The effect of heterogeneous interventions on the spread of infectious diseases

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Summary

Everybody is equal before the law, but not before infectious diseases. Various kinds of disparities like genetic disposition and differing contact rates influence each individual's risk to acquire infection or develop disease. Medical interventions add further levels of heterogeneity.

It may be surprising that the health of unvaccinated individuals can strongly be influenced by a campaign in which they do not participate. Because of vaccinations, the infection can no longer spread well in the population. This has the positive effect that some unvaccinated individuals will escape infection. The reduced spread of the infection goes along however with a higher age at infection, which may be dangerous due to an increased risk of disease.

National and sub-national immunisation days, which aim to cover as many children as possible once or twice a year, will be compared with respect to their effectiveness and efficacy. They have been shown to be extremely effective in reducing the incidence of poliomyelitis.

Selective vaccination of contact persons of smallpox cases has greatly contributed to the global eradication of this dreaded disease. It will be explored whether this strategy will also be suitable for other infections for which eradication programmes are envisaged.

1 Introduction

Infectious diseases remain one of the major public health challenges in the 21st century. On the individual level the dynamics of the immune system plays a vital role and at the

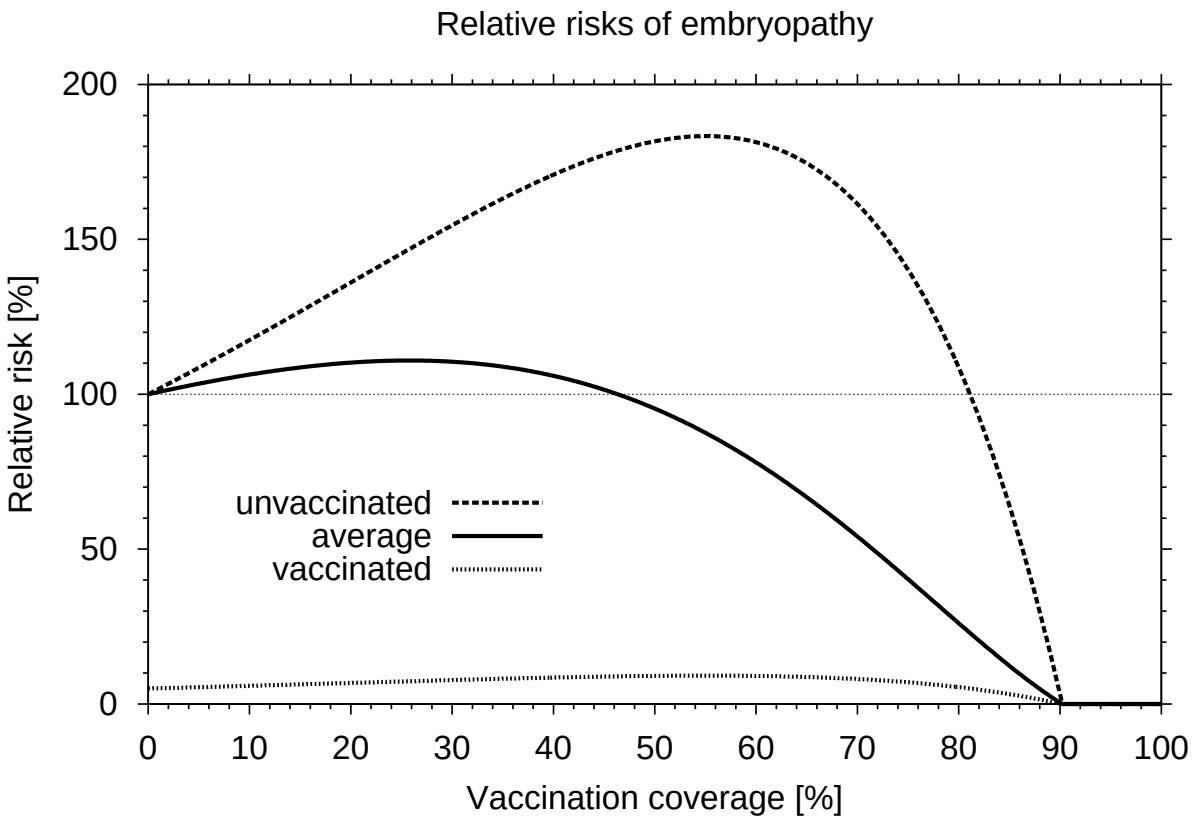

Figure 1: Relative risk of rubella infection during pregnancy (dashed line: unvaccinated women; dotted line: vaccinated women; full line: weighted population average; horizontal line at 100 %: reference line for comparison with the pre-vaccination value).

Parameter values: basic reproduction number = 7; life expectancy = 60 years; infants are vaccinated shortly after birth; vaccine efficacy = 95 %; age at pregnancy is normally distributed with mean 26 years and SD 3 years.

population level complex contact patterns have to be considered. We will show that well-intended interventions can lead to astonishing and sometimes counter-intuitive results.

2 Vaccination against rubella

Although rubella usually is a mild disease, infections during the first 3 to 4 months of pregnancy can result in spontaneous abortion, stillbirth, and congenital rubella syndrome (Cooper 1985). Vaccinations not only prevent disease but also infection and, therefore, reduce the ability of the infection to spread in a population. As a consequence, nonvaccinated individuals tend to be older when they become infected. Vaccinations, therefore, protect those who have successfully been vaccinated, but they also increase the average age at infection (and thereby the risk of infection during pregnancy) for those who were not vaccinated or were unsuccessfully vaccinated (Edmunds *et al.* 2000, Knox 1980).

