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Modelling the population impact of vaccination

Dr Margarita Pons-Salort (with slides from Prof Nicholas Grassly and Dr Isobel Blake)

Overview

1. How mathematical models are helpful in vaccine epidemiology
2. Revision and definitions
3. Vaccine coverage and the age at infection: analysing models at equilibrium (statics)
4. Incidence of infection following the introduction of vaccination: analysing model dynamics

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Questions addressed by mathematical models of vaccination

- What will be the population impact of a vaccine (incl. herd immunity)?
- What coverage will achieve elimination?
- What is the target product profile?
- What is the cost-effectiveness of alternative immunisation programmes?
- Who should receive vaccine and when?
- Etc…

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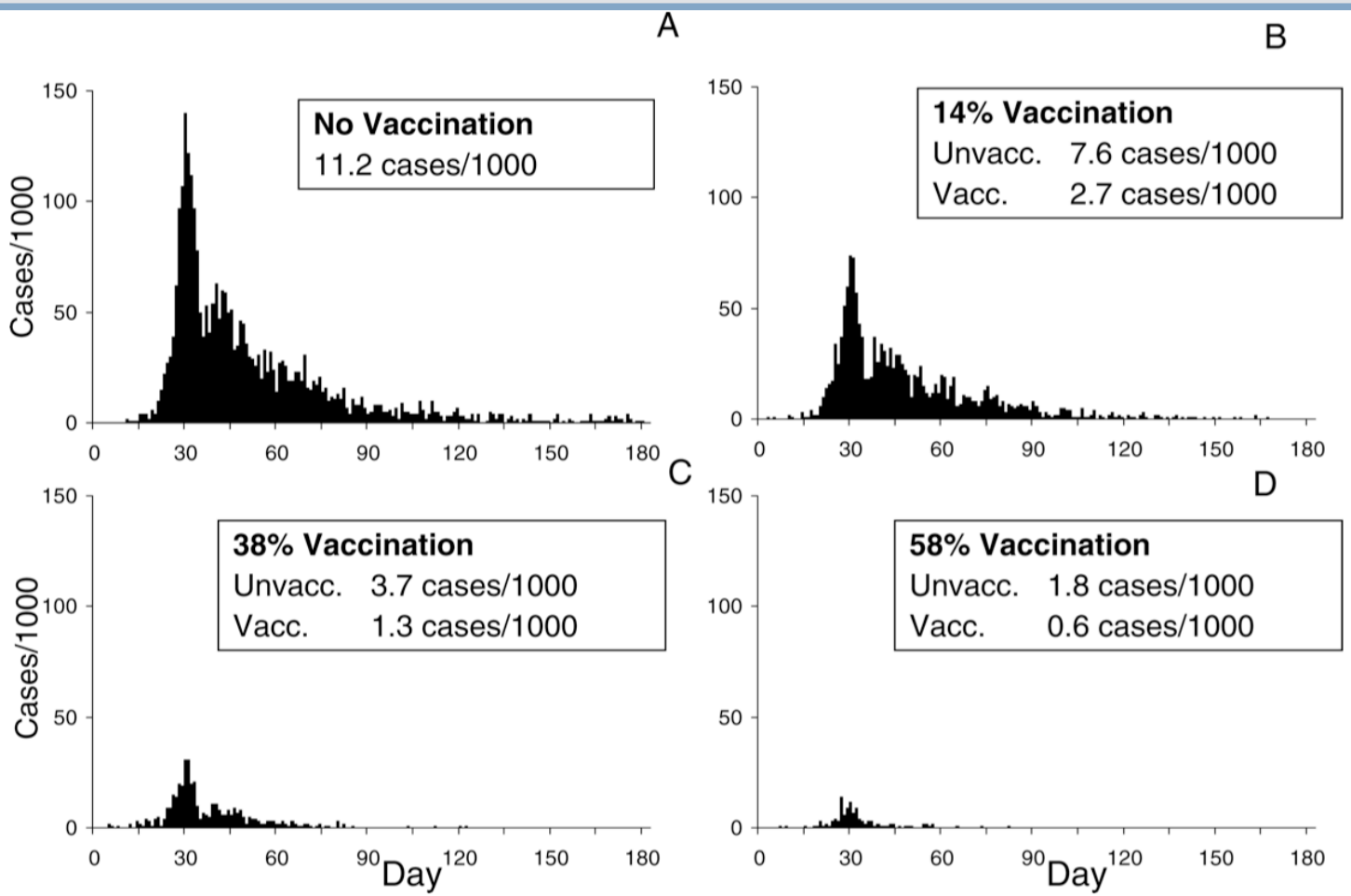
Predicted population impact of a partially protective ("leaky") oral cholera vaccine in Bangladesh



Assuming 70% vaccine effectiveness against infection and 50% against infectiousness a significant herd effect is expected

Longini et al. 2007

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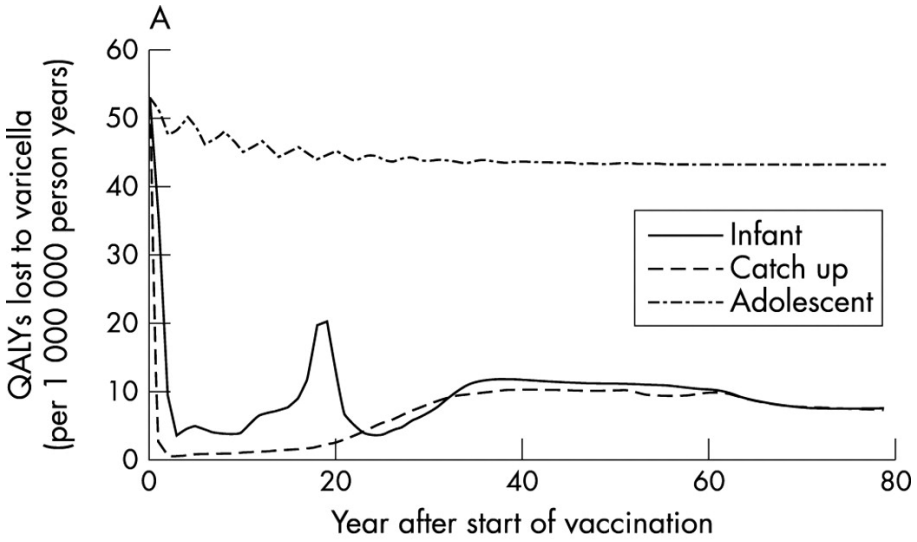
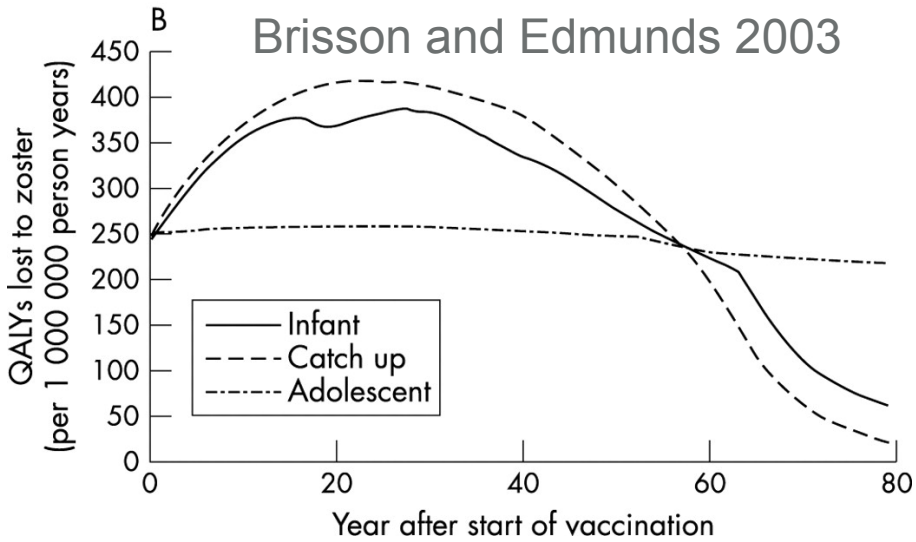
Should the UK vaccinate against varicella zoster (chickenpox)?





