American Journal of Epidemiology
Vol. 143, No. 8

Eradication of Poliomyelitis: When Can One Be Sure That Polio Virus Transmission Has Been Terminated?

M. Eichner[1,2] and K. Dietz[1]

Most polio virus infections are silent. Vaccination reduces the incidence of infection, and the period between clinical cases of poliomyelitis becomes longer. As the point of eradication is approached, it becomes increasingly difficult to use the case-free period to determine whether silent infections have ceased. In this paper, the authors use stochastic computer simulations to relate case-free periods to the presence or absence of silent infections. After 2 years without paralytic cases in a population of 200,000 inhabitants, the probability for the presence of silent infections can still be as high as 38%. The case-free period must exceed 3 years before one can be 95% certain that there has been local extinction of the wild polio virus infection. Even after 5 years without cases, the probability of silent polio virus transmission can still be in the range of 0.1–1.0%. 1996;143:816–22.

computer simulation; mathematical computing; models, theoretical; poliomyelitis; poliovirus vaccine; poliovirus vaccine, oral

The Somalian Ali Maow Maalin was the last person to be naturally infected with the smallpox virus. Except for some laboratory infections, no smallpox cases have been reported since October 26, 1977. Therefore, the World Health Organization was able to declare in 1979 that smallpox has been eradicated throughout the world (1). If worldwide eradication of poliomyelitis succeeds, then the very last person to be infected with wild polio virus will surely not be known as most individuals develop no clinical signs after infection. Vaccination reduces the incidence of polio virus infection and therefore increases the interval between clinical cases. Long intervals between cases of paralysis present difficulties in determining whether transmission of the wild polio virus infection has ceased. This is of practical importance for the plan of global eradication as well as for local vaccination campaigns.

The present study uses stochastic computer simulations based on epidemiologic models to determine how long the case-free period must be before one can draw the conclusion that extinction has occurred with a specified error probability.

Received for publication August 18, 1994, and in final form June 30, 1995.

Abbreviations: OPV, oral polio virus vaccine (Sabin vaccine); IPV, inactivated polio virus vaccine (Salk vaccine).

[1] Institut für Medizinische Biometrie, Universität Tübingen, Germany.
[2] Rolf Nevanlinna Institute, University of Helsinki, Finland.

MATERIALS AND METHODS

For details of the simulation procedure, see the Appendix and (2). The following parameter values are intended to represent the situation in a developing country. The population is homogeneously mixing and grows at a constant rate of 2 percent per year. The initial population size is set at 200,000 inhabitants. The average life expectancy is 45 years. The basic reproduction number, i.e., the number of secondary cases that one case could generate in a completely susceptible population, is 12 for the wild polio virus infection. (This number is derived from age-specific antibody data (3–5); a survey of estimation procedures is given in (6).) If a susceptible individual contacts an infectious person, he or she becomes infectious after an incubation period of 1 week. Unless otherwise stated, one in 200 infections leads to paralytic poliomyelitis. The average duration of the infectious period is 1 month (7, 8). After loss of infectivity, the individual becomes completely and permanently immune. The transition from the incubating state to the infective state and from the infective state to the immune state is modeled as a two-step process. This has no influence on the infectivity of the individual but allows simulation of more realistic distributions for the incubation and infectious periods (for details see Appendix).

Newborn infants are susceptible unless they are vaccinated. Vaccination is performed immediately after birth. Two different vaccines are considered: the

inactivated polio virus vaccine and the oral polio virus vaccine.

Inactivated polio virus vaccine (IPV)

Only a fraction of the vaccinated infants become fully immune. The remaining infants are only partially protected against infection and, upon infection, the infectious period is decreased (9, 10). Following a wild virus infection, a partially susceptible individual becomes completely immune. It is assumed that 70 percent are only partially protected after IPV vaccination. The probability that a contact leads to the infection of a partially protected individual is reduced to 50 percent. The duration of the infectious period is then reduced to 20 percent. All individuals who are successfully vaccinated (both partially and fully immune) will never develop paralytic poliomyelitis.