In our model, we assume that individuals are vaccinated shortly after birth and that 95 % of vaccinations are successful. To evaluate the effect of rubella vaccinations, we also

make the simplifying assumption, that the probability of being pregnant can be described by the density of a normal distribution with a mean of 26 years and standard deviation of 3 years (ie 95 % of pregnancies occur between 20 and 32 years of age). Figure 1 shows the relative risks of rubella-caused embryopathy for vaccinated and unvaccinated individuals and a weighted population average. The risk before vaccination was set to 100 % for comparison. The relative risk of unvaccinated individuals increases with the vaccination coverage and reaches a maximum of more than 180 % when about 50 to 60 % of the population are vaccinated. Even the population average increases up to 110 % for low vaccination coverage. Only if more than 46 % of the newborn individuals become vaccinated, the herd immunity inferred by vaccination out-weights the damaging effects of the increased infection age, and the expected number of embryopathy cases in the population drops below the pre-vaccination value. Transmission ceases and no cases will occur among vaccinated and unvaccinated individuals alike, if the vaccination coverage increases above 90 %.

Not only infants but also juveniles and women can be vaccinated selectively against rubella. If only girls before puperty or women after their first pregnancy are vaccinated, they can be protected against rubella without contributing much to herd immunity. In that case, the infection can spread freely through the population and most women will enjoy natural or vaccine conferred immunity, but those few women who escaped earlier infection and refused vaccination are under much higher risk of acquiring the infection during pregnancy.

These results are confirmed by a recent review on the epidemiology of rubella in Greece (Panagiotopoulos *et al.* 1999), where vaccination coverage was lower than 50 % before 1990. Concommittant to rubella vaccination, the susceptible fraction of pregnant women increased from 12 % in the early seventies to 36 % in the early nineties, and the peak of the age distribution of notified rubella cases shifted from the age-class of 5 to 9 year old children (in 1986) to that of 15 to 19 year old juveniles (in 1993) with more than 25 % of cases being over 20 years of age. In 1993, a rubella epidemic occurred in Greece which led to a record incidence of 25 serologically confirmed cases of congenital rubella syndrome (24.6 per 100,000 life births) which exceeded the total of all notified cases from 1950 to 1992.

3 National and local immunisation days

So-called national immunisation days contributed greatly to the elimination of poliomyelitis in many tropical countries (CDC 2001). On these immunisation days, all children under five years of age are offered attenuated polio virus vaccine (OPV), irrespective of previous vaccinations. Children who were successfully vaccinated with OPV become infected with

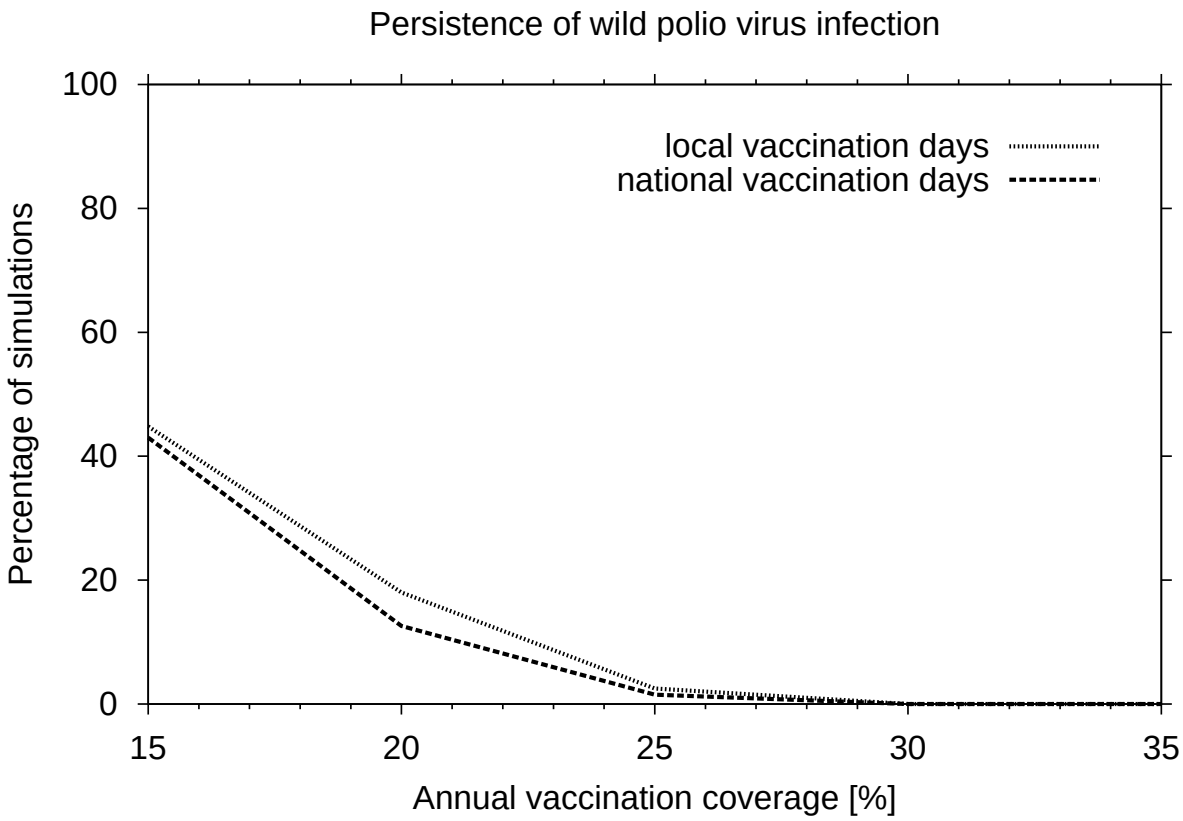

Figure 2: Frequency at which wild polio virus infection persists for at least ten years instead of immunisation days at the given annual coverage. (dashed line: national immunisation days; dotted line: local immunisation days)

