Analytic Methods for Infectious Disease Lectures 4: Deterministic Models

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Framework

Deterministic models

- SIR models
- Basic Reproductive Number, R_0
- Endemic versus Epidemic Models

Vaccination

- Simple insights from R_0
- SIR models with vaccination

Two-host models

- General
- Ross-Macdonald Malaria Model

Types of Models: Single Population and Epidemic

- State Space
  - Discrete
  - Continuous
- Index Set (time)
  - Discrete
  - Continuous
- Structure
  - Deterministic
  - Stochastic

Types of Models: continued

- Triplet (State, Index, Structure)
- Many other important parameters and functions of parameters.

Deterministic transmission models

- often based on differential equations (ordinary or partial)
- get the same answer every time
- force of infection and rates act on groups in compartments
- mass action models

Deterministic models

- Advantages:
  - computationally fairly efficient
  - amenable to analytic solutions and insight
- Disadvantages:
  - do not follow individuals
  - always take off if $R > 1$
  - limited exploration of variability

Simple S-I-R model

$$\begin{aligned}
\text{change in susceptibles :} \quad \frac{dS(t)}{dt} &= -\beta \frac{S(t)I(t)}{N} \\
\text{change in infectives :} \quad \frac{dI(t)}{dt} &= \beta \frac{S(t)I(t)}{N} - \nu I(t) \\
\text{change in immunes :} \quad \frac{dR(t)}{dt} &= \nu I(t) \\
N &= S(t) + I(t) + R(t)
\end{aligned}$$

- β =transmission coefficient
- ν = recovery rate

Simple S-I-R model

$$
\begin{aligned}
\frac{dX(t)}{dt} &= -\beta \frac{X(t)Y(t)}{N} \\
\frac{dY(t)}{dt} &= \beta \frac{X(t)Y(t)}{N} - \nu Y(t) \\
\frac{dZ(t)}{dt} &= \nu Y(t)
\end{aligned}
$$

$$
N = X(t) + Y(t) + Z(t)
$$

- β =transmission coefficient
- ν = recovery rate

Model Parameters

- β =transmission coefficient
  - approximately cp = contact rate x transmission probability
- ν = recovery rate
  - exponential assumption
  - d = duration of infection period
  - $\nu = 1/d$
  - If $d = 4 days$, $\nu = 1/4$per day $= 0.25 \text{day}^{-1}$

Basic Reproductive Number, R_0

- the average number of new infectious hosts that a *typical* infectious host will produce during his or her infectious period
- in a large population (absence of density-dependent effects)
- if the population were completely susceptible

Basic Reproductive Number, R_0

- heuristically, thought of as product of
  - contact rate, c
  - transmission probability, p
  - duration of infectious period, d
- $R_0 = cpd$
- $R_0 = \beta/\nu$

(Net or effective) Reproductive Number, R

- if not all susceptible, or after intervention
- need $R > 1$ for an epidemic to take off or sustained transmission
- at equilibrium, $R = 1$
- goal is to reduce R, and if possible < 1
- monitoring R in real-time can aid in evaluating success of intervention

Simple S-I-R model, open population

$$\begin{aligned}
\frac{dS(t)}{dt} &= bN - \beta\frac{SI}{N} - \mu S \\
\frac{dI(t)}{dt} &= \beta\frac{SI}{N} - \nu I - \mu I \\
\frac{dR(t)}{dt} &= \nu I - \mu R \\
\\
N(t) &= S(t) + I(t) + R(t)
\end{aligned}$$

- $\mu =$ death rate, $b =$ birth rate
- no disease-dependent death
- constant population

S-I-R model, open population

$$\begin{aligned}
\frac{dS(t)}{dt} &= bN - \beta\frac{SI}{N} - \mu S \\
\frac{dI(t)}{dt} &= \beta\frac{SI}{N} - (\nu + \mu + \alpha)I \\
\frac{dR(t)}{dt} &= \nu I - \mu R \\
\\
N(t) &= S(t) + I(t) + R(t)
\end{aligned}$$

- μ =death rate, b = birth rate
- α = disease-dependent death rate
- $bN(t)$ = number of births

Basic Reproductive Number, R_0

$$R_0 = \frac{\beta}{\nu + \mu + \alpha}$$

- As $\alpha \uparrow$, $R_0 \downarrow$
- Evolutionary consequences

Simple S-I-R: (C,C,D)