Oral polio virus vaccine (OPV)

Infants who are successfully vaccinated become infectious with the vaccine virus and can spread it to contacts (10). Vaccine virus infectivity is lost at the same rate as wild virus infectivity (11, 12) and causes full and permanent protection against infection and disease. The basic reproduction number of the vaccine virus infection is assumed to be a quarter of that of the wild virus infection.

Unless stated otherwise, the simulations start at the endemic equilibrium (without vaccination) of the underlying deterministic model (see Appendix) and are terminated after 10 years. The time between two consecutive epidemiologic events (birth, infection, and the transition from the incubating to the infective state or from the infective to the immune state) and the type of the event are calculated with random numbers (see Appendix for details). At the onset of infectivity, a new random number is chosen to determine whether the infected person becomes ill. It is assumed that a clinical case occurred shortly before the start of the simulations. On a monthly basis, the times since the last paralytic case and the presence or absence of wild polio virus infection are recorded. Finally, the probability that an observed case-free period of length t coincides with the absence of wild polio virus infection is calculated by dividing the number of all case-free periods of length t without wild virus transmission by the total number of case-free periods of length t of all the simulations.

RESULTS

Starting at the endemic equilibrium of wild polio virus infection in a population of 200,000 inhabitants, 60 percent of the newborn infants are effectively vaccinated with OPV or 80 percent with IPV. Extinction of wild polio infection occurs at a frequency of 87.2 and 75.1 percent within 10 years of OPV and IPV vaccination, respectively (studies that address the probability of extinction for different vaccination strategies will be published elsewhere). Figure 1 depicts the probability that wild polio virus infection is still present although no paralytic cases have been observed for a given time. Even if no cases are observed for 2 years, silent infections are still present in up to 20 percent of the simulations (figure 1) if one of 200 infections leads to paralysis. Only after at least 4 years without paralytic cases is local extinction likely, with