Parameter values: basic reproduction number = 12 for wild polio virus and 4 for vaccine virus; simulated population structure: 1×100,000 + 10×10,000 + 100×1,000 growing at 2 % per year; life expectancy = 45 years; further parameter values see Appendix.

the vaccine virus (which can be spread to contact persons) and finally acquire a permanent and full protection against infection and disease (Henry *et al.* 1966). We evaluate this strategy with stochastic computer models that consider that the vaccine virus causes an infection of the vaccinated child and is able to spread to contact persons. The simulated population initially consists of one major city of 100,000 inhabitants, ten towns of 10,000 inhabitants each, 100 villages of 1,000 inhabitants each and 1,000 small settlements of 100 inhabitants each (ie a total of 400,000 individuals) and grows at a rate of 2 % per year. Each individual has the same average number of contacts. A fraction of contacts which depends on the size of the individual's subpopulation occurs in the place where he or she lives and the remaining contacts are spend at random with any other individual of the remaining population. The population is unvaccinated and in endemic equilibrium at the beginning of the simulations. An effective vaccination coverage less than 35 % per year causes extinction of wild polio virus infection within ten years in the vast majority of the simulations (Fig. 2; dashed line). It is logistically less demanding if each village or town has its own local immunisation day (which is repeated annually) instead of having

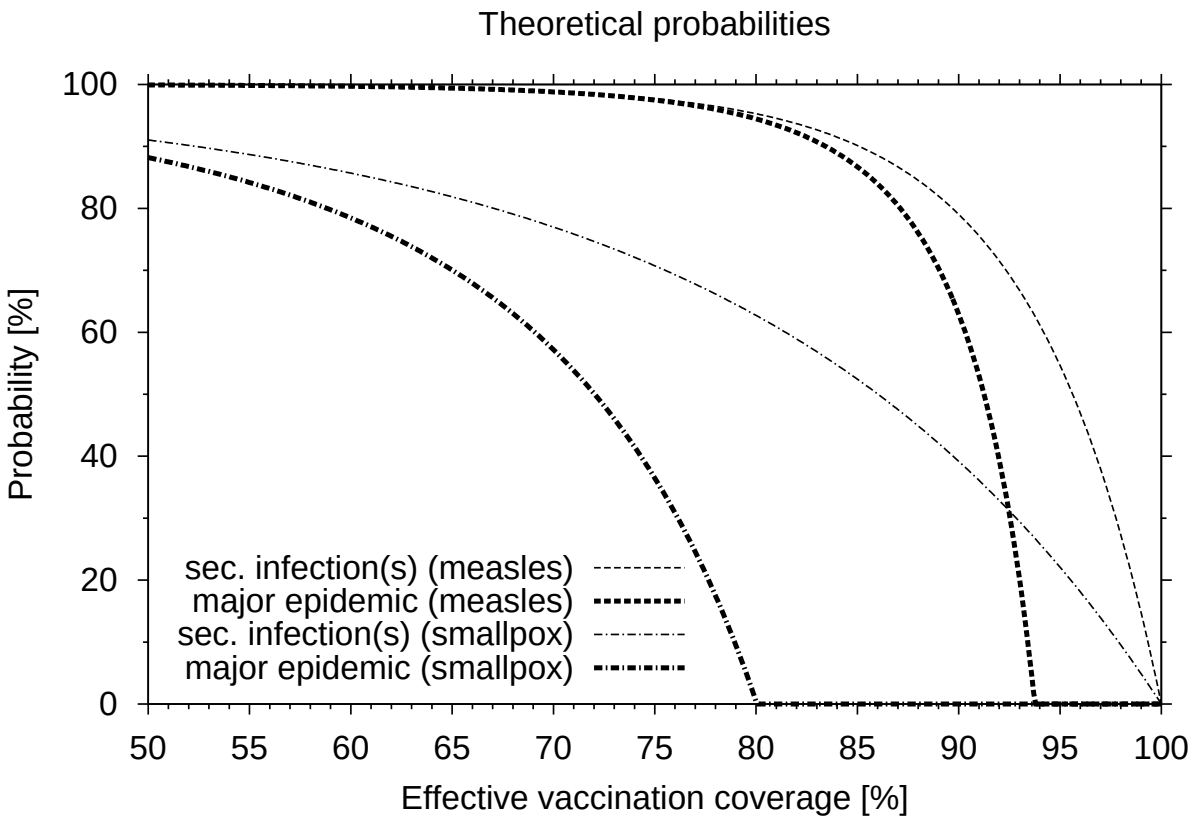

Figure 3: Frequency at which reintroduced infection leads to secondary infections (thin lines) or to a major epidemic (thick lines), respectively; dashed lines: measles; dash-dot lines: smallpox.