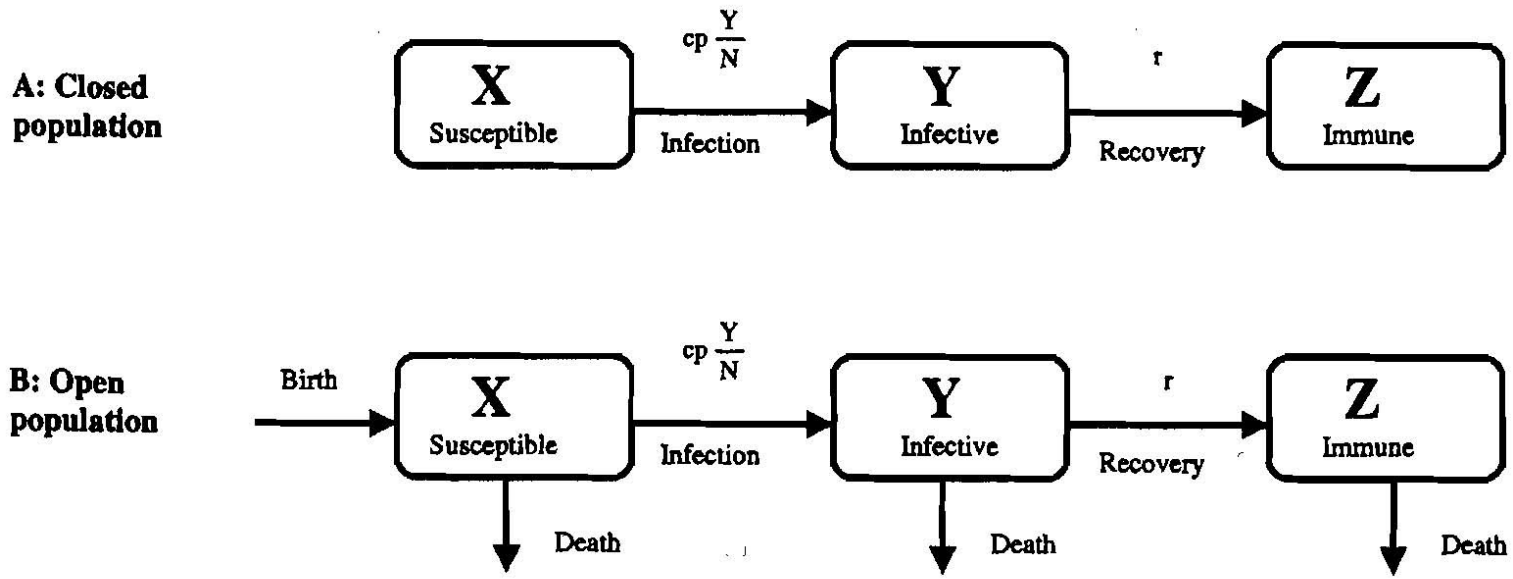
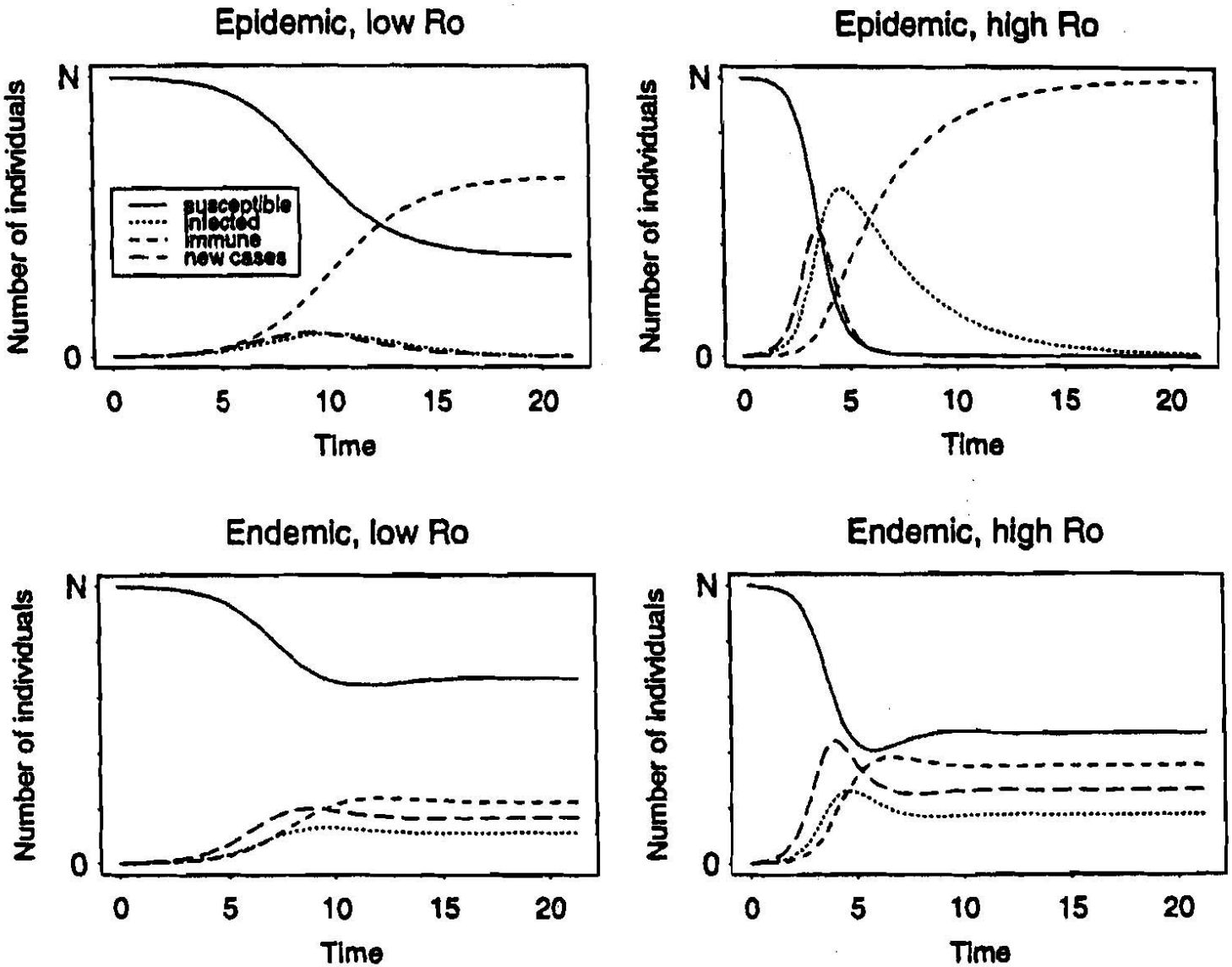


Figure 4–8A,B. Transmission model for an infectious disease in a host population. The three compartments represent susceptible (X), infective (Y), and immune (Z) hosts at time t. The total host population is of size $N = X + Y + Z$. Susceptible hosts become infected at an incidence rate (force of infection) of cpY/N, where c is the contact rate, p is the transmission probability, and Y/N is the prevalence of infective hosts at time t. The rate of recovery is r. Arrows represent transitions in and out of compartments.


