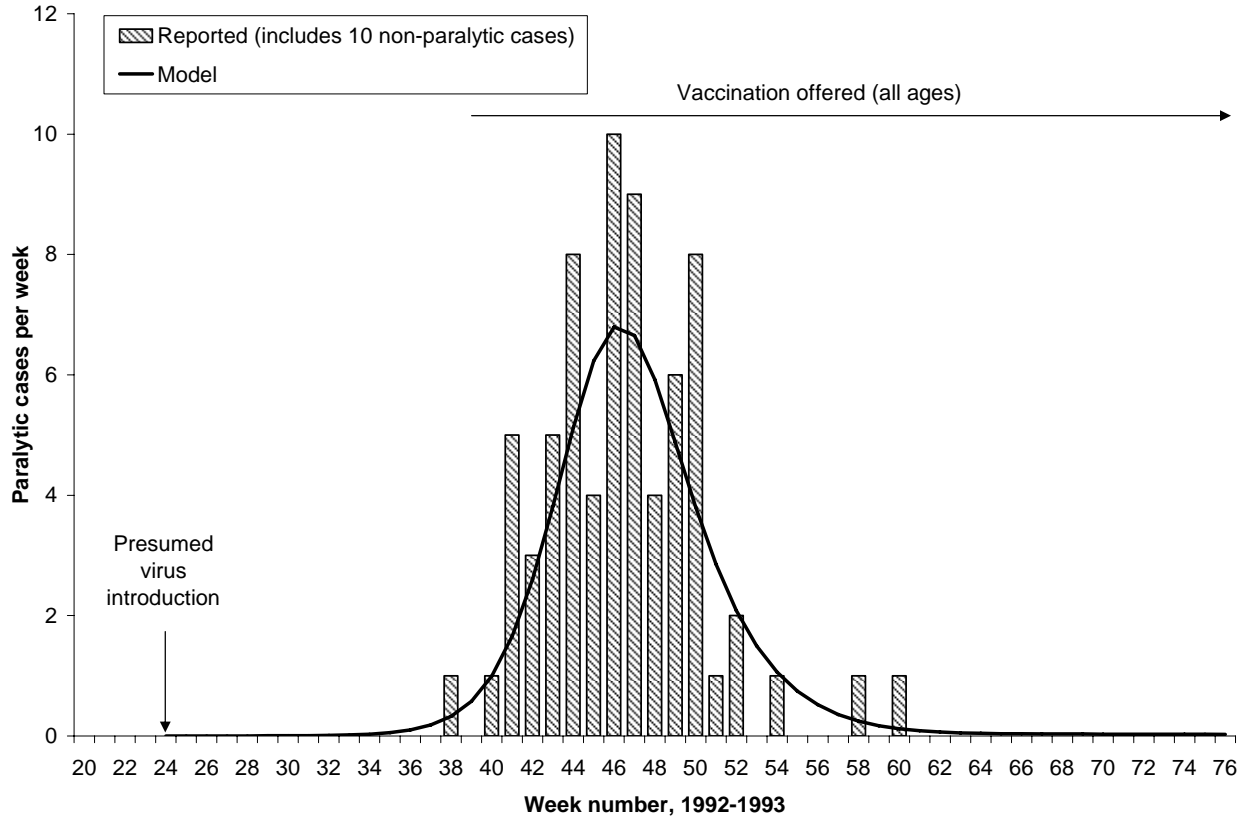


FIGURE A7. Influence of rate of paralytic polio per infection on weekly incidence of polio cases in the Dutch outbreak; reported data from Ref. (42)