Parameter values: basic reproduction number = 5 for smallpox, 16 for measles; life expectancy = 45 years; further parameter values and derivation of probabilities see Appendix.

only one immunisation day for the whole population. The dotted line in Fig. 2 shows that we can achieve equally promising results if each subpopulation has its own local immunisation day and if the subpopulations are vaccinated at random order.

4 Reintroduction of infection

As the attempts of global eradication of poliomyelitis and measles proceed, many regions become free of these infections. As long as there are regions on earth where the infection is still transmitted, there remains a risk of reintroduction (Gani & Leach 2001, Orenstein *et al.* 2002). Even after global eradication it can be feared that infections could be released by terrorists as biological weapons as recently has been speculated about smallpox (Barbera *et al.* 2001, Henderson 2002). In the final phase of smallpox eradication, localized vaccination campaigns, called "ring vaccinations", successfully prevented further spread of smallpox: all nonimmune people who lived in the vicinity of a newly emerging case or who might have had contact with the case were offered a vaccination (Fenner *et al.* 1988). Measles and poliomyelitis differ in several respects from smallpox. Measles is

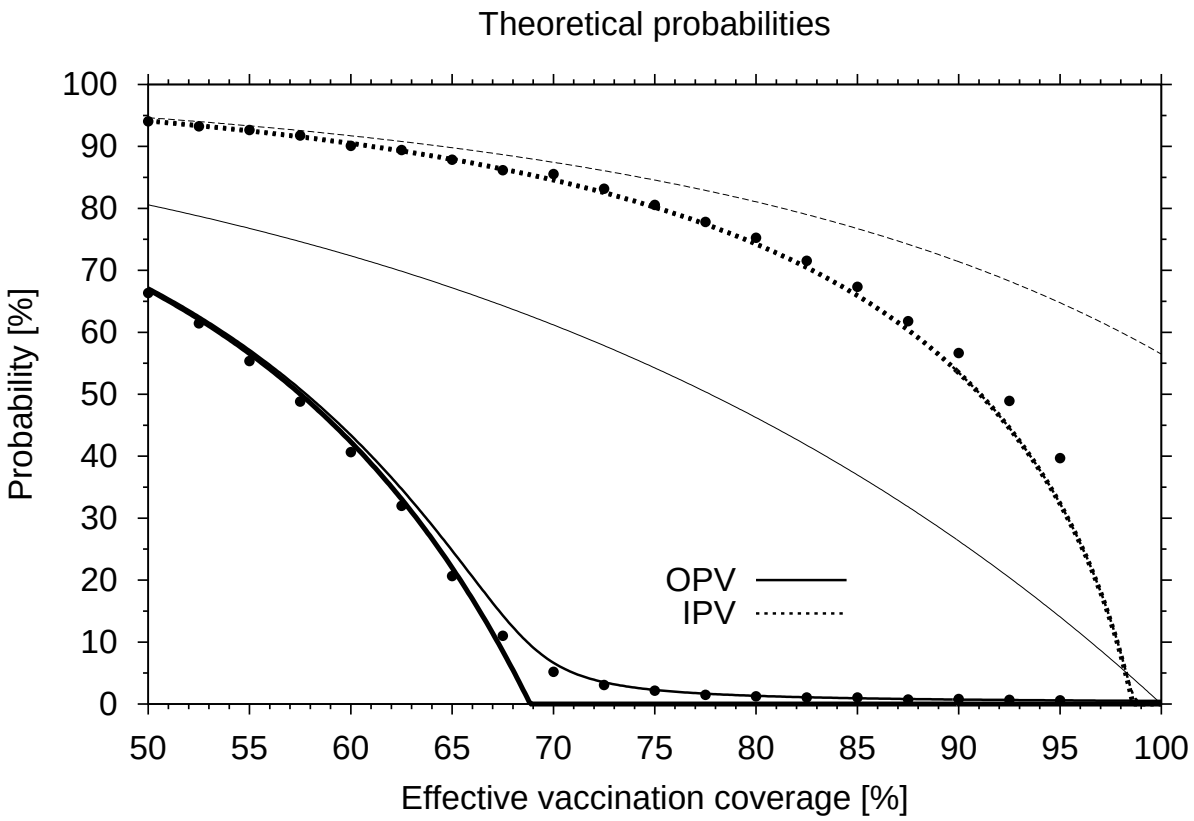

Figure 4: Frequency at which reintroduced wild polio virus infection leads to secondary infections (thin lines), to at least one clinical case (intermediate lines) to a major epidemic (thick lines), respectively; dotted lines: IPV vaccination (the lines for secondary cases and for major epidemics coincide); full lines: OPV vaccination; the dots compare the theoretically derived curves to the results of 25,000 simulation each.

Parameter values: basic reproduction number = 12 for wild polio virus and 4 for vaccine virus; simulated population structure: 1×100,000 + 10×10,000 +100×1,000 + 1,000×100 growing at 2 % per year; life expectancy = 45 years; further parameter values, details of computer simulation and derivation of probabilities see Appendix.

much more contagious than smallpox and an infected individual can spread the infection before typical clinical symptoms appear. Poliomyelitis is not only more contagious than smallpox, but typical clinical symptoms (infantile paralysis) are the exception rather than the rule: only one in about 200 infectives becomes clinically ill (Eichner & Dietz 1996, Horstmann 1955).