Epidemic, low Ro
Epidemic, high Ro
Endemic, low Ro
Endemic, high Ro
Number of individuals
N
0
0
5
10
15
20
Time
susceptible
infected
immune
new cases

Simple S-I-S model

$$\begin{aligned} \frac{dS(t)}{dt} &= -\beta\frac{SI}{N} + \nu I \\ \frac{dI(t)}{dt} &= \beta\frac{SI}{N} - \nu I \\ N(t) &= S(t) + I(t) \end{aligned}$$

- $\nu =$ recovery rate, no immunity
- no disease-dependent death
- constant population
- $R_0 = \beta/\nu$

S-E-I-R model, open population, loss of immunity

$$\begin{aligned}
\text{change in susceptibles :} \quad \frac{dS(t)}{dt} &= bN - \beta\frac{SI}{N} - \mu S + \gamma R \\
\text{change in latents :} \quad \frac{dE(t)}{dt} &= \beta\frac{SI}{N} - (\sigma + \mu)E \\
\text{change in infectives :} \quad \frac{dI(t)}{dt} &= \sigma E - (\nu + \mu + \alpha)I \\
\text{change in immunes :} \quad \frac{dR(t)}{dt} &= \nu I - (\mu + \gamma)R \\
N(t) &= S(t) + E(t) + I(t) + R(t)
\end{aligned}$$

- $\sigma =$ rate of latent compartment becoming infective
- $\gamma =$ rate of loss of immunity

Basic Reproductive Number, R_0

$$R_0 = \frac{\sigma}{\sigma + \mu} \times \frac{\beta}{\nu + \mu + \alpha}$$

- What is $\frac{\sigma}{\sigma+\mu}$?
- What is $\frac{\alpha}{\alpha+\nu}$ or $\frac{\alpha}{\alpha+\nu+\mu}$?
- Relation to the case-fatality rate

Berkeley Madonna

- Introduction
- Simple models

Attack rate and R_0

$$\begin{aligned} \text{change in susceptibles}: \quad \frac{dS(t)}{dt} &= -\beta \frac{S(t)I(t)}{N} \qquad (1) \\ \text{change in immunes}: \quad \frac{dR(t)}{dt} &= \nu I(t) \\ S(0) &\approx N, \qquad R(0) = 0. \end{aligned}$$

Substitute for $I(t)$ in equation 1

$$\begin{aligned} \frac{dS(t)}{dt} &= -\frac{\beta}{\nu} \frac{S(t)R(t)dt}{N} \\ \frac{dS(t)}{S(t)} dt &= -R_0 \frac{R(t)dt}{N} \end{aligned}$$

Attack rate and R_0

$$\int_0^T \frac{dS(t)}{S(t)} = -\int_0^T R_0 \frac{R(t)dt}{N}$$

$$\log \frac{S(T)}{S(0)} = -R_0 \frac{(R(T) - R(0))}{N}$$

$$1 - AR(T) = \exp\{-R_0 AR(T)\}$$

$$AR(T) = 1 - \exp\{-R_0 AR(T)\}$$

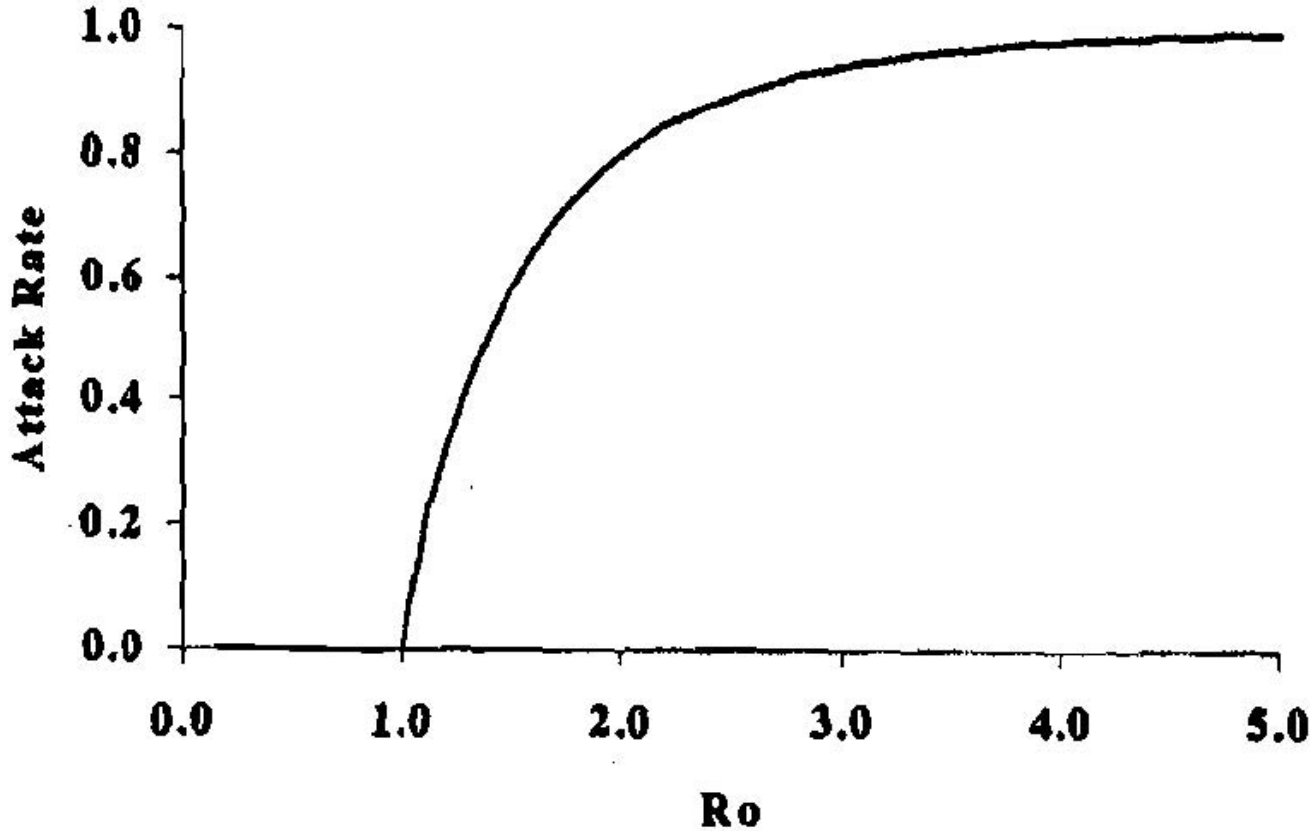


Figure 4–10. The attack rate as a function of the basic reproductive number, R_0.