Brisson and Edmunds 2003

Vaccination against chickenpox was shown not to be cost-effective given cost of vaccine and impact on zoster (shingles) cases

"Epidemiological modelling predicts … an increase in herpes zoster incidence for the first 40 to 60 years following the introduction of a vaccination programme. ... Vaccinations against herpes zoster would only be expected to partly offset this increase, as the expected increase in herpes zoster incidence would occur predominantly in middle-aged adults too young to be targeted for herpes zoster vaccination." UK JCVI statement 2010

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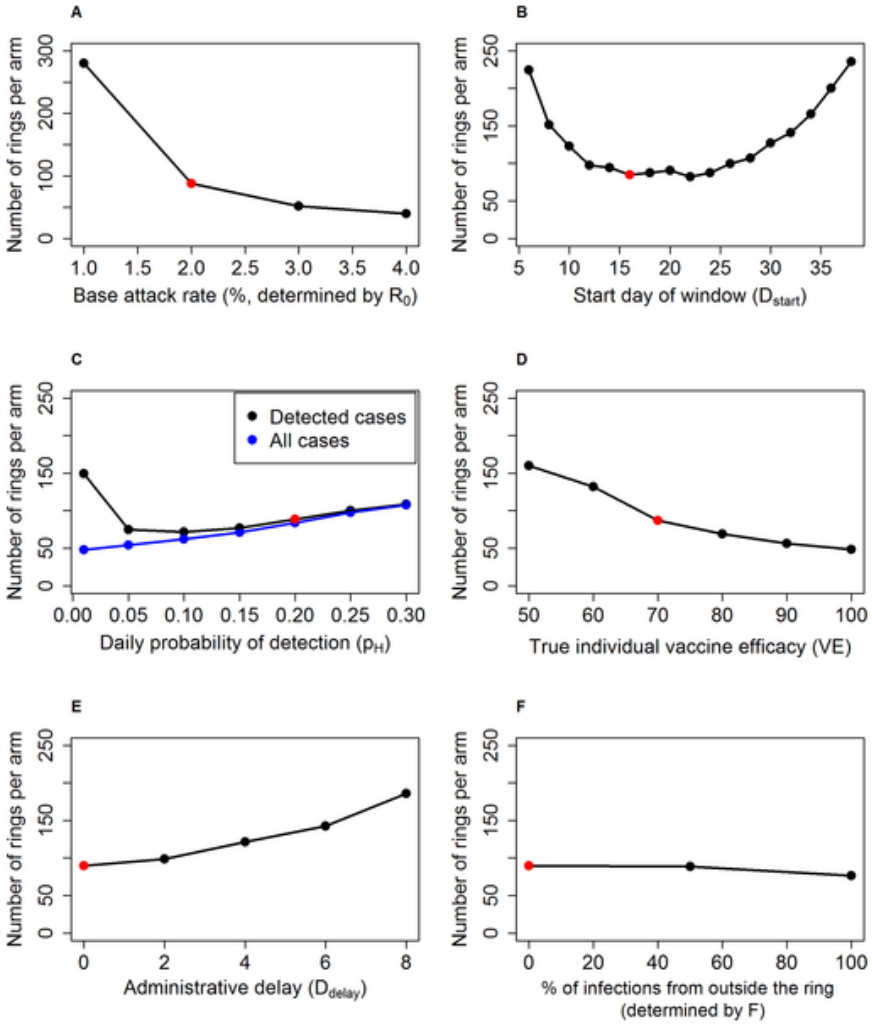
Informing trial design to estimate vaccine efficacy: Evaluating the required sample size by disease, vaccine and population characteristics



Hitchings MDT, Grais RF, Lipsitch M (2017) Using simulation to aid trial design: Ring-vaccination trials. PLOS Neglected Tropical Diseases 11(3): e0005470. https://doi.org/10.1371/journal.pntd.0005470

http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005470

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Vaccine efficacy

Protection offered by vaccine (1 or more doses) against infection or disease

vaccine efficacy = 1 – RR

where RR is the relative risk of infection or disease in the vaccinated group compared to unvaccinated

e.g. in a randomised controlled trial with 100 vaccinated and 100 unvaccinated children:

incidence in vaccinated group = 5 infections

incidence in unvaccinated group = 15 infections

vaccine efficacy = 1 – 5/15 = 67%

See Halloran et al. 1997

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Immunogenicity versus efficacy

Immunogenicity of a vaccine typically refers to the amount of antibody in the serum following vaccination or to measures of antigen-specific cellular immunity

Efficacy refers to protection against infection or disease; vaccines may be efficacious against disease but not infection

Efficacy sometimes correlates with measures of immunogenicity (e.g. serum antibodies), but not always

Effectiveness is sometimes distinguished from efficacy and defined as efficacy in the ‘real world’ (i.e. as part of an immunisation programme)

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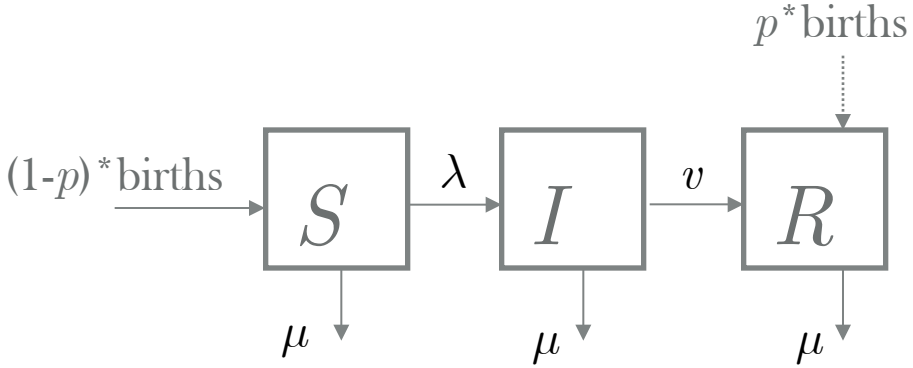
Statics: SIR model with vaccination at birth



$$\frac{dS}{dt} = (1-p)\mu N - \lambda S - \mu S$$

$$\frac{dI}{dt} = \lambda S - \nu I - \mu I$$

$$\frac{dR}{dt} = p\mu N + \nu I - \mu R$$

$$\lambda = \beta I / N$$

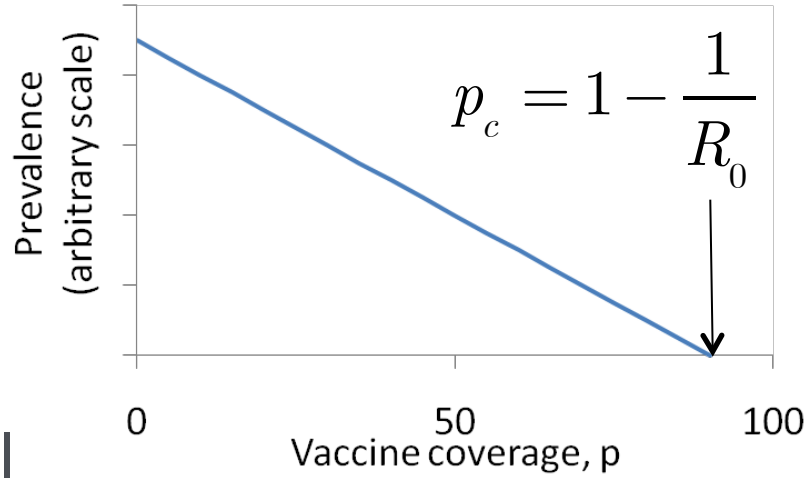
Statics: SIR model with vaccination at birth

At equilibrium

$$S^* = N^* / R_0$$

$$I^* = N^* \frac{\mu}{\mu + \nu}\left(1 - \frac{1}{R_0} - p\right)$$

cf. earlier lectures on SIR model



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Mean age at infection and the basic reproductive number for the SIR model

In a simple SIR model with a constant mortality rate at equilibrium (indicated by *)

Mean age at infection = A (=1/rate of death+infection)

Mean life expectancy = L (=1/rate of death)