To address the question whether ring vaccinations might nevertheless be applied in the fight against measles or poliomyelitis, we use computer simulations to study to what extent reintroduced infections can spread before a vaccination campaign can be launched. In the simulations, we use the same type of highly structured population as was described in the previous section. The initial fraction of immune individuals is solely determined by the coverage and type of the vaccine. One individual is chosen at random to become the initial infective case. Whereas smallpox and measles vaccination simply lead to life-long

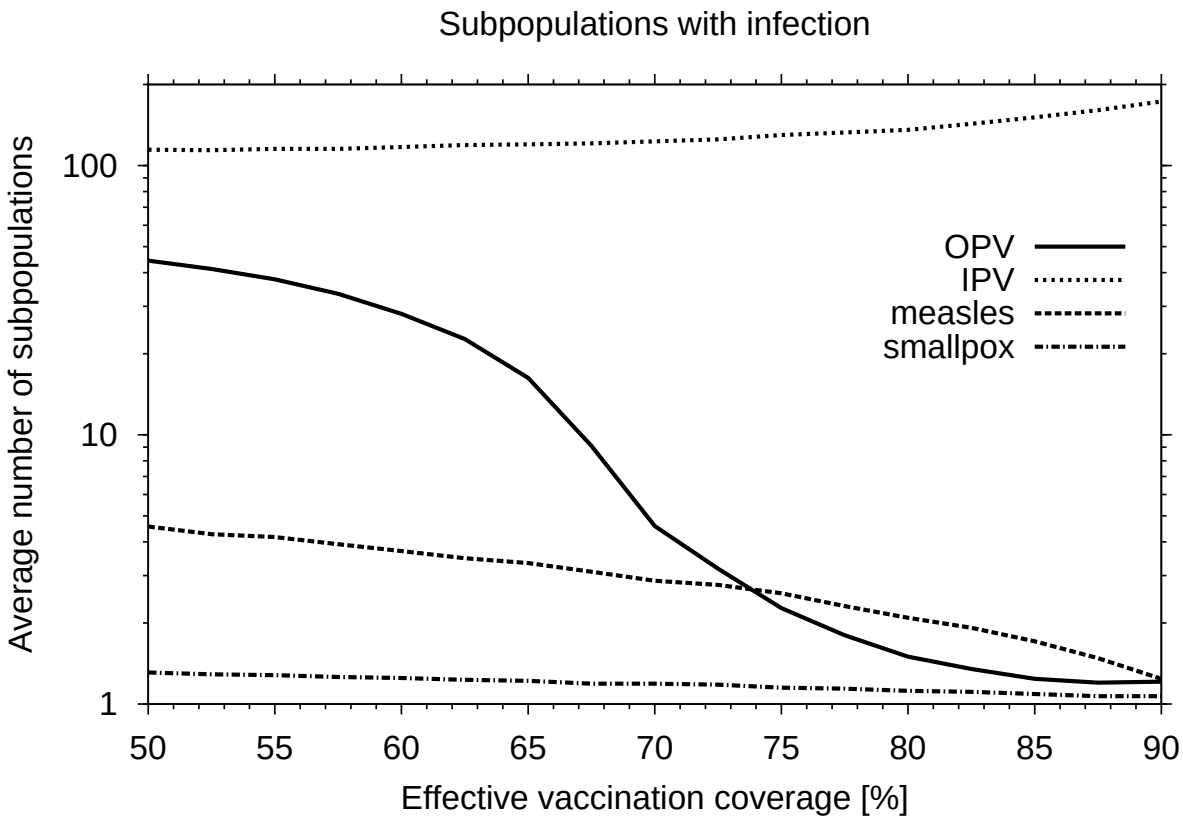

Figure 5: Average number of subpopulations with infected individuals one week after the occurrence of the first clinical case (results based on 25,000 simulations each); dotted line: IPV vaccination; full line: OPV vaccination; dashed line: measles; dash-dot line: smallpox.
Parameter values: basic reproduction number = 12 for wild polio virus and 4 for OPV vaccine virus, 5 for smallpox and 16 for measles; 30 % of IPV vaccinated individuals become fully immune, the remaining fraction is only partly protected against infection (50 %) and will become infective for a reduced period of time (20 %); simulated population structure: 1×100,000 + 10×10,000 +100×1,000 + 1,000×100 growing at 2 % per year; life expectancy = 45 years; one in 200 polio infections leads to clinical symptoms; further parameter values and details of computer simulation see Appendix.

protection against infection and disease, we have to distinguish two completely different types of vaccine in the case of polio virus transmission: (1) children who were successfully vaccinated with the oral polio vaccine (OPV) become infected with the vaccine virus, can spread it to contact persons and finally acquire a permanent and full protection against infection and disease (Henry *et al.* 1966); (2) children vaccinated with the in-activated polio vaccine (IPV) also are fully protected against the disease but may still acquire and spread the infection (although to a lesser extent; Cohen 1987).