Vaccination

- $x =$ proportion susceptible
- $1 - x =$ proportion immune
- $f =$ proportion vaccinated with completely protective vaccine
- simple random mixing, homogeneous population

$$\begin{aligned} R &= R_0 x \\ R &= R_0(1-f) < 1 \\ f &> 1 - \frac{1}{R_0} \text{ for } R < 1. \end{aligned}$$

Example: Threshold Vaccination

- $R_0 = 3$
- $f =$ proportion vaccinated with completely protective vaccine
- simple random mixing, homogeneous population

$$f \quad > \quad 1 - \frac{1}{3} = 0.67 \text{ for } R < 1.$$

- Caveats....

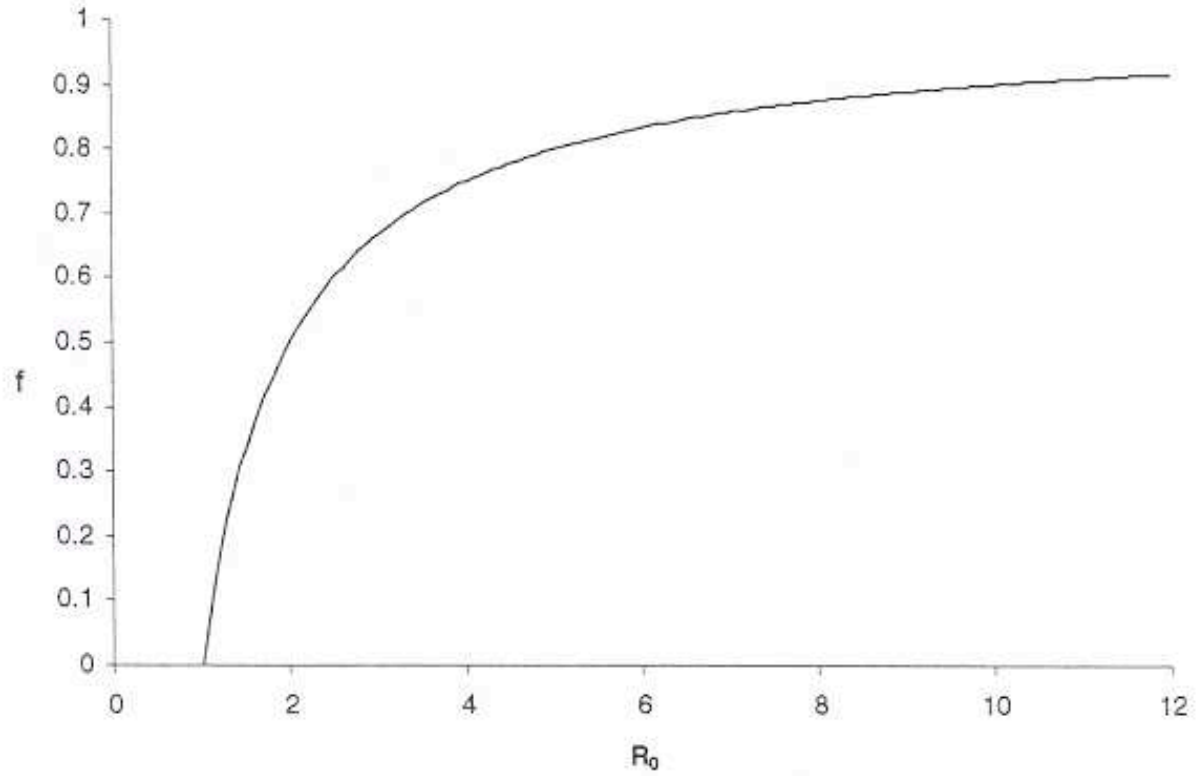


Figure 4–4. The fraction, f, of a population needed to be vaccinated with a completely protective vaccine to eliminate transmission as a function of R_0, the basic reproductive number.

Threshold vaccination: all-or-none

- f = proportion vaccinated
- h = proportion vaccinated who are completely protected
- $1-h$ = proportion of complete failures in vaccinated
- simple random mixing, homogeneous population

$$\begin{aligned} R &= R_0(1-hf) \\ f &> \frac{1-1/R_0}{h} \quad \text{for} \quad R<1. \end{aligned}$$

Example: Threshold Vaccination: all-or-none

- $R_0 = 3$
- $f =$ proportion vaccinated
- $h = 0.85$ proportion of vaccinated completely protected (VE=0.85)
- $1 - h = 0.15$ proportion of failures in vaccinated
- simple random mixing, homogeneous population

$$f > \frac{1 - 1/3}{0.85} = \frac{0.67}{0.85} = 0.79 \quad \text{for } R < 1.$$

- If $h < 0.60$, then $f > 1.0$

Threshold vaccination: leaky

- $\theta =$ proportion residual infection probability ($\mathrm{VE}_S = 1 - \theta$)
- $\phi =$ proportion residual transmission from infective ($\mathrm{VE}_I = 1 - \phi$)
- Assume everyone vaccinated
- simple random mixing, homogeneous population

$$\begin{aligned} R &= \theta\phi R_0 < 1 \\ \theta\phi &< \frac{1}{R_0} \quad \text{for} \quad R < 1. \\ (1 - \mathrm{VE}_S)(1 - \mathrm{VE}_I) &< \frac{1}{R_0} \quad \text{for} \quad R < 1. \end{aligned}$$

- symmetry of VE_S and VE_I
- heterogeneous and more complex expressions possible

Simple S-I-R model: all-or-none vaccination

$$
\begin{aligned}
\frac{dS(t)}{dt} &= -\beta \frac{S(t)I(t)}{N} \\
\frac{dI(t)}{dt} &= \beta \frac{S(t)I(t)}{N} - \nu I(t) \\
\frac{dR(t)}{dt} &= \nu I(t)
\end{aligned}
$$

$$
\begin{aligned}
S(0) &= (1-f)N(0) \\
R(0) &= fN(0) \\
N &= S(t) + I(t) + R(t)
\end{aligned}
$$