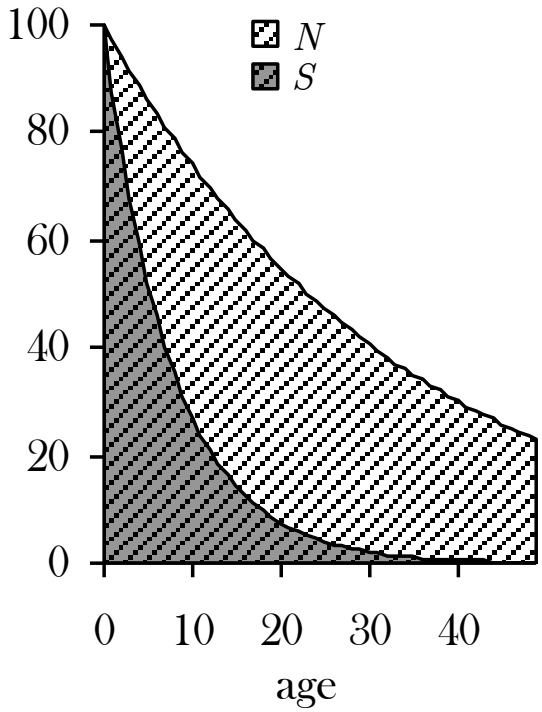
Then the average proportion of the population who remain susceptible at equilibrium

$S^*/N^* = A/L$ (since area under curve is proportional to the mean age at infection (or death))

Solving the SIR model at equilibrium gave

$$R_0 = N^*/S^*$$

and so the relationship between R_0 and A is simply $R_0 = L/A$



see Anderson and May 1991

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Pre-vaccination R_0 estimates for England and Wales

Infection	A	R_0	p_c
Rubella	9 - 10	8 - 9	88-89%
Chickenpox	12 - 17	5 - 7	80-85%
Measles	4 - 5	15 - 19	93-95%

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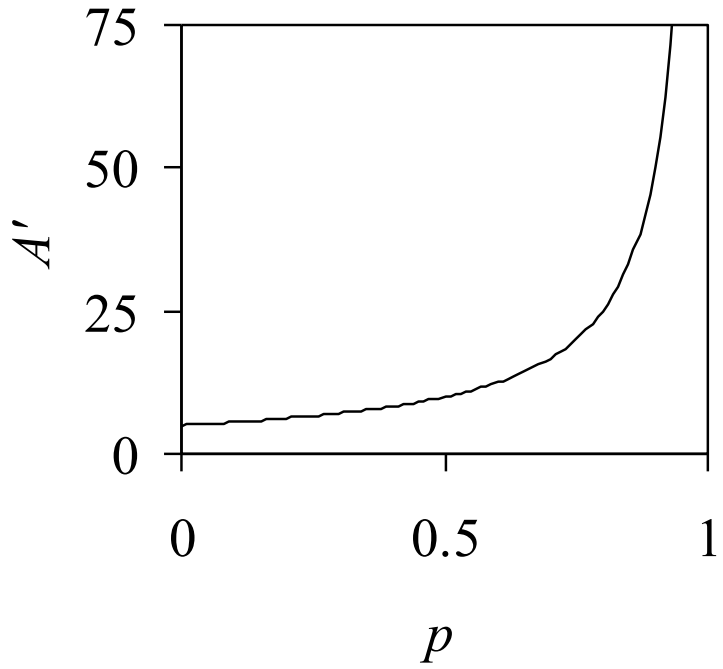
Vaccination in the basic SIR model and the mean age at infection

For vaccination at birth the new mean age at infection

$$A' = L / (R_0(1-p))$$

and

$$A' \to L \text{ as } p \to p_c$$



These calculations can be extended to situations where vaccination occurs at later ages (Anderson & May 1991).

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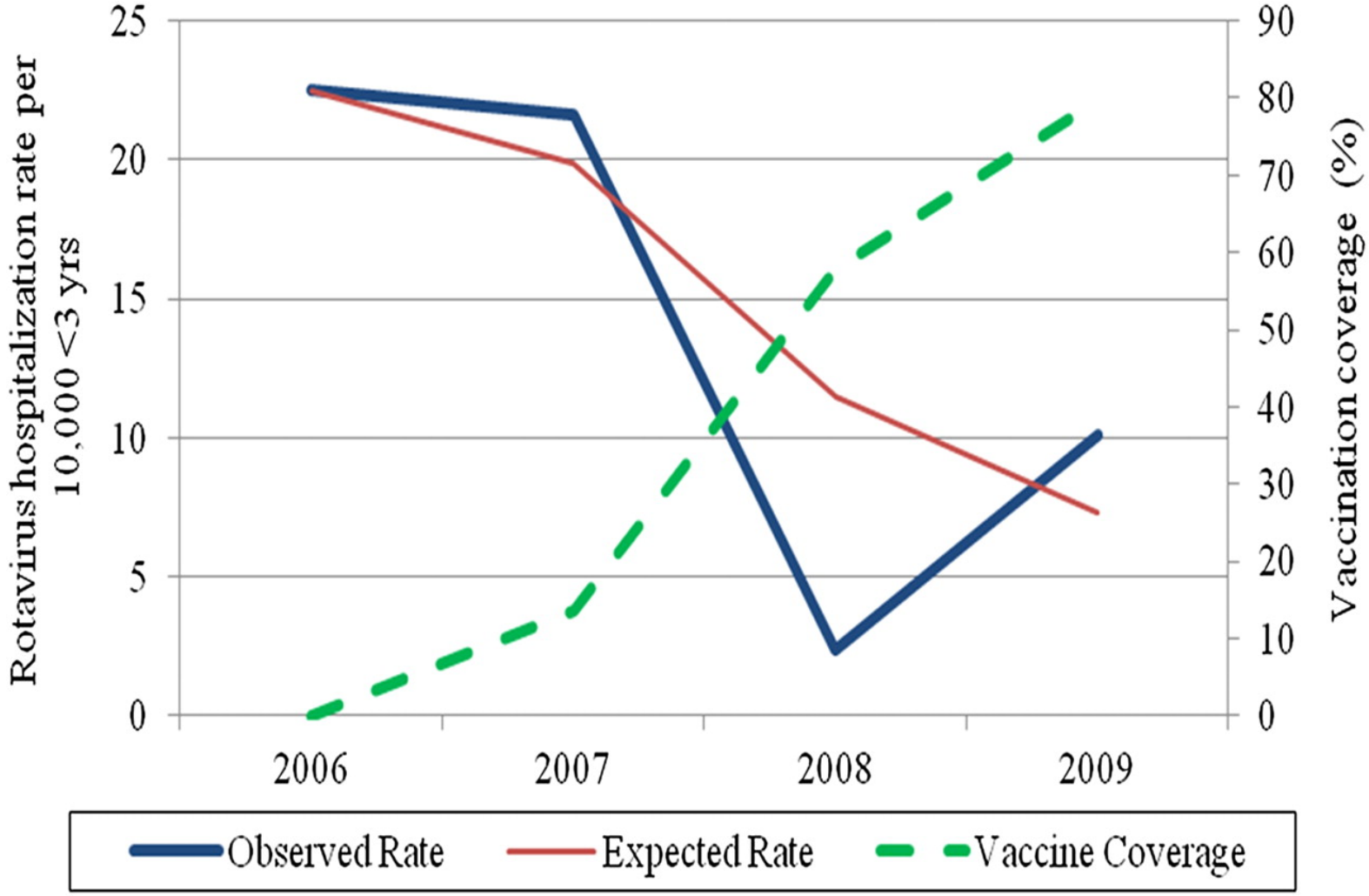
Observed New Vaccine Surveillance Network (NVSN) hospitalization rates in the USA, compared with those hospitalization rates that would be expected on the basis of NVSN vaccine effectiveness and NVSN vaccine coverage, 2006–2009.