Even at comparatively low vaccination coverage, reintroduced smallpox infections frequently failed to cause secondary infections or major epidemics (Fig. 3, dash-dot lines). Irrespective of vaccination coverage, infections can be found on average in only one to two subpopulations one week after the first onset of clinical symptoms (Fig. 5, dash-dot line). Because of this low potential of spread and the easy recognition of clinical symp-

toms which preceded infectivity, smallpox could easily be controlled by ring vaccinations. Measles is much more contagious and frequently leads to secondary cases and causes major epidemics unless the vaccination coverage exceeds about 95 % (Fig. 3, dashed lines). Reintroduced measles infections usually spread to a few neighboring settlements within one week after the first onset of clinical symptoms (Fig. 5, dashed line). This calls for a less localized vaccination campaign in response to emerging measles cases. Like measles, wild polio virus is highly contagious, but rarely leads to typical clinical symptoms (we incorporated the risk of one clinical case per 200 infections). Reintroduced wild polio virus infection frequently causes major epidemics if the IPV vaccination coverage is below 85–95 % or if the effective OPV coverage is below 55–65 %, respectively (Fig. 4). One week after the first paralytic case occurs in one of the settlements, polio virus infection has most frequently spread to a multitude of surrounding villages and towns (Fig. 5, dotted and full line). Whole regions (rather than a limited group of individuals) need, therefore, be vaccinated to appropriately respond to re-emerging polio cases.

Concluding Remarks

Smallpox transmission was successfully interrupted in 1978 by ring vaccination, i.e. targeted vaccination among actual and potential contacts of cases. This highly successful vaccination approach was not adopted as a result of careful planning, let alone mathematical reasoning. It was used as an emergency measure on the occasion of vaccine shortage due to logistic problems. So far the prevailing strategy had been based on achieving herd immunity. For the first time we show in this paper that the epidemiologic characteristics of small pox explain the success of this selective approach and investigate the effects if a similar situation arises with respect to the other two infectious dieseases for which global eradication is actually attempted (polio) or contemplated (measles).

Appendix: Reintroduction after local extinction

List of parameters and variables that are common to all models

S_i susceptible individuals in subpopulation i

$L_{i,k}$ individuals with latent wild virus infection (stage $k = 1 \ldots 32$) in subpopulation i

$I_{i,k}$ wild virus infective individuals (stage $k = 1 \ldots 32$) in subpopulation i

N_i total number of individuals in subpopulation i
initially 1x100,000, 10x10,000, 100x1,000, 1,000x100 individuals

p successfully vaccinated fraction of newborn infants

μ death rate = 1/life expectancy = 0.022 per year

α population growth rate = 0.02 per year

δ transition rate for latency = 32/duration of latency
= 973.3 per year for smallpox; 1168.0 for measles; 1668.6 per year for polio

γ transition rate for infectivity = 32/duration of infectivity
= 556.2 per year for smallpox; 1460.0 per year for measles; 389.3 per year for polio

β average number of sufficiently close contacts per individual per year
= 87.1 per year for smallpox; 730.7 per year for measles; 146.5 per year for polio

R_0 basic reproduction number = 5 for smallpox; 16 for measles; 12 for polio

ℓ probability of paralysis = 1/200 for polio

List of parameters and variables that are specific to the OPV model

$L_{i,k,v}$ individuals with latent vaccine virus infection (stage $k = 1 \ldots 32$) in subpopulation i

$I_{i,k,v}$ vaccine virus infective individuals (stage $k = 1 \ldots 32$) in subpopulation i

b relative infectivity of vaccine virus infective individuals = 0.25

List of parameters and variables that are specific to the IPV model

$\tilde{S}_i$ individuals partly protected by IPV in subpopulation i

$\tilde{L}_{i,k}$ as $L_{i,k}$ but infected individual is partly protected by IPV in subpopulation i

$\tilde{I}_{i,k}$ as $I_{i,k}$ but infected individual is partly protected by IPV in subpopulation i

a probability that an individual becomes fully immune by IPV vaccination = 0.3

c probability that a contact with an infectious individual leads to infection
of a partly susceptible individual = 0.5

$\tilde{\gamma}$ rate for (stepwise) transition from infectivity to immunity
= 32/duration of infectivity of partly protected individuals = 1946.7 per year

Contact matrix

The rate $\beta_{j,i}$ of sufficiently close contacts per unit of time of an infective individual of subpopulation i with individuals of subpopulation j is given by

$$\beta_{j,i} = \begin{cases} \beta N_j \left(a_i / \sum_{k \neq i} N_k + a_j / \sum_{k \neq j} N_k \right) & \text{for } i \neq j \\ \beta - \sum_{i \neq j} \beta_{i,j} > 0 & \text{for } i = j \end{cases}$$

where $a_i = 0.001 + 0.3 \exp(-N_i/15000)$.

Model for OPV

Individuals are born susceptible S_i at rate $(\mu+\alpha)N_i$. A fraction p is vaccinated and starts incubating the vaccine virus $L_{1,i,v}$. Individuals pass their latency period in a step-wise process at rate δ and become infective. Infective individuals pass their infective period in a step-wise process at rate γ and become immune. Susceptible individuals become infected with wild or vaccine virus at rates λ_i and $\lambda_{i,v}$, respectively. Mortality was neglected during the relatively short latent and infectious period.