- f = fraction vaccinated with a completely protective vaccine

S-I-R model, open, all-or-none

$$\begin{aligned}
\frac{dS(t)}{dt} &= (1-f)bN - \beta\frac{SI}{N} - \mu S \\
\frac{dI(t)}{dt} &= \beta\frac{SI}{N} - (\nu+\mu+\alpha)I \\
\frac{dR(t)}{dt} &= fbN + \nu I - \mu R
\end{aligned}$$

$$\begin{aligned}
S(0) &= (1-f)N(0) \\
R(0) &= fN(0) \\
N(t) &= S(t) + I(t) + R(t)
\end{aligned}$$

- μ =death rate, α = disease-dependent death rate
- $bN(t)$ = births

S-I-R model, open, leaky

$$
\begin{aligned}
\frac{dS_0(t)}{dt} &= (1-f)bN - \beta\frac{S_0[I_0+\phi I_1]}{N} - \mu S_0 \\
\frac{dS_1(t)}{dt} &= fbN - \beta\frac{\theta S_1[I_0+\phi I_1]}{N} - \mu S_1 \\
\frac{dI_0(t)}{dt} &= \beta\frac{S_0[I_0+\phi I_1]}{N} - (\nu+\mu+\alpha)I_0 \\
\frac{dI_1(t)}{dt} &= \beta\frac{\theta S_1[I_0+\phi I_1]}{N} - (\nu+\mu+\alpha)I_1 \\
\frac{dR(t)}{dt} &= \nu[I_0+I_1] - \mu R
\end{aligned}
$$

$$
\begin{aligned}
S_0(0) &= (1-f)N(0) \\
S_1(0) &= fN(0) \\
N(t) &= S_0(t)+S_1(t)+I_0(t)+I_1(t)+R(t)
\end{aligned}
$$

Anderson and May (1991)

22 *Infectious diseases of humans*

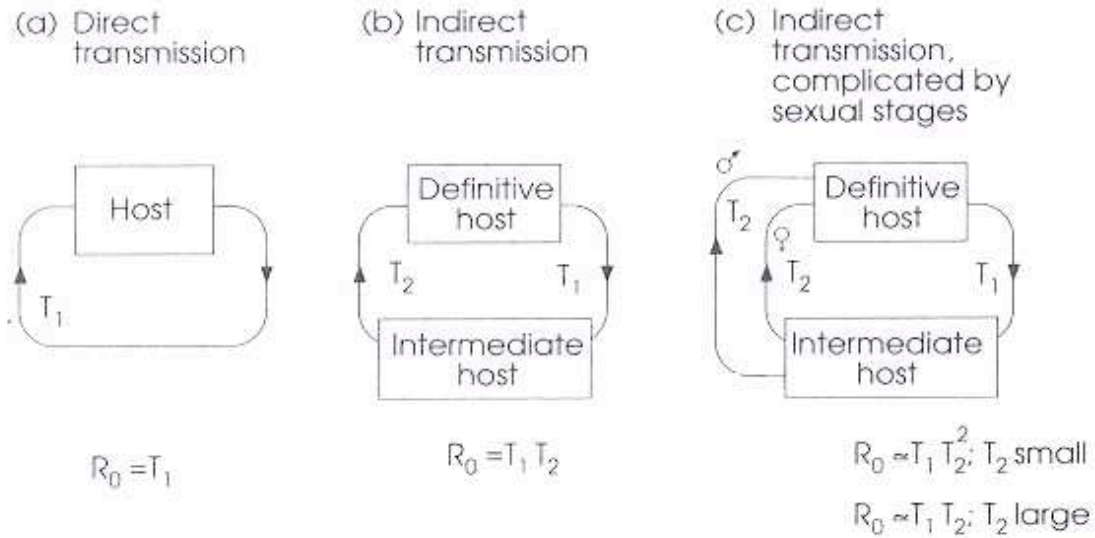


Fig. 2.4. Diagrammatic representation of direct and indirect transmission and the complications introduced by the sexual stages of macroparasitic organisms. The quantities T_1 and T_2 denote summary transmission parameters for the flow of parasites from definitive host to intermediate host (T_1) and intermediate host to definitive host (T_2). (See text for details.).

Malaria cycle

- Human malaria: *Plasmodium falciparum*, *P. vivax, P. malariae*, *P. ovale*.
- Transmitted by female anopheline mosquitoes
- Mosquitos inject sporozoites into humans
- Sporozoites migrate to the liver, develop via asexual reproduction
- Merozoites invade blood cells and burst cells
- Sometimes develop into gametocytes, ingested by mosquitoes
- Micro- and macrogametes (male and female) in mosquitoes for sexual cycle
- Sporozoites in salivary glands .....

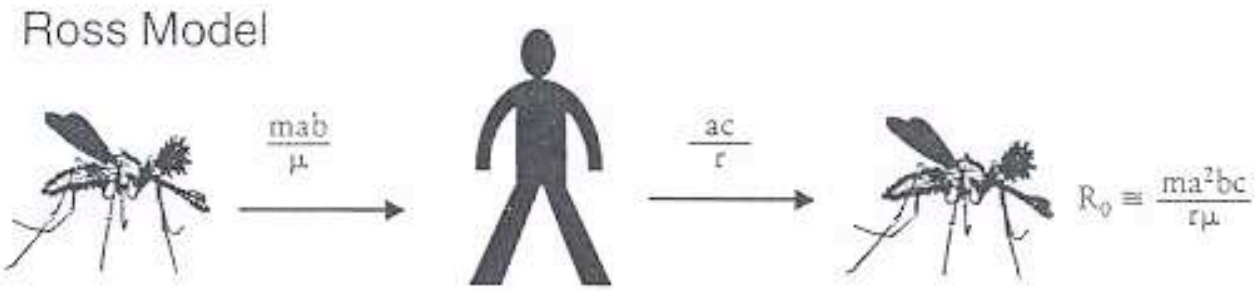
Ross and Macdonald

- Sir Ronald Ross 1916
- 2nd Nobel Prize in Medicine : elucidation of mosquitos as malaria transmitters
- George Macdonald (1903–1967)
- Transmission models of malaria