Payne D C et al. Clin Infect Dis. 2011;53:245-253

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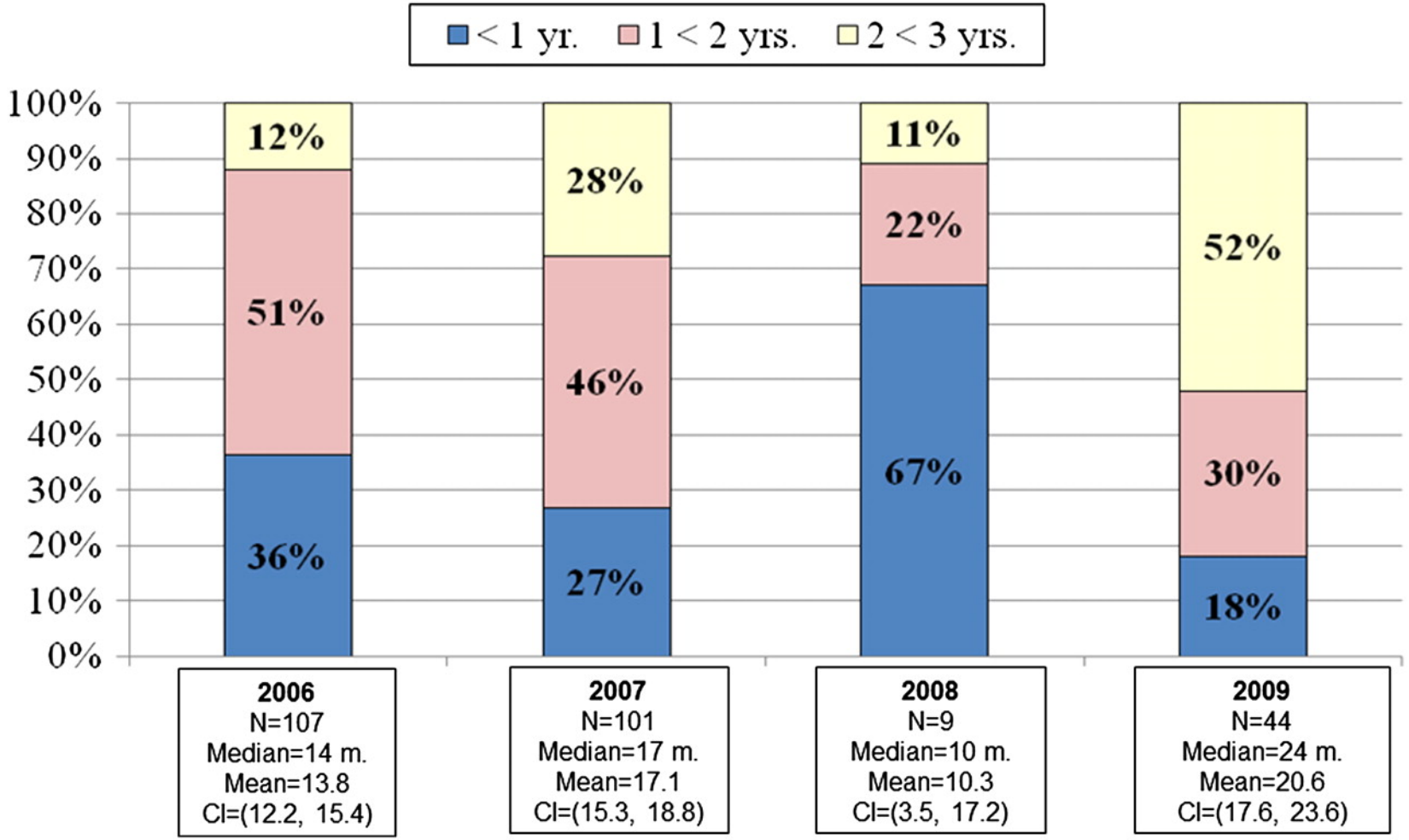
Age distributions for hospitalized rotavirus cases.



Payne D C et al. Clin Infect Dis. 2011;53:245-253

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Potential for perverse outcomes following the introduction of vaccination

Increasing the age at infection could cause problems if disease following infection is more common at older ages

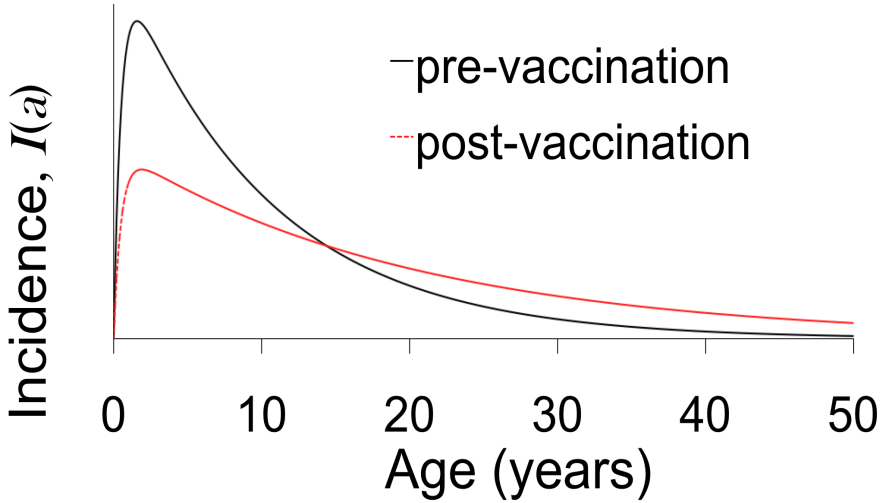
e.g. Congenital Rubella Syndrome (CRS)

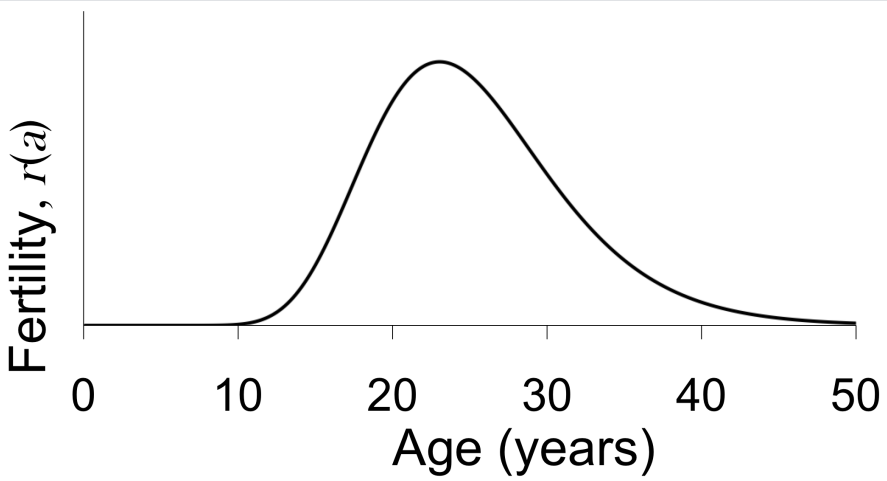
Symptoms: cataracts, brain damage, cardiac defects

Prevalence: Occurs in about 80% of infants born to women infected in the first trimester, dropping thereafter

Rubella is otherwise a mild, often inapparent infection of children

Illustration of perverse outcome in basic SIR model



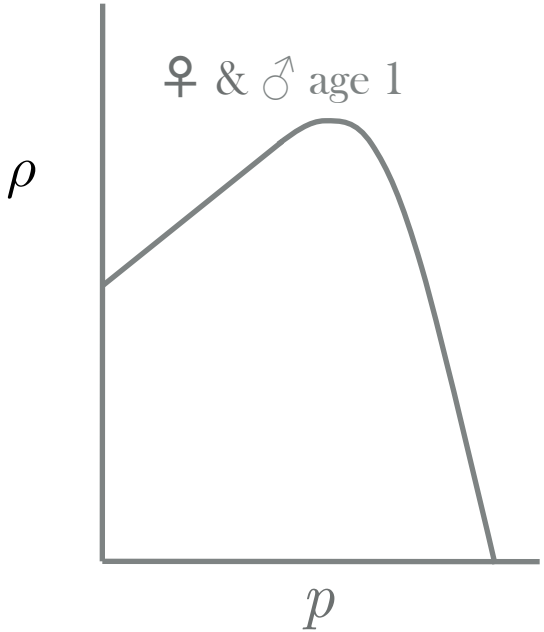


Number of cases of disease pre-vaccination

$$C = \int I(a) r(a)\, da$$

C' is the number of cases post-vaccination

$$\rho = C' / C$$



Anderson & May 1991

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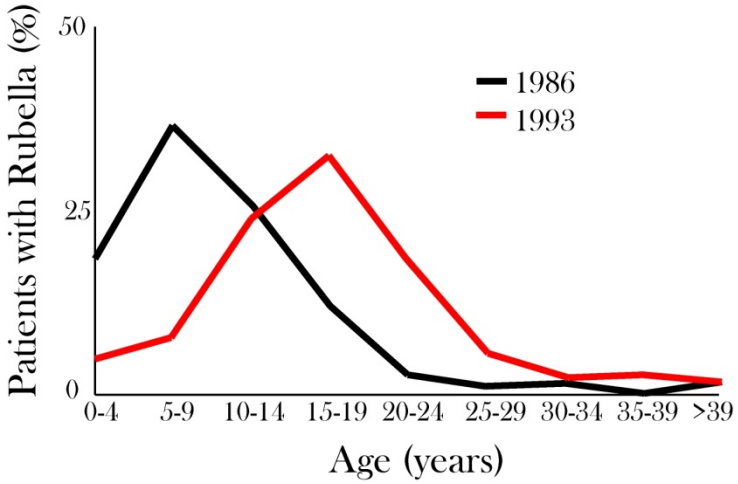
Example of perverse outcome following use of MMR vaccine at low coverage in Greece

