Population models of infection transmission

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Spread of parasite in host population is similar to colonization/survival in fragmented environment (meta-population view). But here host population (environment) plays active dynamic role.

Questions to answer:

- Will infection spread
- What fraction of host population is affected
- Prevalence of endemic disease
- Control and eradication
- The effect of age structure

Outline

Basic SIR methodology of infection transmission

a. BRN: its meaning and implications
b. Control strategies: treatment, vaccination/culling, quarantine
c. Extension to multiple-host transmission: zoonotics and vector-born diseases?
d. Age structured populations

Simple SIR and SEIR

Basic host strata:

- S – susceptible
- E – exposed (non-infectious)
- I -infectious
- R – recovered

- Total population: $S+I+R=N$, or $S+E+I+R=N$

Compartmental diagrams with arrows indicating transitions from one group to another

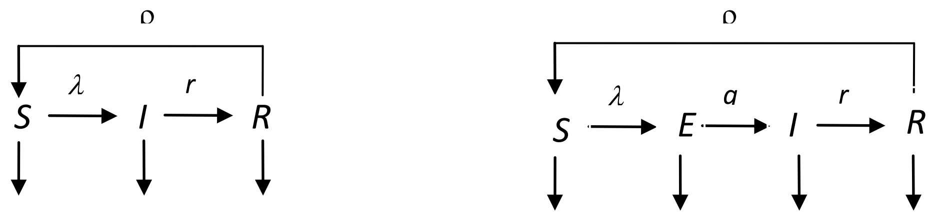


Figure 1: SIR and SEIR diagrams

Parameters:

Table 1

λ	-	Force of infection
q	-	1/"latency period"
r	-	recovery tare (= 1/"mean duration")
μ	-	Mortality (natural and/or disease associated)
ρ	-	Immune loss

Continuous DE models

$$\text{(SIR)}\quad \begin{aligned} \frac{dS}{dt} &= -(\lambda+\mu)S+\rho R+B \\ \frac{dI}{dt} &= \lambda S-(r+\mu)I \\ \frac{dR}{dt} &= rI-(\rho+\mu)R \end{aligned} \qquad \text{(SEIR)}\quad \begin{aligned} \frac{dS}{dt} &= -(\lambda+\mu)S+\rho R+B \\ \frac{dE}{dt} &= \lambda S-(q+\mu)E \\ \frac{dI}{dt} &= qE-(r+\mu)I \\ \frac{dR}{dt} &= rI-(\rho+\mu)R \end{aligned} \tag{1}$$

B – source of susceptible. Force of infection λ depends on specifics of transmission.

Example: $\lambda=\beta*\frac{I}{N}*S$ - with transmission coefficient $\beta=\omega b$ ("mean contact rate ω" x "probability of infection/contact"), I/N - infective fraction of contacts. The key dimensionless parameter is BRN:

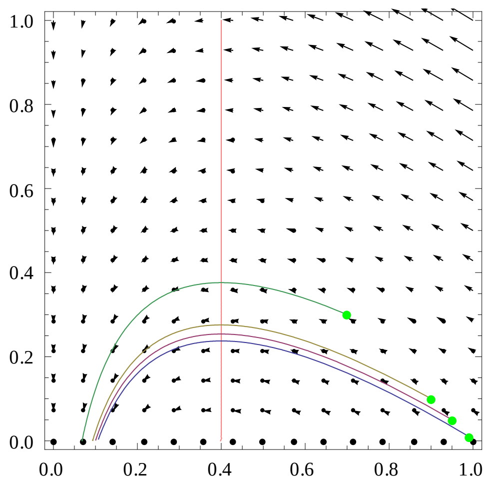
$$R_0 = \frac{\beta}{(r+\mu)} \text{ - transmission/"recovery +loss"} \quad (2)$$

SIR with permanent immunity ($\rho = 0$): outbreaks

BRN determines outbreak ($R_0 > 1$), or elimination ($R_0 < 1$). Jacobian matrix at "0" initial state $S_0 \approx 1; I_0 \approx 0$:

$$A = \begin{bmatrix} -\beta I & -\beta S \\ \beta I & \beta S - r \end{bmatrix} \approx r \begin{bmatrix} 0 & -R_0 \\ 0 & R_0 - 1 \end{bmatrix} \quad (3)$$

Hence initial growth rate of $I(t) \approx I_0 e^{(R_0-1)rt}$



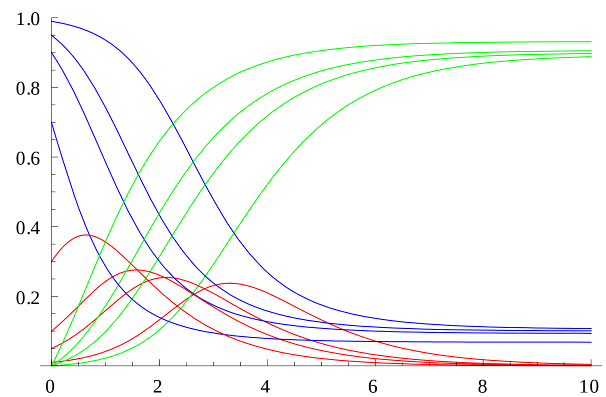


Figure 2: Phase-plane and solution curves at several initial values I_0

Analytic solution for prevalence DS:

$$\begin{cases} \dot{S} = -\beta SI \\ \dot{I} = \beta SI - rI \end{cases} \Rightarrow \frac{dI}{dS} = \frac{\beta S - r}{-\beta S} \Rightarrow \boxed{I(S) = (1-S) + \frac{1}{R_0} \ln(S/S_0)}$$