CONCEPTS OF TRANSMISSION AND DYNAMICS

Table 4–1 Quantities for the R_0 for Malaria

Term	Meaning
N	the size of the human population
M	the size of the female mosquito population
m	= M/N, the number of female mosquitoes per human host
a	the rate of biting on humans by a single mosquito (number of bites per unit time)
b	the transmission probability from an infective mosquito to a human
c	the transmission probability from an infective human to a mosquito
r	the recovery rate for humans
μ	the mortality rate for mosquitoes
τ	the latent period of the malaria parasite in the mosquito



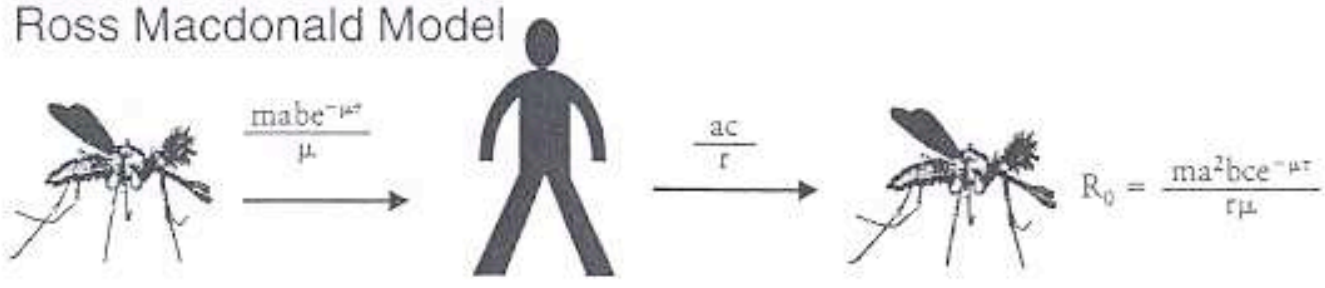


Figure 4–6. R_0 expression for two different malaria models.
Source: Mosquito image used with permission from the American Museum of Natural History.

Simple Malaria Model

- Simple model without incubation period in the mosquito, no immunity

$$\text{Infected humans} \quad \frac{dx}{dt} = (abM/N)y(1-x) - rx$$

$$=$$

$$\text{Infected mosquitoes} \quad \frac{dy}{dt} = acx(1-y) - \mu y$$

$$R_0 = \frac{ma^2bc}{r\mu}$$

Malaria R_0 with extrinsic incubation period

- With extrinsic incubation period τ:

$$R_0 = \frac{ma^2bce^{-\mu\tau}}{r\mu}$$

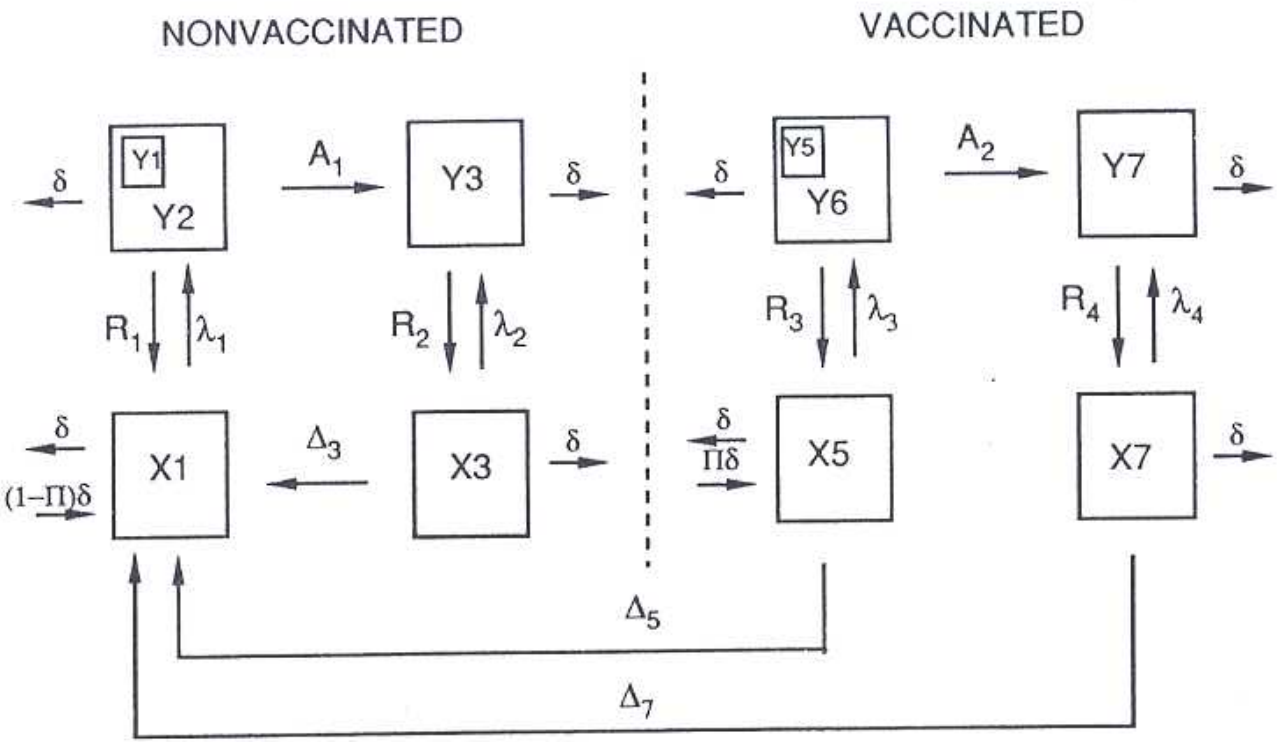


FIG. 1. Generalized transitions among epidemiologic categories in the human vaccinated and unvaccinated compartments for vaccines dependent on natural boosting. (Modified from [51, 68].)