MMR for ♀ & ♂ aged 1 year available since 1975 in private sector

MMR only became public policy in 1989

Vaccine coverage < 50% throughout 1980s



Modified from Panagiotopoulos et al 1999

Continued rubella transmission with increased mean age at infection

Epidemic in 1993 leading to 25 cases of CRS (probably largest epidemic in Greece since 1950)

Caveats

$R_0 \neq \frac{L}{A}$ if

i. growing population

$R_0 \simeq \frac{G}{A}$ where G = 1/birth rate

ii. age dependent transmission

e.g. declining with age => $R_0 < \frac{L}{A}$

iii. Spatial, social or genetic heterogeneity

typically proportion susceptible at equilibrium $> 1 / R_0$

and the relationship between R_0 and A is likely to be complex

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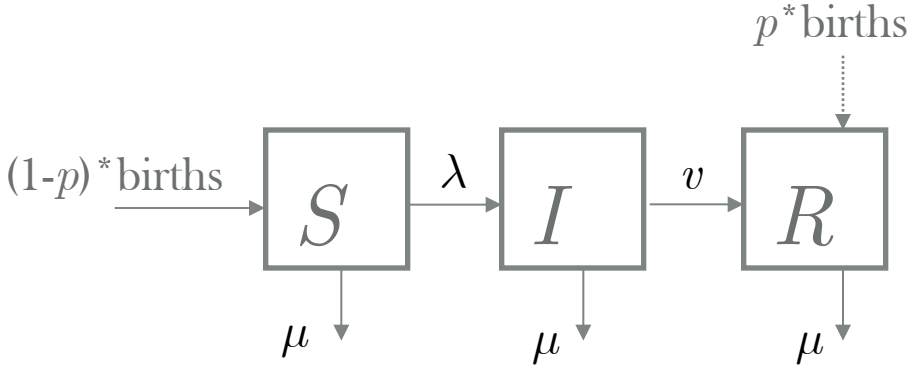
Dynamics: SIR model with vaccination at birth



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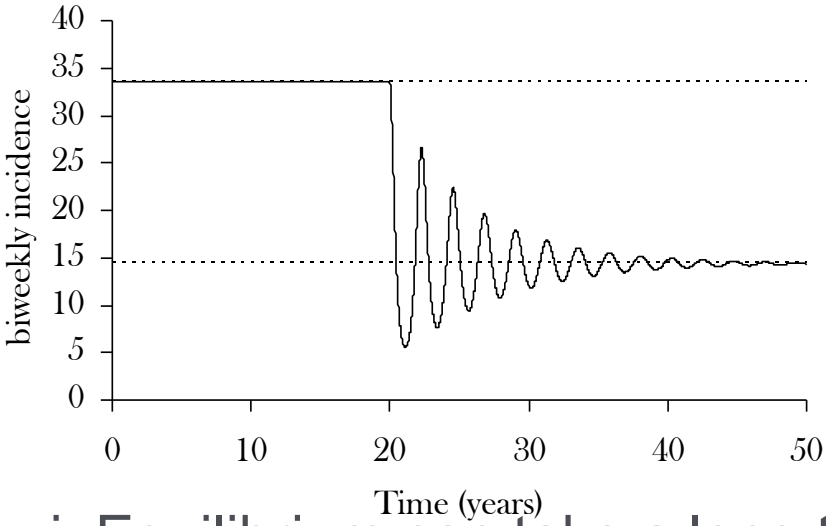
SIR model with vaccination



i. Equilibrium can take a long time to be reached

ii. It is approached via damped oscillations in incidence

iii. The period of these oscillations T and the characteristic damping time can be calculated by local stability analysis of the equilibrium (see Appendix C in Anderson and May 1991)

$$T \simeq 2\pi\sqrt{A'D} \text{ where } D = 1/\upsilon \text{ and } \upsilon >> \mu$$

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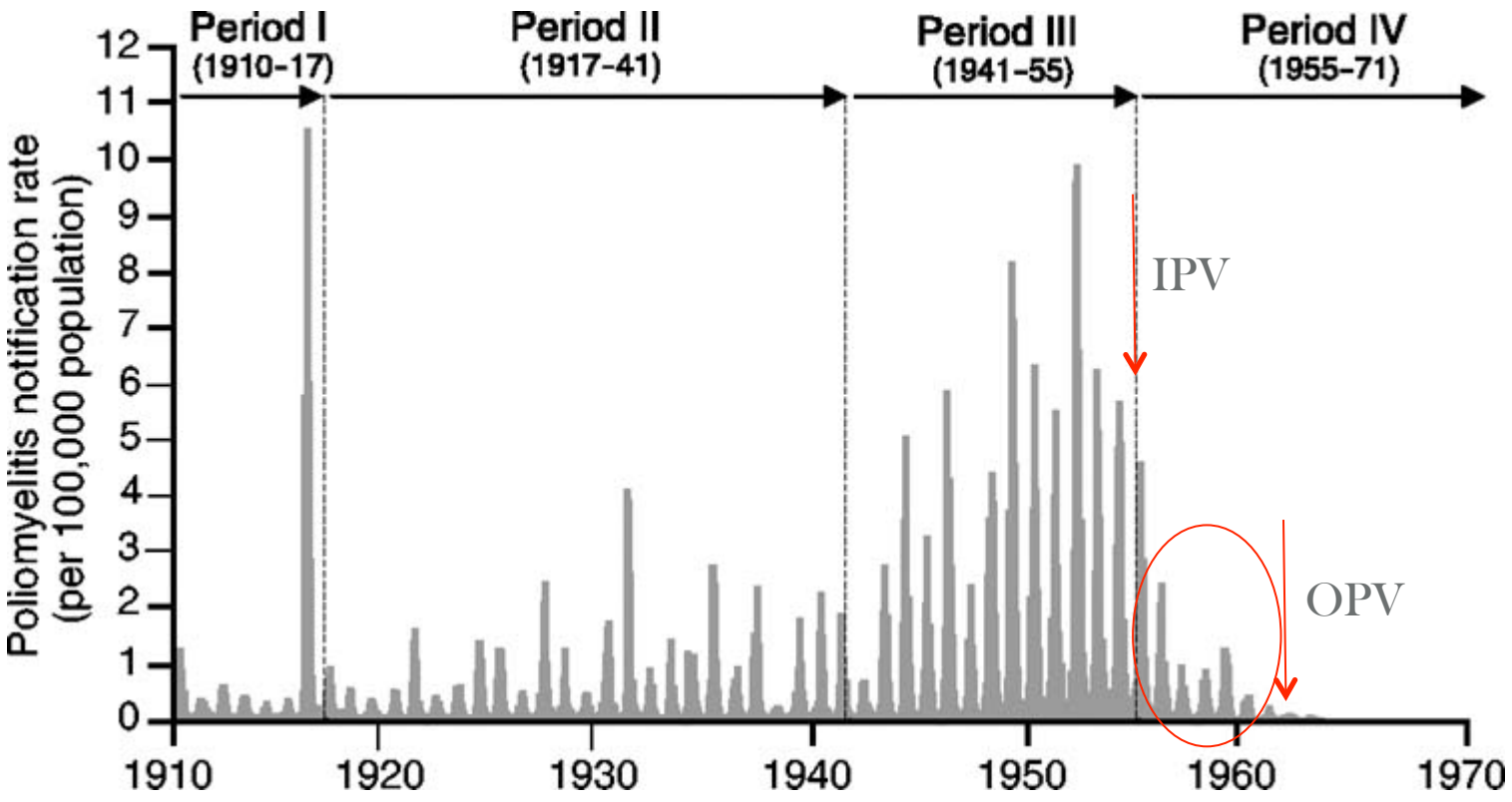
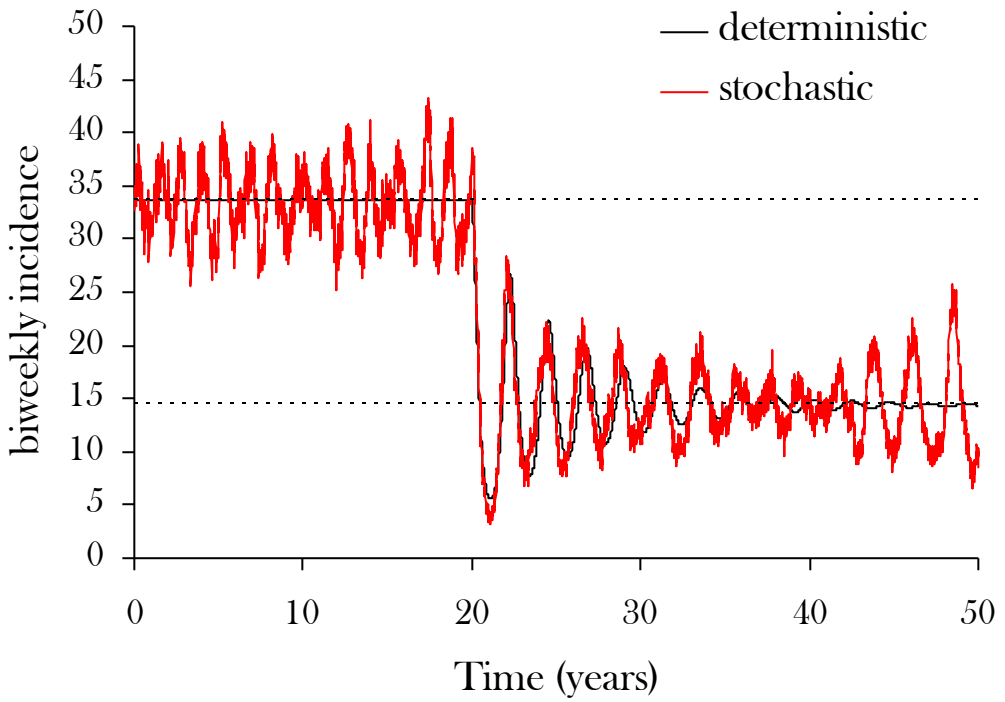
Polio incidence in the United States, 1910-1971