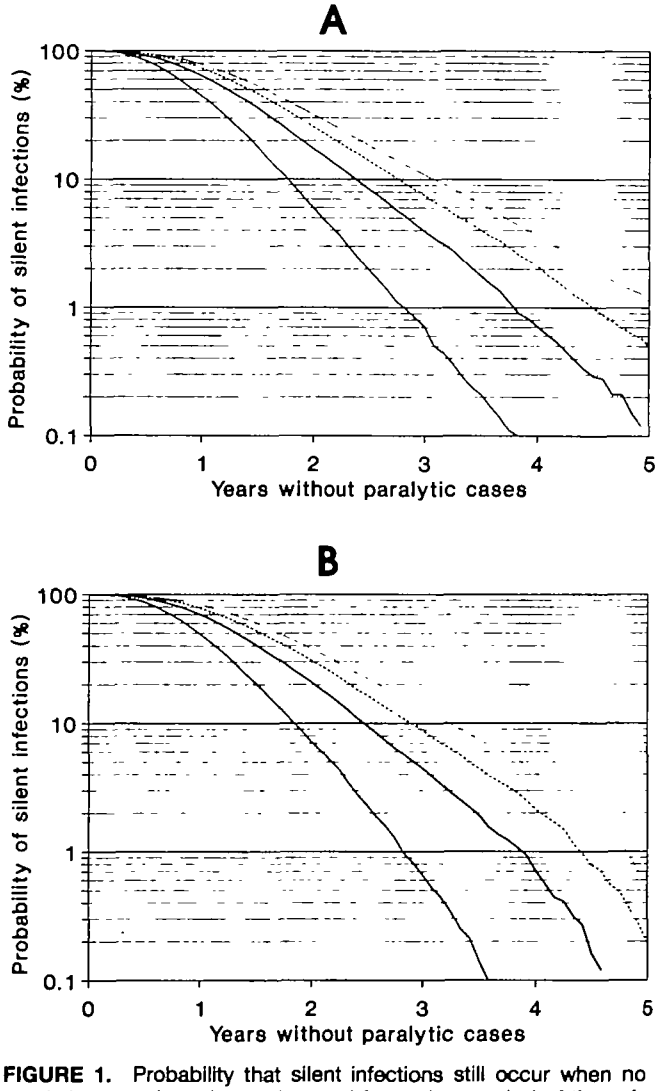

FIGURE 1. Probability that silent infections still occur when no paralytic cases have been observed for a given period of time. A, 60% of the newborn infants are vaccinated with OPV. B, 80% are vaccinated with IPV. The proportion of paralytic cases per infection is varied between one per 400 and one per 100. All other parameter values correspond to the basic set of parameters in tables 1 and 2 for which 10,000 simulations were performed. [———], one case per 100 infections; [— — —], one case per 200 infections; [--------], one case per 300 infections; [.....], one case per 400 infections.

a probability of 99 percent. If less than one in 200 infections causes paralysis, silent infections occur in 0.1–1.1 percent of the simulations even if no cases have been observed for 5 years. To examine the effect of the chosen parameter values on the results, each parameter is varied individually while the remaining set of basic parameters (footnoted in tables 1 and 2) is held constant. Tables 1 and 2 show the case-free periods for which the probability of wild polio virus extinction reaches the 95 percent level. The ratio of cases to infections is most influential on the results: If one in 100 infections leads to a paralytic case, the necessary duration of the case-free period is only about 2 years, whereas it is more than 3.5 years if only one in 400 infections leads to a paralytic case. The second most influential parameter is the effective vaccination coverage: Greater coverage results in more reliable case-free periods. The vaccination parameters determine the amount of herd immunity and therefore influence the results in the same way as the vaccination coverage. The wild virus basic reproduction number R_w and the demographic parameters have a surprisingly small influence on the outcome. Variation in the simulation time or in the initial number of infective and immune individuals also has little effect on the outcome (results not shown).

DISCUSSION

According to the World Health Organization (13), there must have been a period of 3 years when active surveillance revealed neither cases of poliomyelitis nor circulation of wild polio viruses before local extinction of polio virus infection could be claimed. According to the simulation results, the probability of local extinction reaches 95 percent after case-free periods of about 3 years. This result strongly depends on the case-infection ratio, on the effective vaccination coverage, and on the type of vaccine (tables 1 and 2). According to Fox et al. (14), the fraction of contacts that lead to paralytic poliomyelitis could be much lower than the standard value of one in 200 that was used. Polio virus infection would then be recognized less often, and the probability that a case-free period was a reliable sign of extinction would be much lower (tables 1 and 2).

It is assumed in our simulations that no infections enter the study population from outside. A reintroduced wild polio virus infection can spread unrecognized for several months or for more than a year in a population with a high vaccination coverage (unpublished results). Another important factor that is not considered in the simulation studies is the age-dependent risk of paralysis. Adults and adolescents are at a greater risk of developing the disease than children

TABLE 1. Case-free period (years) after which the probability that wild polio virus infections still occur in the population is reduced to 5% if oral polio virus (Sabin) vaccine is used*

Varied parameter	Simulations				
	1,000	1,000	10,000†	1,000	1,000
Effective vaccination coverage (%)	50	55	60	65	70
Case-free period (years)	3.1	3.3	2.9	2.3	1.9
Initial population size		100,000	200,000	300,000	400,000
Case-free period (years)		2.6	2.9	2.9	2.9
Annual population growth (%)	0	1	2	3	
Case-free period (years)	2.6	2.7	2.9	2.8	
Paralytic case/infection		1/100	1/200	1/300	1/400
Case-free period (years)		2.1	2.9	3.3	3.6
R_v/R_w‡(%)	15	20	25	30	35
Case-free period (years)	2.8	2.9	2.9	2.4	2.1
Life expectancy (years)		40	45	50	
Case-free period (years)		2.7	2.9	2.9	
R_w‡	8	10	12	14	16
Case-free period (years)	2.7	2.6	2.9	2.8	3.0

* One parameter of the basic set of parameters is varied. Additional parameters are 1) the duration of the incubation is 1 week, and 2) the duration of infectivity is 1 month.