$$\begin{array}{ll}
dN_i/dt = \alpha N_i & dS_i/dt = (\mu+\alpha)(1-p)N_i - (\lambda_i + \lambda_{i,v} + \mu)S_i \\
dL_{i,1}/dt = \lambda_i S_i - \delta L_{i,1} & dL_{i,1,v}/dt = (\mu+\alpha)pN_i + \lambda_{i,v}S_i - \delta L_{i,1,v} \\
dL_{i,2}/dt = \delta(L_{i,1} - L_{i,2}) & dL_{i,2,v}/dt = \delta(L_{i,1,v} - L_{i,2,v}) \\
\ldots & \ldots \\
dL_{i,32}/dt = \delta(L_{i,31} - L_{i,32}) & dL_{i,32,v}/dt = \delta(L_{i,31,v} - L_{i,32,v}) \\
dI_{i,1}/dt = \delta L_{i,32} - \gamma I_{i,1} & dI_{i,1,v}/dt = \delta L_{i,32,v} - \gamma I_{i,1,v} \\
dI_{i,2}/dt = \gamma(I_{i,1} - I_{i,2}) & dI_{i,2,v}/dt = \gamma(I_{i,1,v} - I_{i,2,v}) \\
\ldots & \ldots \\
dI_{i,32}/dt = \gamma(I_{i,31} - I_{i,32}) & dI_{i,32,v}/dt = \gamma(I_{i,31,v} - I_{i,32,v})
\end{array}$$

$$\text{with } \lambda_i = \sum_{m=1}^{1111} \frac{\beta_{i,m}}{N_i} \sum_{k=1}^{32} I_{m,k} \quad \text{and } \lambda_{i,v} = \sum_{m=1}^{1111} \frac{b\beta_{i,m}}{N_i} \sum_{k=1}^{32} I_{m,k,v}$$

Initial conditions: the wild virus free state can be approximated by
$\bar{S}_i \approx N_i \left(bR_0 + 1 - \sqrt{(bR_0-1)^2 + 4pbR_0} \right) / (2bR_0) = N_i \, s_{\text{OPV}}$,
$\bar{L}_{i,k,v} \approx N_i \left(bR_0 - 1 + \sqrt{(bR_0-1)^2 + 4pbR_0} \right) (\mu+\alpha)/(2bR_0\delta)$ for latency stages $k = 1 \ldots 32$,
$\bar{I}_{i,k,v} \approx L_{i,1,v} \, \delta/\gamma$ for infectious stages $k = 1 \ldots 32$.

Model for IPV, measles and smallpox

Individuals are born susceptible S_i at rate $(\mu+\alpha)N_i$. A fraction p is vaccinated. A fraction $1-a$ of the vaccinated individuals becomes partly susceptible $\tilde{S}_i$. Fully or partly

susceptible individuals become infected at rate λ_i and $c\lambda_i$, respectively, and start incubating the infection. Individuals pass their latent period in a step-wise process at rate δ and become infective. Infective individuals pass their infective period in a step-wise process and become immune. Mortality was neglected during the relatively short latent and infectious period.

$$
\begin{array}{ll}
dS_i/dt = (\mu+\alpha)(1-p)N_i - (\lambda_i+\mu)S_i & d\tilde{S}_i/dt = (\mu+\alpha)(1-a)pN_i - (c\lambda_i+\mu)\tilde{S}_i \\
dL_{i,1}/dt = \lambda_i S_i - \delta L_{i,1} & d\tilde{L}_{1,i}/dt = c\lambda_i \tilde{S}_i - \delta \tilde{L}_{i,1} \\
dL_{i,2}/dt = \delta(L_{i,1} - L_{i,2}) & d\tilde{L}_{2,i}/dt = \delta(\tilde{L}_{i,1} - \tilde{L}_{i,2}) \\
\ldots & \ldots \\
dL_{i,32}/dt = \delta(L_{i,31} - L_{i,32}) & d\tilde{L}_{32,i}/dt = \delta(\tilde{L}_{i,31} - \tilde{L}_{i,32}) \\
dI_{i,1}/dt = \delta L_{i,32} - \gamma I_{i,1} & d\tilde{I}_{1,i}/dt = \delta \tilde{L}_{i,32} - \tilde{\gamma}\tilde{I}_{i,1} \\
dI_{i,2}/dt = \gamma(I_{i,1} - I_{i,2}) & d\tilde{I}_{2,i}/dt = \tilde{\gamma}(\tilde{I}_{i,1} - \tilde{I}_{i,2}) \\
\ldots & \ldots \\
dI_{i,32}/dt = \gamma(I_{i,31} - I_{i,32}) & d\tilde{I}_{32,i}/dt = \tilde{\gamma}(\tilde{I}_{i,31} - \tilde{I}_{i,32}) \\
dN_i/dt = \alpha N_i & \lambda_i = \sum_{m=1}^{1111} \frac{\beta_{i,m}}{N_i} \sum_{k=1}^{32} (I_{m,k} + \tilde{I}_{m,k})
\end{array}
$$

Initial conditions (virus-free state with vaccination): $S_i = N_i(1-p) = N_i\ s_{\mathrm{IPV}}$ and $\tilde{S}_i = p(1-a) = N_i\ \tilde{s}_{\mathrm{IPV}}$. The models for measles and smallpox are obtained by setting $a = 1$.

Simulation procedure

The deterministic models above provide the basis for the simulated stochastic models. The type of event and the duration between two consecutive events are calculated using random numbers. The simulations start at the wild virus free equilibrium in which the number of susceptibles only depends on the vaccination coverage. First a susceptible individual is chosen at random to become the initial infective individual. Then, for each step the sum ξ of all the rates that change the current state of the system is calculated. For the OPV model, it is ξ = birth rates + death rates + latency transition rates + infection transition rates:

$$\xi = \sum_{i=1}^{1111} \left[(\alpha+2\mu)N_i + (\lambda_{w,i} + \lambda_{v,i})S_i + \delta \sum_{k=1}^{32} (L_{i,k} + L_{i,k,v}) + \gamma \sum_{k=1}^{32} (I_{i,k} + I_{i,k,v}) \right]$$

A uniformly distributed random number $r \epsilon [0,1]$ is then chosen and the time $\Delta T = \ln(1/r)/\xi$ 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 $r \epsilon [0, \xi[$ is chosen and the first transition in the order whose cumulative rate is larger than r is performed. If, e.g., 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 is given by Gillespie (1976).