Modeling Chickenpox Vaccination in U.S.

- early 1990's, pre-licensure
- Problem: What would the effect of childhood vaccination against chickenpox be at the population level?
- Worries: partially protective vaccine, waning immunity, low coverage
- Serious sequelae more common in older age groups and infants
- Halloran, Cochi, Lieu, Wharton, Fehrs, AJE 140:81-104 (1994)

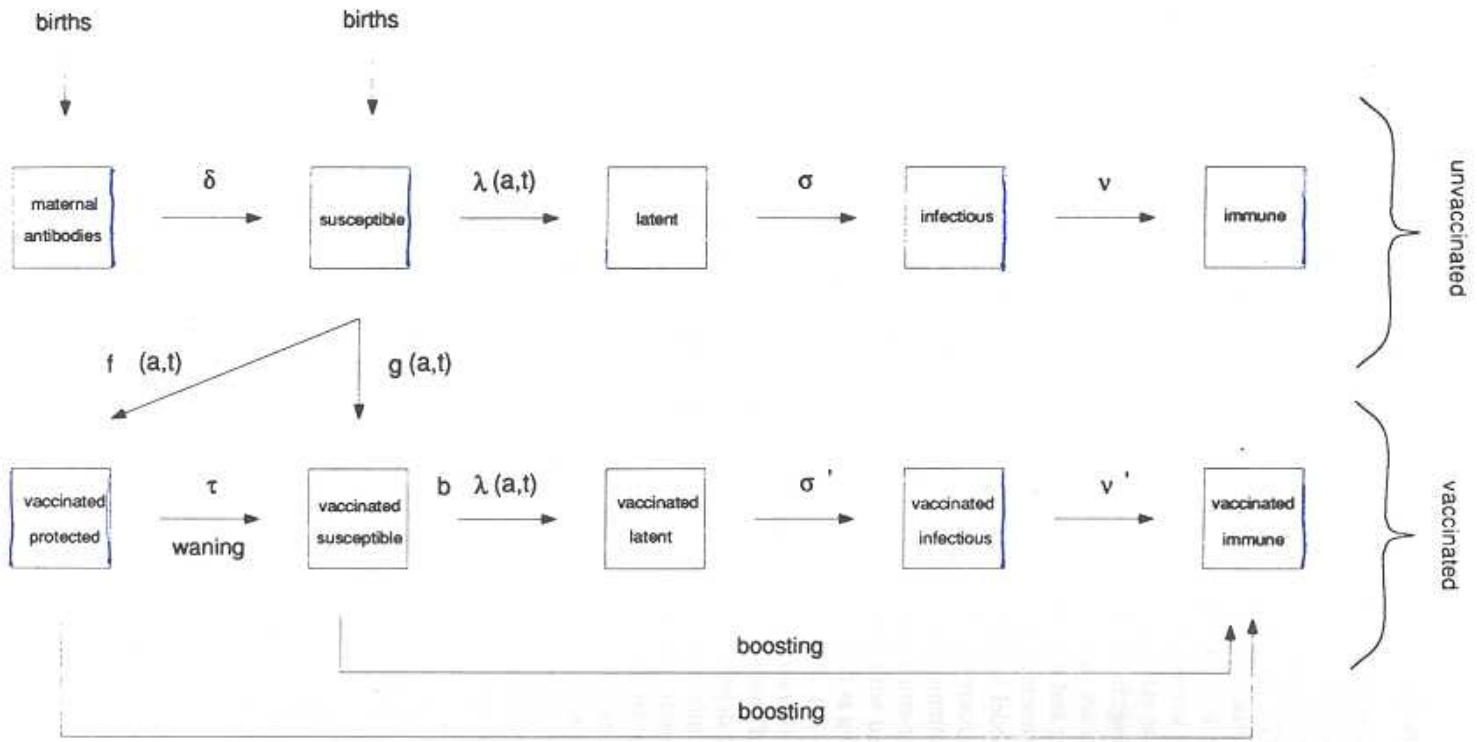


FIGURE 2. The unvaccinated and vaccinated compartments of the varicella transmission model. All compartments are time- and age-dependent. The rate of infection $\lambda(a, t)$ is a function of the number of infective people in the population at any time. The parameter b is the relative residual susceptibility of a vaccinated susceptible. The parameter τ is the rate of waning of vaccine-induced protection against chickenpox. The rates σ, ν and σ', ν' are the rates of becoming infectious and of developing immunity in the unvaccinated and vaccinated compartments, respectively. $f(a, t)$ is the proportion of those vaccinated who acquire complete protection against disease, and $g(a, t)$ is the proportion who remain at least partially susceptible.