† Column of basic parameters.

‡R_w, basic reproduction number of the wild polio virus; R_v/R_w, ratio of the vaccine virus basic reproduction number divided by the wild virus basic reproduction number.

TABLE 2. Case-free period (years) after which the probability that wild polio virus infections still occur in the population is reduced to 5% if inactivated polio virus (Salk) vaccine is used*

Varied parameter	Simulations				
	1,000	1,000	10,000†	1,000	1,000
Effective vaccination coverage (%)	70	75	80	85	90
Case-free period (years)	2.9	3.0	2.9	2.5	2.1
Initial population size		100,000	200,000	300,000	400,000
Case-free period (years)		2.8	2.9	3.2	3.0
Annual population growth (%)	0	1	2	3	
Case-free period (years)	3.0	3.0	2.9	2.9	
Paralytic case/infection		1/100	1/200	1/300	1/400
Case-free period (years)		2.1	2.9	3.4	3.7
Full protection caused by IPV (%)	10	20	30	40	50
Case-free period (years)	3.0	2.9	2.9	3.0	2.9
Susceptibility reduced by IPV (%)	0	25	50	75	100
Case-free period (years)	2.7	2.7	2.9	3.0	3.1
Life expectancy (years)		40	45	50	
Case-free period (years)		2.9	2.9	2.9	
R_w‡	8	10	12	14	16
Case-free period (years)	2.7	2.9	2.9	3.0	2.8

* One parameter of the basic set of parameters is varied. Additional parameters are 1) the duration of the infectious period of partially protected individuals (from the inactivated polio virus vaccine) is reduced to 20%, 2) the duration of the incubation is 1 week, and 3) the full duration of infectivity is 1 month.

† Column of basic parameters.

‡ R_w, basic reproduction number of the wild polio virus.

and infants (15). In a country with highly endemic polio virus transmission, most adolescents and adults are immune as a result of infection during childhood. Vaccinations reduce the spread of polio virus, and so the average age of infection increases. Because of this, the fraction of infections that leads to paralytic poliomyelitis also increases. This unpleasant effect has the consequence that infections become recognized more often, and the absence of paralytic cases becomes a more reliable sign of local extinction. If older children are vaccinated rather than newborns, then many of the polio infections occur within the prevaccination age groups. In this case, infections only rarely cause clinical signs and therefore are recognized less often. Other factors not included in the models are seasonality and spatial factors that affect the spread of the infection.

The results suggest that a case-free period of 3 years is only borderline sufficient to declare local extinction with a 5 percent error probability. Depending on vaccination coverage and strategy, some locations might require case-free periods of 3.5–4 years. As long as polio virus infection can possibly be imported from abroad, polio vaccination must not be discontinued.

ACKNOWLEDGMENTS

Dr. Eichner received financial support from Evangelisches Studienwerk eV, Haus Villigst, Schwerte, Germany. The authors acknowledge the support by the Prudential Fellowship during their stay at the Isaac Newton Institute, Cambridge, England, in 1993. Dr. Dietz also thanks the University of Tübingen, Germany, for granting leave of absence.