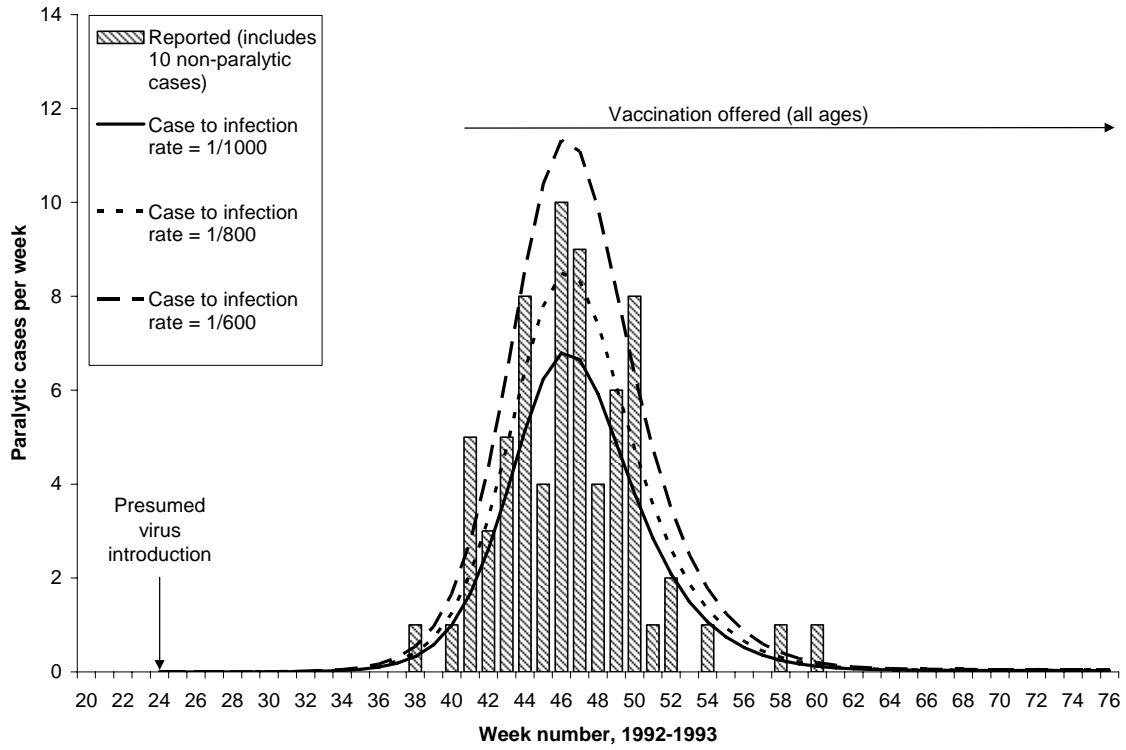
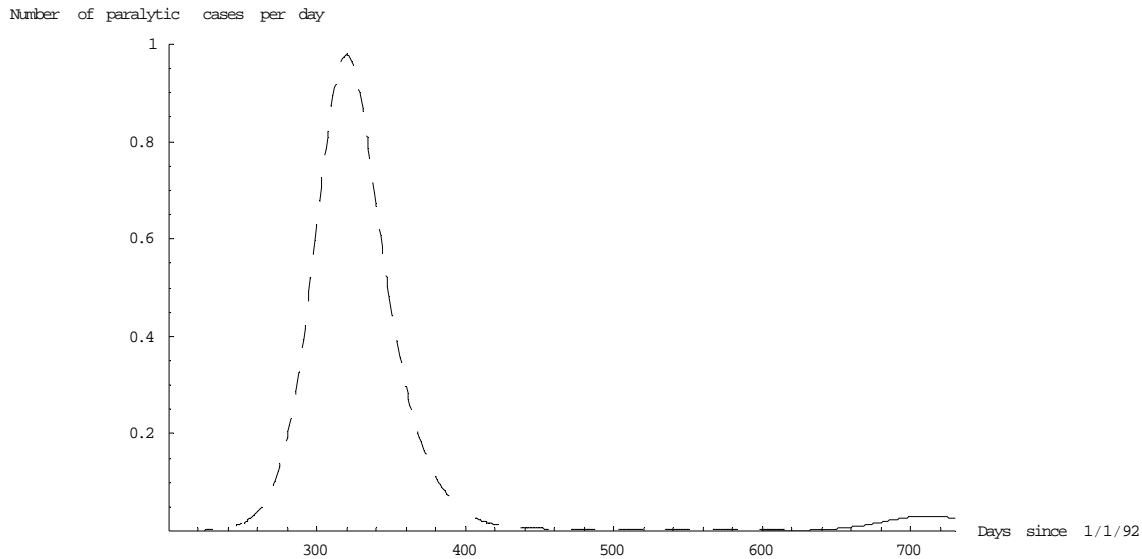


FIGURE A8. Modeled daily incidence of paralytic cases during the Dutch outbreak in the religious communities (dashed line) and the general population (solid line)



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.