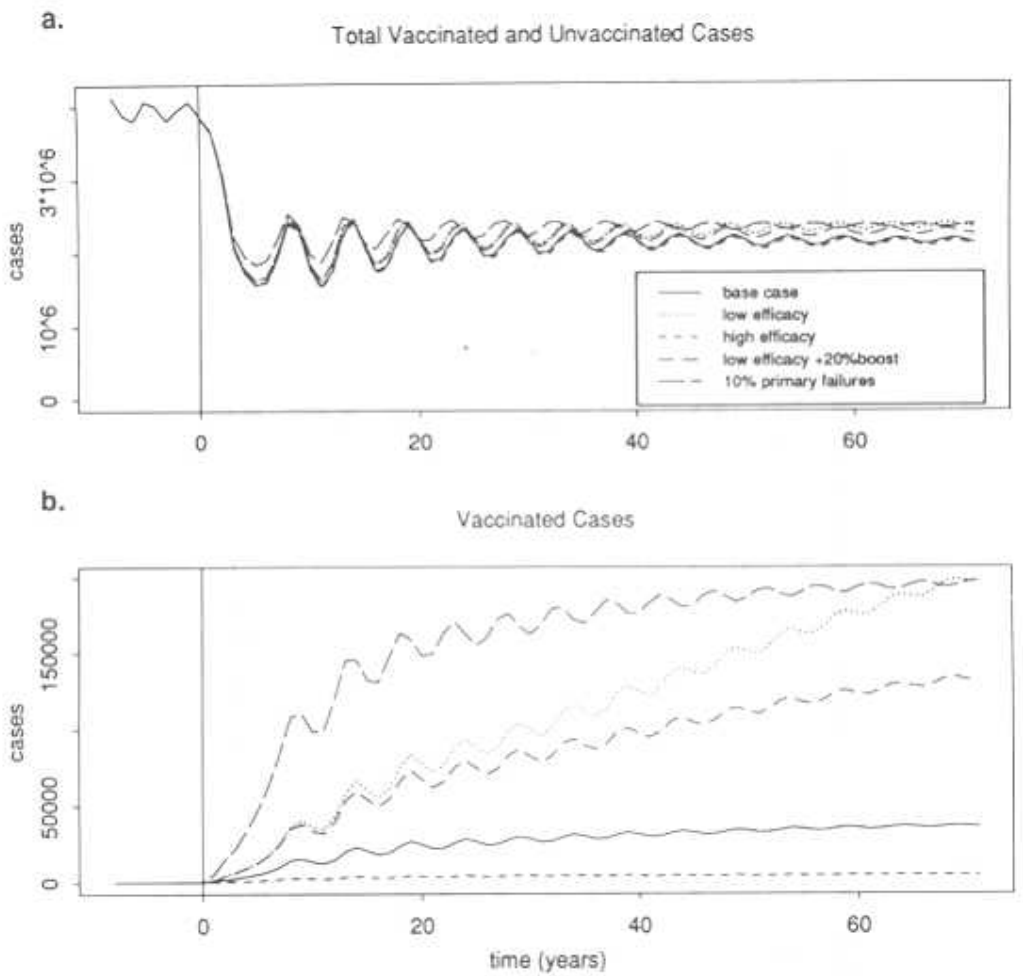


FIGURE 3. Comparison of the number of varicella cases over time under five vaccine models at 50% coverage of preschool children (without the catch-up program). *a*, total cases; *b*, vaccinated cases. The numbers of cases for the low efficacy model with 20% boosting and the base case vaccine model with unchanged infectiousness always lay somewhere between those produced by the high efficacy and low efficacy vaccine models. The range bounded by the results using these latter two vaccine models is given in table 3. With 10% primary failures, the number of cases was sufficiently higher to warrant reporting it separately.

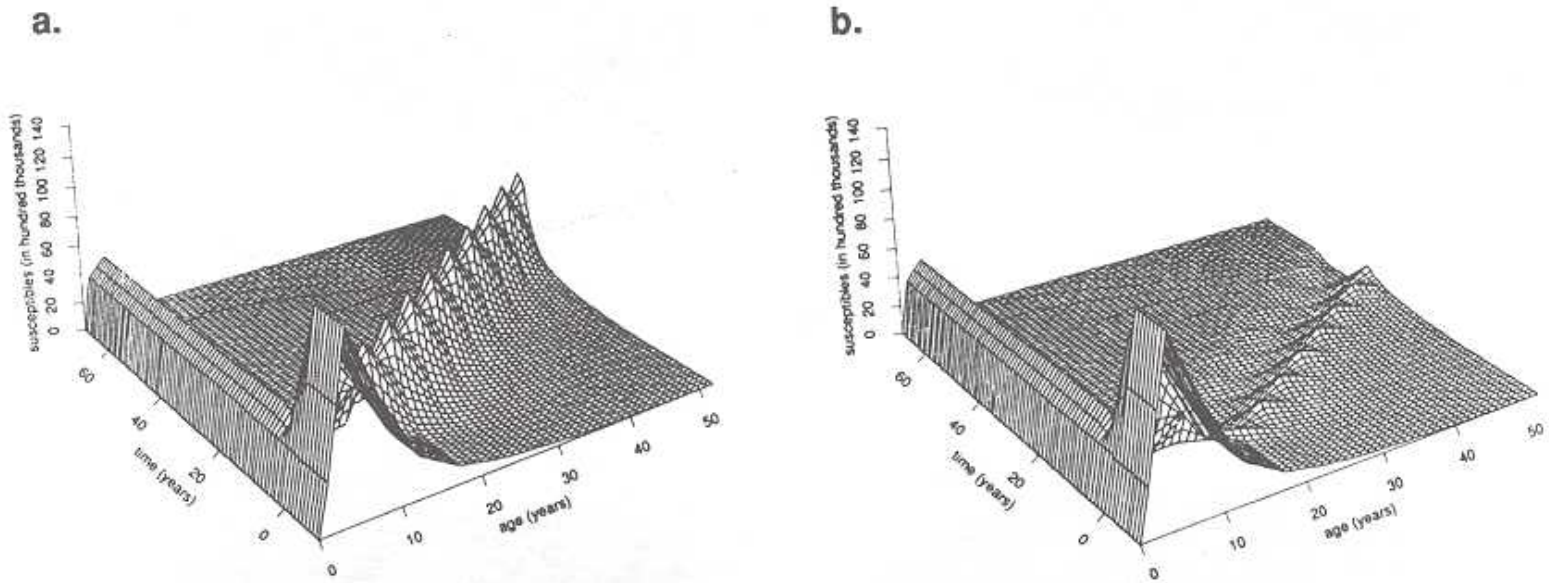


FIGURE 6. Age-specific number of unvaccinated persons susceptible to varicella over time without (*a*) and with (*b*) implementation of a catch-up program in 12-year-olds, using the base case vaccine model with 97% coverage. The three-dimensional plots were made from the total output summed for the age groups <1, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, and 50–54 years. For improved readability, the surface plots are shown rather than columns. To preserve a reasonable scale on the plots, only the age groups up to 50–54 years are shown.