REFERENCES

1. Fenner F, Henderson DA, Arita I, et al, eds. Smallpox and its eradication. Geneva: World Health Organization, 1988.
2. Gillespie DT. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. J Comput Phys 1976;22:403–34.
3. Gear JHS, Measroch V. Poliomyelitis in Southern Africa: In: Poliomyelitis: papers and discussions presented at the Second International Poliomyelitis Conference, 1952;437–41.
4. Gelfand HM, Miller MJ. Poliomyelitis in Liberia. Prevalence of the disease, sero-immunity resulting from subclinical infection, and indications for prophylactic vaccination. Am J Trop Med Hyg 1956;5:791–6.
5. Paul JR, Melnick JL, Barnett VH, et al. A survey of neutralizing antibodies to poliomyelitis virus in Cairo, Egypt. Am J Hyg 1952;55:402–13.
6. Dietz K. The estimation of the basic reproduction number for infectious diseases. Stat Methods Med Res 1993;2:23–41.

7. Gelfand HM, LeBlanc DR, Fox JP, et al. Studies on the development of natural immunity to poliomyelitis in Louisiana. II. Description and analysis of episodes of infection observed in study group households. Am J Hyg 1957;65: 367–85.
8. Marine WM, Chin TDY, Gravelle CR. Limitation of fecal and pharyngeal poliovirus excretion in Salk-vaccinated children: a family study during a type 1 poliomyelitis epidemic. Am J Hyg 1962;76:173–95.
9. Ghendon YZ, Sanakoyeva II. Comparison of the resistance of the intestinal tract to poliomyelitis virus (Sabins strains) in persons after naturally and experimentally acquired immunity. Acta Virol (Praha) 1961;5:265–73.
10. Henry JL, Jaikaran ES, Davies JR, et al. A study of poliovaccination in infancy: excretion following challenge with live virus by children given killed or living poliovaccine. J Hyg 1966;64:105–20.
11. Ogra PL, Karzon DT. Formation and function of poliovirus antibody in different tissues. Prog Med Virol 1971;13: 156–93.
12. Lepow ML, Warren RJ, Gray N, et al. Effect of Sabin type 1 poliomyelitis vaccine administered by mouth to newborn infants. N Engl J Med 1961;264:1071–8.
13. Henderson RH. The World Health Organization's plan of action for global eradication of poliomyelitis by the year 2000. Ann NY Acad Sci 1989;569:69–85.
14. Fox JP, Gelfand HM, LeBlanc DR, et al. Studies on the development of natural immunity to poliomyelitis in Louisiana. I. Over-all plan, methods and observations as to patterns of seroimmunity in the study group. Am J Hyg 1957;65: 344–66.
15. Horstmann DM. Poliomyelitis: severity and type of disease in different age groups. Ann NY Acad Sci 1955;61:956–67.
16. Dietz K. Transmission and control of arbovirus diseases. In: Ludwig D, Cooke KL, eds. Epidemiology. Philadelphia: Society for Industrial and Applied Mathematics, 1975:104–21.
17. Hethcote HW. Asymptotic behavior and stability in epidemic models. Lecture Notes Biomath 1974;2:83–92.
18. Eichner M, Hadeler KP. Deterministic models for the eradication of poliomyelitis: vaccination with the inactivated (IPV) and attenuated (OPV) polio virus vaccine. Math Biosci 1995; 127:149–66.

APPENDIX

Variables and parameters that are common for the IPV and OPV model

N	total size of the population	β	rate of contacts that are sufficiently close for transmission of wild virus
S	number of susceptible individuals	λ_w	force of infection with respect to the wild polio virus
W_{1j}	number of individuals incubating a wild virus infection, $j = 1, 2$	δ	transition rate of incubation distribution = 1/(two times the duration of the incubation period)
W_{2j}	number of wild virus infective individuals, $j = 1, 2$	γ	transition rate of infectivity distribution = 1/(two times the duration of infectivity)
μ	death rate = 1/life expectancy	p	fraction that is vaccinated successfully at birth
ν	per capita birth rate = population growth rate + death rate		

Variables and parameters of the OPV model

V_{1j}	number of individuals incubating a vaccine virus infection, $j = 1, 2$	b	relative infectivity of the vaccine virus (compared with that of the wild polio virus)
V_{2j}	number of vaccine virus infective individuals, $j = 1, 2$	λ_v	force of infection with respect to vaccine virus