Stochastic SIR model with vaccination



$N = 1$ million

i. Stochastic nature of contact and births ('demographic stochasticity') continually perturbs equilibrium

ii. Oscillations in incidence are sustained with period T as for the deterministic model

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Predicted and observed epidemic period *T*

Infection	T (obs.) (yrs)	T^* (pred.) (yrs)	A (yrs)	$D+D'$ (days)	Place and time
Measles	2	2	4-5	12	England & Wales 1948-68
	1	1-2	2		Yaounde, Cameroon 1968-75
Diptheria	4-6	4-5	11	16-20	England & Wales 1897-1979
Polio	3-5	4-5	11-12	15-23	England & Wales 1948-65
Smallpox	5	4-5	12	10-14	India, 1868-1948

*allowing for a latent period D'
then $T = 2\pi\sqrt{A(D+D')}$

adapted from Anderson & May 1991

Extensions to the basic SIR model with vaccination

Incomplete protection by vaccination

Waning immunity

Age dependent transmission and vaccination

Spatial or social heterogeneity in transmission and targeted vaccination (e.g. ring vaccination or vaccination of high risk groups)

Different infection natural histories (vector-borne diseases, diseases with complex natural histories, etc.)

Transmission blocking vaccines (e.g. malaria)

Vaccination at different ages or at specific times (pulse vaccination)

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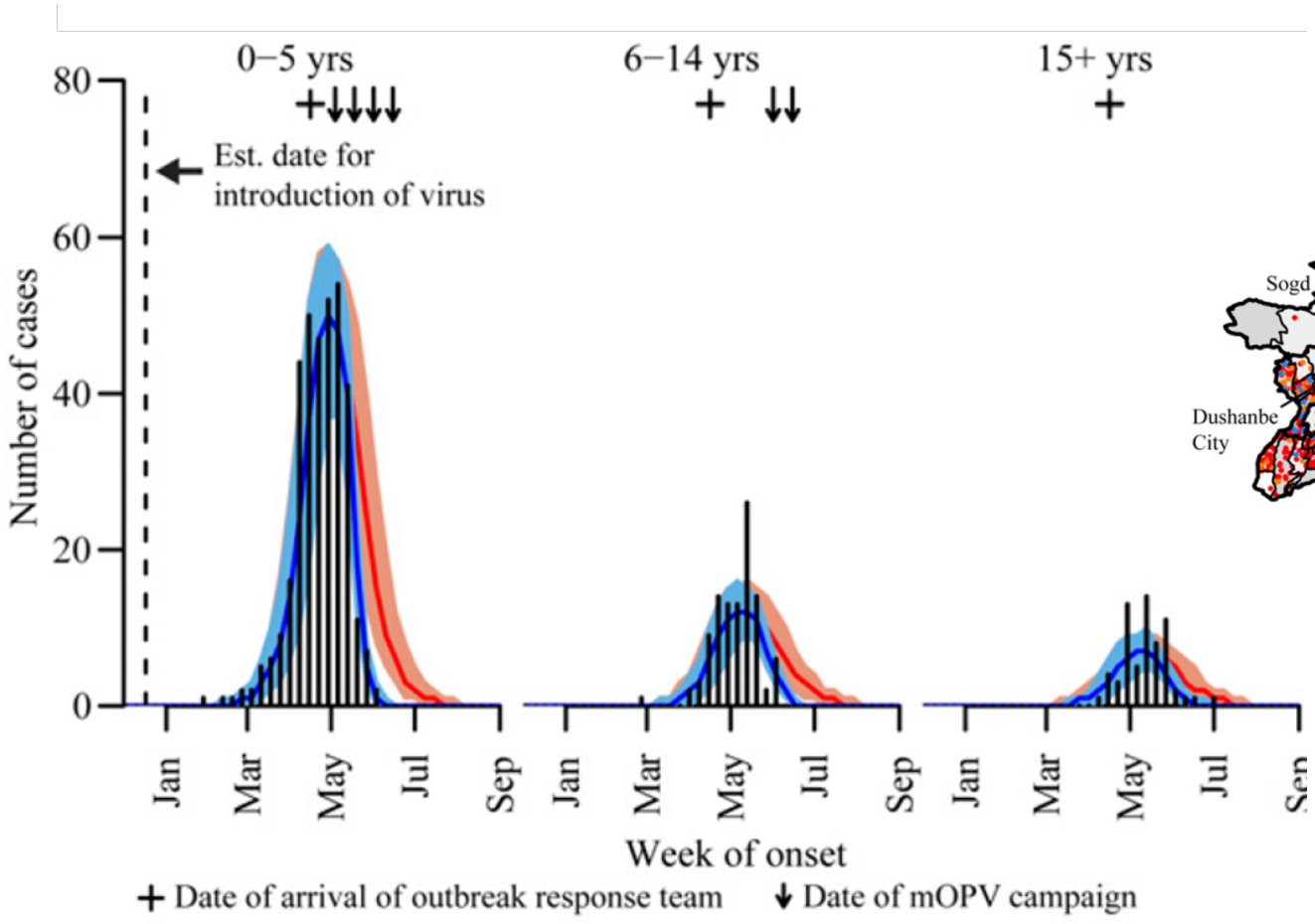
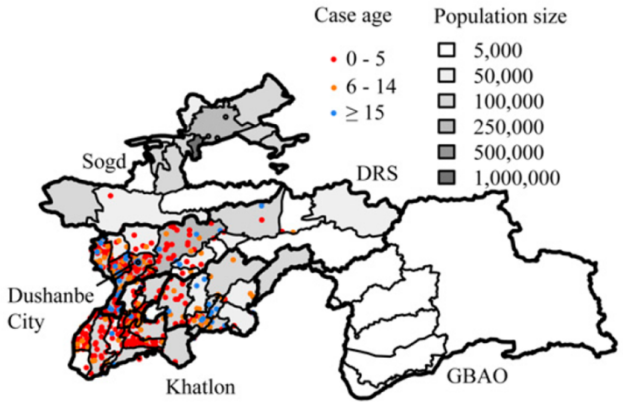
Fitting models to data: Tajikistan polio outbreak, 2010





Blake et al. 2014 *PNAS*

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Fitting models to data: Tajikistan polio outbreak, 2010

Table 1. Estimated parameters (95% CI) for the best-fit poliovirus transmission model to the 2010 Tajikistan outbreak

Parameter	Estimate
Reproduction number for children 0–5 y of age at the start of the outbreak*	2.18 (2.06–2.45)
Reproduction number for older children and adults at the start of the outbreak*	0.46 (0.42–0.52)
Duration of infectiousness, d†	4.6 (3.6–7.0)
Date of first infection in Tajikistan	December 17, 2009 (November 21, 2009 to January 6, 2010)
Vaccine effectiveness (per campaign) (efficacy of mOPV1 × campaign coverage)	69% (55–80%)
Reported case: infection ratio before April 16	1/210 (1/278–1/160)
Percentage of people ≥15 y of age susceptible to infection at the start of the outbreak	2.8% (2.3–3.7%)

AIC = 806.