Theoretical probabilities

In the following, we calculate the probabilities of secondary infections, of the occurrence of paralytic cases and of the occurrence of a major epidemic, respectively, from the properties of Markov chains. This only approximates the simulated results as we had to assume "infinitely large" populations.
If infection is lost in n steps (here: $n = 32$), the duration t of infectious individuals is Gamma-distributed with density

$$\gamma^n t^{n-1} \mathrm{e}^{-n\gamma t}/(n-1)!$$

Contacts of infective individuals with susceptible ones are Poisson distributed with parameter βst where s is the susceptible fraction. The probability generating function for the number of infective contacts within a given time t is, therefore,

$$\sum_{i=0}^{\infty} (\beta st)^i \mathrm{e}^{-\beta st} z^i/i! = \mathrm{e}^{-\beta st(1-z)}.$$

Integrating over all possible durations of the infectious period yields the probability generating function for the number of infective contacts within the infectious period

$$G(z) = \int_0^\infty \frac{\gamma^n t^{n-1} \mathrm{e}^{-n\gamma t}}{(n-1)!} \mathrm{e}^{-\beta st(1-z)} dt = (1 + \beta s(1-z)/\gamma)^{-n} = (1 + R_0 s(1-z)/n)^{-n}$$

with $\beta/\gamma = R_0/n$. The probability P_s that at least one infection occurs is

$$P_s = 1 - G(0) = 1 - (1 + R_0 s/n)^{-n}\,.$$

The probability P_e that a major epidemic occurs can be calculated numerically from $1 - P_e = G(1 - P_e)$, from which we get

$$P_e = 1 - (1 + R_0 s P_e/n)^{-n}\,.$$

The probability generating function for the total number of infections is given by

$$H(z) = z\, G(H(z)) = z(1 + R_0 s(1 - H(z))/n)^{-n}.$$

If ℓ is the probability that an infected individual develops paralysis, $F(y) = 1 - \ell + \ell y$ is the probability generating function for developing a paralysis. Replacing z by $F(y)$ gives us the probability generating function $L(y)$ for the total number of paralytic cases

$$L(y) = H(F(y)) = \frac{1 - \ell + \ell y}{(1 + (1 - L(y))R_0 s/n)^n}.$$

The probability that at least one paralytic case occurs is then given by

$$P_\ell = 1 - L(0) = 1 - (1-\ell)(1 + P_\ell R_0 s/n)^{-n}.$$

(a) For the OPV model we only have to set $s = s_{\rm OPV}$:

$$P_s^{\rm OPV} = 1 - (1 + R_0 s_{\rm OPV}/n)^{-n}\,,$$

$$P_e^{\rm OPV} = 1 - (1 + P_e^{\rm OPV} R_0 s_{\rm OPV}/n)^{-n}\,,$$

$$P_\ell^{\rm OPV} = 1 - (1-\ell)\,(1 + P_\ell^{\rm OPV} R_0 s_{\rm OPV}/n)^{-n}\,.$$

(b) With the IPV model we we have to differentiate between initial cases who were completely susceptible before ($s_{\rm IPV}$) and initial cases who have been vaccinated before ($c\tilde{s}_{\rm IPV}$). The average probabilities are then calculated as weighted averages

$$P_s^{\rm IPV} = \frac{s_{\rm IPV}\,\pi_s + c\tilde{s}_{\rm IPV}\,\tilde{\pi}_s}{s_{\rm IPV} + c\tilde{s}_{\rm IPV}}$$

with $\pi_s = 1 - (1 + R_0 s_{\rm IPV}/n)^{-n}$ and $\tilde{\pi}_s = 1 - \left(1 + \tilde{R}_0 c\tilde{s}_{\rm IPV}/n\right)^{-n}$, where $\tilde{R}_0 = n\beta/\tilde{\gamma}$,

$$P_e^{\rm IPV} = \frac{s_{\rm IPV}\ \pi_e + c\tilde{s}_{\rm IPV}\ \tilde{\pi}_e}{s_{\rm IPV} + c\tilde{s}_{\rm IPV}}$$

with $\pi_e = 1-(1 + R_0(\pi_e\ s_{\rm IPV} + \tilde{\pi}_e\ c\tilde{s}_{\rm IPV})/n)$ and $\tilde{\pi}_e = 1-\left(1 + \tilde{R}_0(\pi_e\ s_{\rm IPV} + \tilde{\pi}_e\ c\tilde{s}_{\rm IPV})/n\right)$,

$$P_\ell^{\rm IPV} = \frac{s_{\rm IPV}\ \pi_\ell + c\tilde{s}_{\rm IPV}\ \tilde{\pi}_\ell}{s_{\rm IPV} + c\tilde{s}_{\rm IPV}}$$

with $\pi_\ell = 1-(1-\ell)\,(1 + R_0(\pi_\ell\ s_{\rm IPV} + \tilde{\pi}_\ell\ c\tilde{s}_{\rm IPV})/n)$ and $\tilde{\pi}_\ell = 1-\left(1 + \tilde{R}_0(\pi_\ell\ s_{\rm IPV} + \tilde{\pi}_\ell\ c\tilde{s}_{\rm IPV})/n\right)$.

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