Variables and parameters of the IPV model

$\tilde{S}$	number of partially susceptible individuals (after IPV vaccination)	$\tilde{\gamma}$	transition rate of infectivity distribution of individuals who were partially susceptible = 1/(two times duration of infectivity of IPV-vaccinated individuals)
$\tilde{W}_{ij}$	number of wild virus infected individuals (as W_{ij}, but the individual was partially susceptible before infection) $i, j = 1, 2$	$\tilde{a}$	fraction becoming fully immune after IPV vaccination
		$\tilde{c}$	reduction in susceptibility by IPV

Short description of the OPV model

Individuals are born susceptible (S) at a rate νN. A fraction p becomes vaccinated and starts incubating the vaccine virus (V_{11}). Incubating individuals go through their incubation in a two-step process (V_{11}, V_{12} and W_{11}, W_{12}, respectively) with rate δ and become infective. Infective individuals also go through their infective period in a two-step process (V_{21}, V_{22} and W_{21}, W_{22}, respectively) with rate γ and finally become immune. Susceptible individuals who come in sufficiently close contact with wild or vaccine virus infective individuals become infected (at rates λ_w and λ_v, respectively) and start incubating the infection. All individuals die according to the rate μ.

OPV model equations

$$
\begin{aligned}
dS/dt &= \nu N(1-p) - (\lambda_w+\lambda_v+\mu)S \\
dW_{11}/dt &= \lambda_w S - (\delta+\mu)W_{11} \\
dW_{12}/dt &= \delta W_{11} - (\delta+\mu)W_{12} \\
dW_{21}/dt &= \delta W_{12} - (\gamma+\mu)W_{21} \\
dW_{22}/dt &= \gamma W_{21} - (\gamma+\mu)W_{22} \\
\lambda_w &= \beta(W_{21}+W_{22})/N
\end{aligned}
\qquad
\begin{aligned}
dN/dt &= (\nu-\mu)N \\
dV_{11}/dt &= \nu N p + \lambda_v S - (\delta+\mu)V_{11} \\
dV_{12}/dt &= \delta V_{11} - (\delta+\mu)V_{12} \\
dV_{21}/dt &= \delta V_{12} - (\gamma+\mu)V_{21} \\
dV_{22}/dt &= \gamma V_{21} - (\gamma+\mu)V_{22} \\
\lambda_v &= \beta b(V_{21}+V_{22})/N
\end{aligned}
$$

Short description of the IPV model

Individuals are born susceptible (S) at a rate νN. A fraction p becomes vaccinated. A fraction $1-\tilde{a}$ of the vaccinated individuals is still partially susceptible ($\tilde{S}$). Incubating individuals go through their incubation in a two-step process (W_{11}, W_{12} and $\tilde{W}_{11}$, $\tilde{W}_{12}$, respectively) with rates δ and become infective. Infective individuals go through their infective period in a two-step process (W_{21}, W_{22} and $\tilde{W}_{21}$, $\tilde{W}_{22}$, respectively) with rates γ (or $\tilde{\gamma}$) and finally become immune. Fully or partially susceptible individuals who come in sufficiently close contact with infective individuals become infected (at rate λ_w and $\tilde{c}\lambda_w$, respectively) and start incubating the infection. All individuals die according to the rate μ.