*Overall reproduction number: 1.88, calculated from the dominant eigenvalue of the next generation matrix.

†Represents duration of infectiousness among asymptomatic infections as these determine the transmission dynamics, representing 99.5% of all infections.

Blake et al. 2014 *PNAS*

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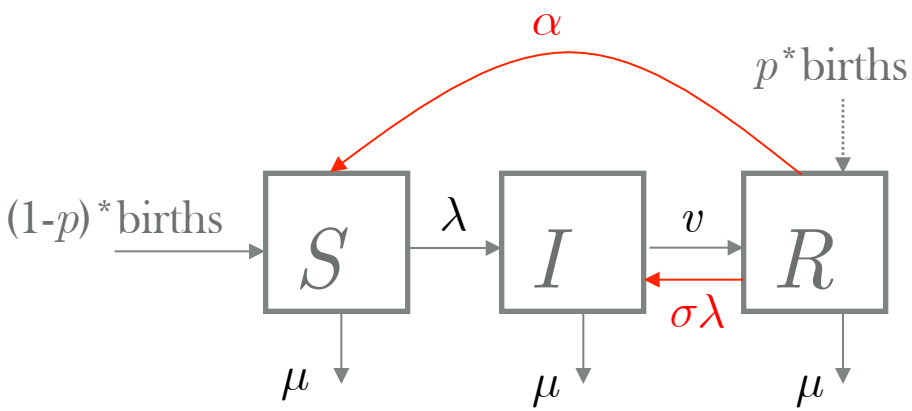
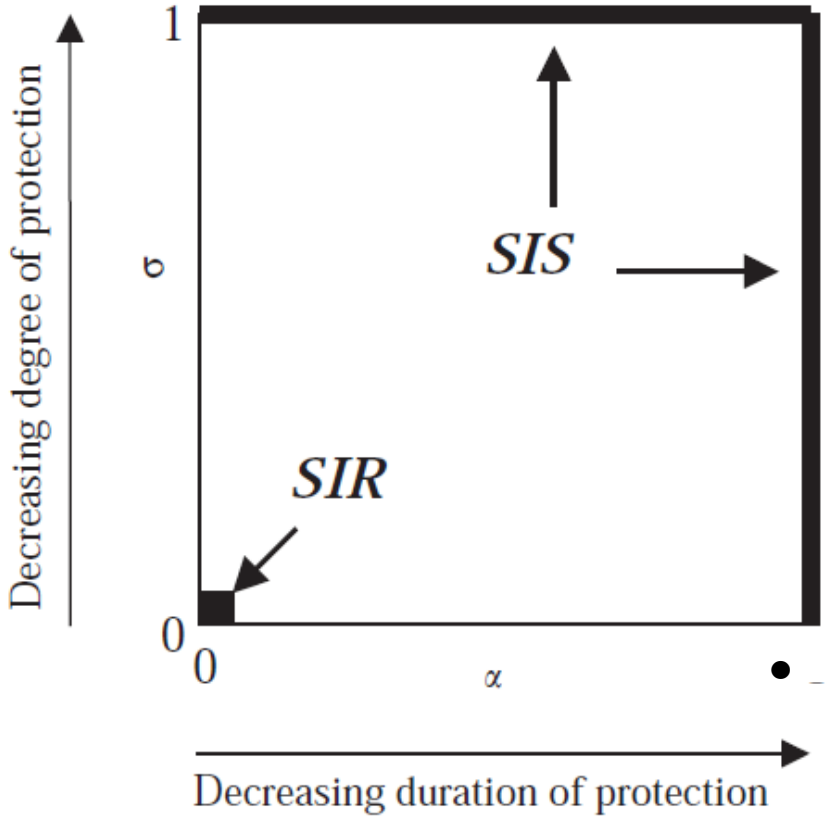
Waning or partial immunity





graph modified from Gomes et al 2004

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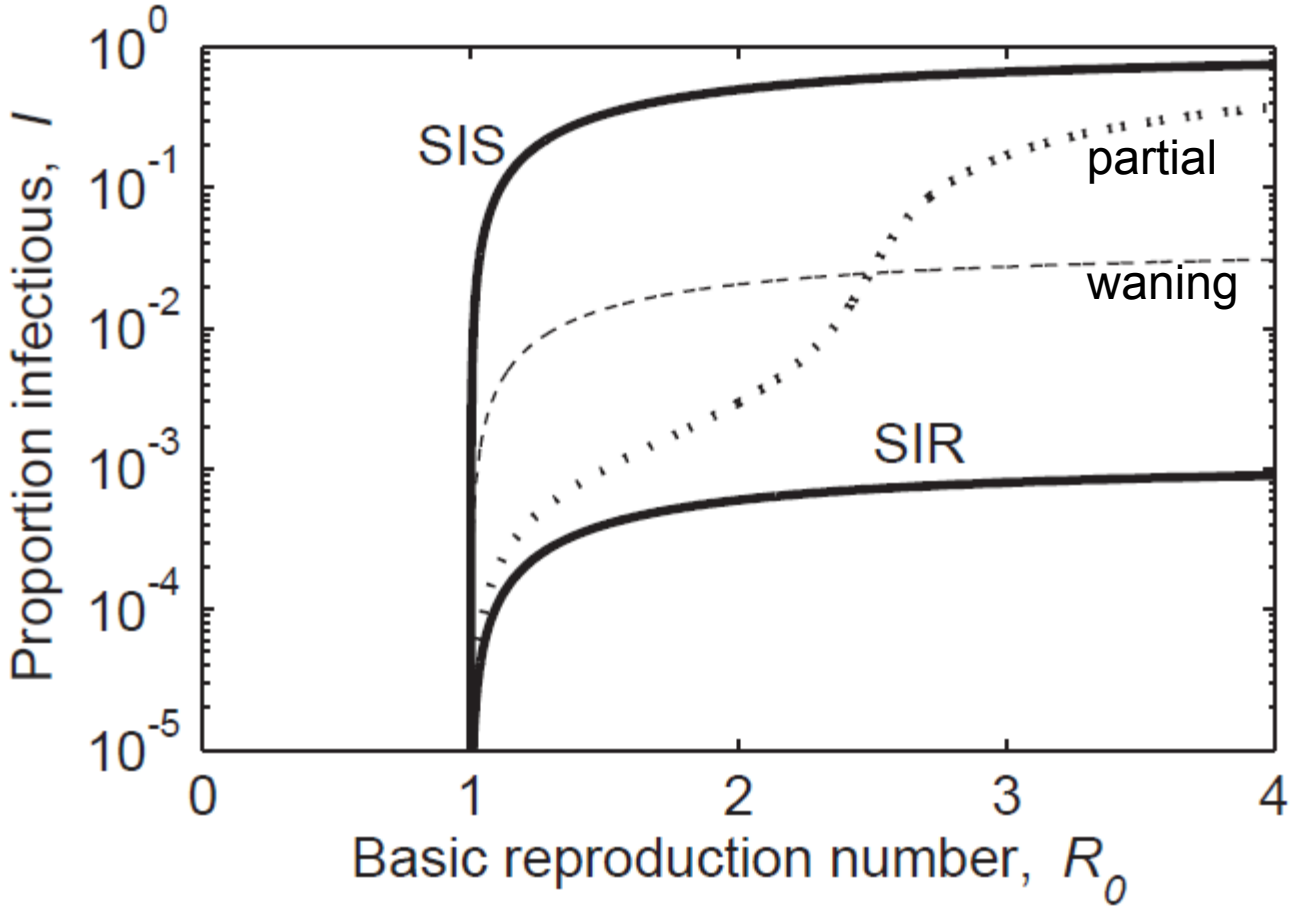
Waning or partial immunity: Statics