IPV model equations

$$
\begin{aligned}
dS/dt &= \nu N(1-p) - \lambda_w S - \mu S \\
dW_{11}/dt &= \lambda_w S - (\delta+\mu)W_{11} \\
dW_{12}/dt &= \delta W_{11} - (\delta+\mu)W_{12} \\
dW_{21}/dt &= \delta W_{12} - (\gamma+\mu)W_{21} \\
dW_{22}/dt &= \gamma W_{21} - (\gamma+\mu)W_{22} \\
dN/dt &= (\nu-\mu)N
\end{aligned}
\qquad
\begin{aligned}
d\tilde{S}/dt &= \nu N(1-\tilde{a})p - \lambda_w\tilde{c}\tilde{S} - \mu\tilde{S} \\
d\tilde{W}_{11}/dt &= \lambda_w\tilde{c}\tilde{S} - (\delta+\mu)\tilde{W}_{11} \\
d\tilde{W}_{12}/dt &= \delta\tilde{W}_{11} - (\delta+\mu)\tilde{W}_{12} \\
d\tilde{W}_{21}/dt &= \delta\tilde{W}_{12} - (\tilde{\gamma}+\mu)\tilde{W}_{21} \\
d\tilde{W}_{22}/dt &= \tilde{\gamma}\tilde{W}_{21} - (\tilde{\gamma}+\mu)\tilde{W}_{22} \\
\lambda_w &= \beta(W_{21}+W_{22}+\tilde{W}_{21}+\tilde{W}_{22})/N
\end{aligned}
$$

Initial conditions

Initial conditions are determined by the endemic equilibrium without vaccination. If no vaccinations are performed and no vaccine virus infections occur ($p = 0$, $V_{11} \equiv V_{12} \equiv V_{21} \equiv V_{22} \equiv \tilde{S} \equiv \tilde{W}_{11} \equiv \tilde{W}_{12} \equiv \tilde{W}_{21} \equiv \tilde{W}_{22} \equiv 0$), the models are identical to an extension of the "SIR model" (16–18) for a growing population and have the following endemic equilibrium:

$$
\begin{aligned}
N(t) &= N(0)e^{(\nu-\mu)t}, \\
S(t)/N(t) &= 1/R_w,
\end{aligned}
$$

$$
\begin{aligned}
W_{11}(t)/N(t) &= (1-1/R_w)\nu/(\delta+\nu), \\
W_{12}(t)/N(t) &= (1-1/R_w)\nu\delta/(\delta+\nu)^2, \\
W_{21}(t)/N(t) &= (1-1/R_w)\nu\delta^2/((\delta+\nu)^2(\gamma+\nu)), \\
W_{22}(t)/N(t) &= (1-1/R_w)\nu\delta^2\gamma/((\delta+\nu)^2(\gamma+\nu)^2),
\end{aligned}
$$

where $R_w = \beta\delta^2(2\gamma+\nu)/((\gamma+\nu)^2(\delta+\nu)^2)$ is the basic reproduction number of the wild virus infection and $R_v = bR_w$ is the basic reproduction number of the vaccine virus infection.

Short description of the simulation procedure

The deterministic models provide the basis for the simulated stochastic models. The kind of epidemiologic events and the duration between two consecutive events are calculated using random numbers. The simulations start at the endemic equilibrium without vaccination (the numbers of susceptible and infective individuals are rounded to integers). In each simulation step, the sum ξ of all the rates that change the current state of the system is calculated. For the OPV model, it is

$$
\begin{aligned}
\xi = {} & \text{birth rate} + \text{death rate} + \text{infection rates} + \\
& \text{transition rates for incubation and infectivity,} \\
\xi = {} & \nu N + \mu N + (\lambda_w+\lambda_v)S + \delta(V_{11}+V_{12} \\
& + W_{11}+W_{12}) + \gamma(V_{21}+V_{22}+W_{21}+W_{22}).
\end{aligned}
$$

A uniformly distributed random number $r \in [0,1]$ is then chosen, and the time $T = -\ln(r)/\xi$ after which the next event occurs is calculated. All transition rates are arranged in an arbitrary order, and cumulative rates are calculated by adding their individual rates. A new uniformly distributed random number $r \in [0,\xi]$ is chosen, and the first transition in the order whose cumulative rate is larger than r is performed. For example, if the event is an infection, one "individual" is removed from the group of susceptible individuals and added to the group of incubating individuals. New rates are calculated after each step, and the procedure is repeated. A more detailed description of the transformation of differential equation models to stochastic models can be found in (2).