from Gomes et al 2004

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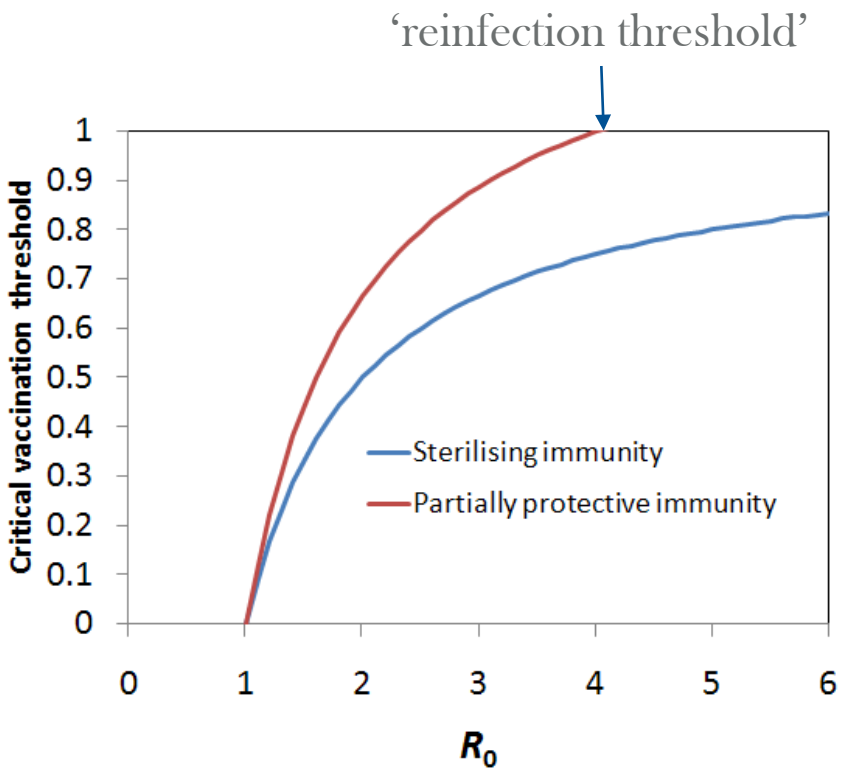
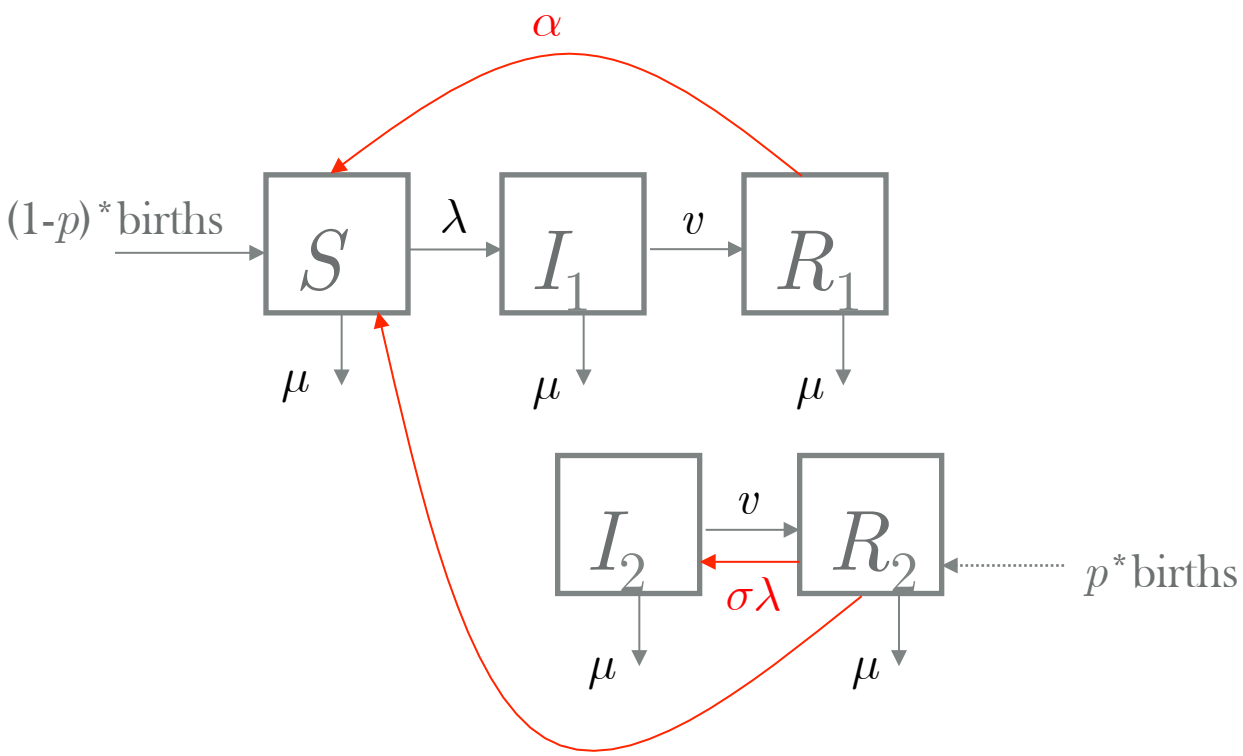
Reinfection threshold with partial immunity



Reinfection threshold $= 1 / \sigma$

e.g. see Gomes et al. 2004

Extending the model further



Etc.

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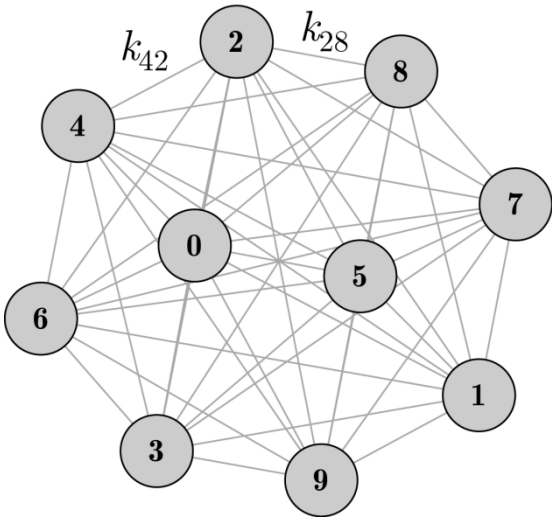
Spatial heterogeneity (1)

$\mathbf{I} = \{I_1, I_2 \ldots I_n\}$ vector of number infected in each of n populations

$\mathbf{I}^{\text{new}} = \mathbf{KI}$ where $\mathbf{K}$ is the 'next generation matrix', such that K_{ij} is the number of new infections in population i from a single infection in population j

$R_0 = \Lambda_{\text{d}}$ where Λ_{d} is the dominant eigenvalue of $\mathbf{K}$



Spatial heterogeneity (2)

Heterogeneity in transmission typically results in a larger R_0 for a fixed mean transmission parameter, and can make disease eradication harder if it is not targeted

For uniform vaccination of all populations it remains the case that

$$p_c = 1 - 1 / R_0$$

Spatial heterogeneity (3)

An optimal strategy minimises the number of vaccine doses required to reach $R_0 \leq 1$

In the cases of spatial heterogeneity in transmission (e.g. due to density effects) it can be shown that

$p_c \geq p_{\text{opt}}$

where the optimal strategy targets populations with the greatest transmission potential until there is no more heterogeneity (for example calculation of p_{opt} see Anderson and May 1991 pp. 307-315)

However, it can be difficult to target vaccination to the correct (high transmission) individuals

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Useful references

Anderson, R. M. & May, R. M. 1991. *Infectious diseases of humans: dynamics and control* (Oxford University Press, Oxford).

Blake, I. M., et al. (2014). "The role of older children and adults in wild poliovirus transmission." Proc Natl Acad Sci U S A. 111(29): 10604-9.

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Gomes, M. G. M., L. J. White, et al. (2004). "Infection, reinfection, and vaccination under suboptimal immune protection: epidemiological perspectives." J Theor Biol 228: 539-549.