Each history reaches its peak-value I_M at time t_M , and leaves S^* - non-infected susceptible fraction, as $t \to \infty$. All three $I_M; t_M; S^*$ depend on BRN R_0 and initial state I_0 , they can be computed analytically

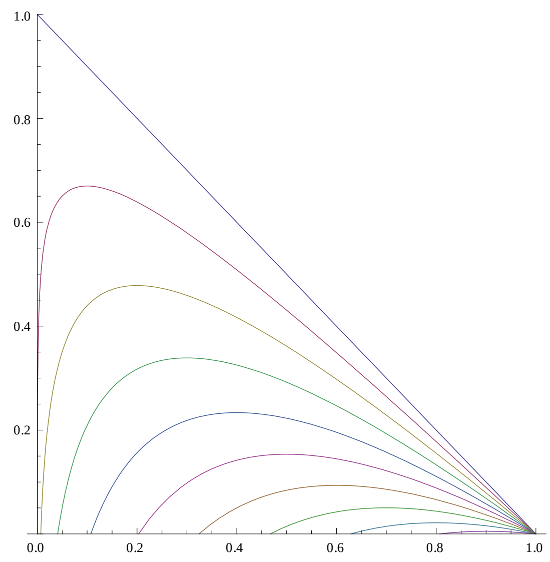


Figure 3: SI-phase trajectories for increasing $1 < R_0 < \infty$

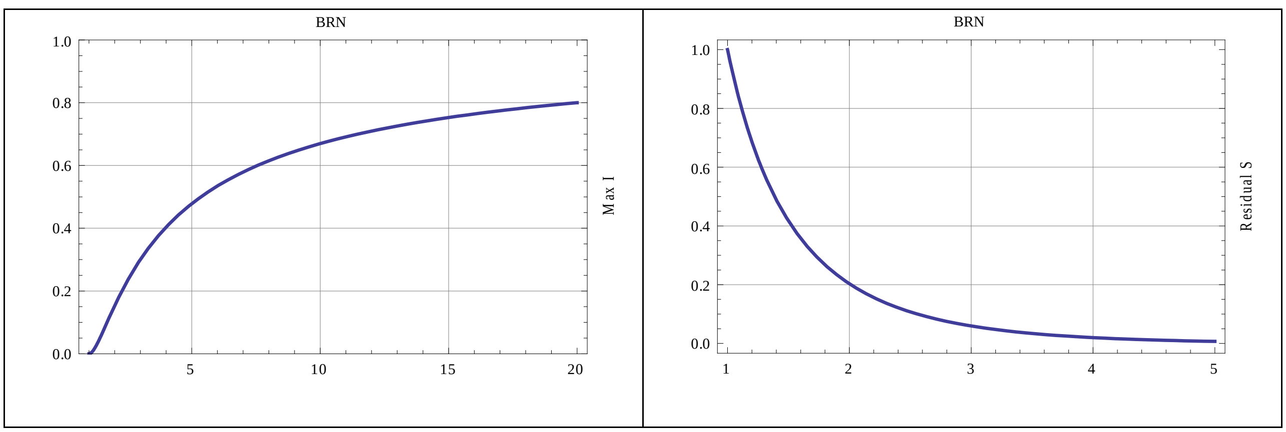


Figure 4: Max-I and residual S as functions of BRN

SEIR (with permanent immunity)

It gives the same BRN, but different (3D) Jacobian

$$A \approx r \begin{bmatrix} 0 & 0 & -R_0 \\ 0 & -\alpha & R_0 \\ 0 & \alpha & -1 \end{bmatrix} \tag{4}$$

with rescaled $\alpha = \dfrac{a}{r+\mu}$. The condition for epidemic outbreak is the same as above SI

$$\det\begin{bmatrix}-\alpha & R_0\\ \alpha & -1\end{bmatrix} = \alpha(1-R_0) < 0 \Rightarrow \text{eigenvalues } \lambda_1 < 0 < \lambda_2$$

Approximate eigenvalues of A for large $\alpha \gg 1$ (short latency) are

$$\lambda_{1,2} \approx \begin{cases} \dfrac{\alpha}{1+\alpha}(R_0 - 1) > 0 \\ -\left(\alpha + \dfrac{1+\alpha R_0}{1+\alpha}\right) < 0 \end{cases} \tag{5}$$

So the max growth rates of I(t) at the start of outbreak is $\lambda_1 \approx \dfrac{\alpha}{1+\alpha}(R_0 - 1)$.

SIR with immune loss

Use populations $X + Y + Z = N$, or prevalences: $S + I + R = 1$

$$\begin{aligned} \frac{dS}{dt} &= -\beta IS + \rho R + \mu I \\ \frac{dI}{dt} &= \beta IS - (r+\mu) I \\ \frac{dR}{dt} &= rI - \rho R \end{aligned} \tag{6}$$

Equilibria and stability

For BRN $R_0 = \dfrac{\beta}{r+\mu}$, and nonzero prevalence I^* get equilibrium solution of (6)

$$\begin{aligned} S^* &= 1/R_0; \\ I^* &= (1 - 1/R_0)\frac{\rho}{r+\rho}; \\ R^* &= (1 - 1/R_0)\frac{r}{r+\rho}; \end{aligned}$$

Table 2

Equilibrium	(1,0,0) -eradication	(S^*, I^*, R^*) - endemic

Jacobian	$\begin{bmatrix} -\rho/\beta & \cdots \\ 0 & (1-1/R_0) \end{bmatrix}$	$\begin{bmatrix} -\left(I^* + \rho/\beta\right) & -(1+r/\beta) \\ I^* & 0 \end{bmatrix}$
$R_0 > 1$	Saddle/ unstable	Sink /stable
$R_0 < 1$	Sink /stable	Saddle/ unstable

Transcritical (saddle-node) bifurcation at $R_0 = 1$

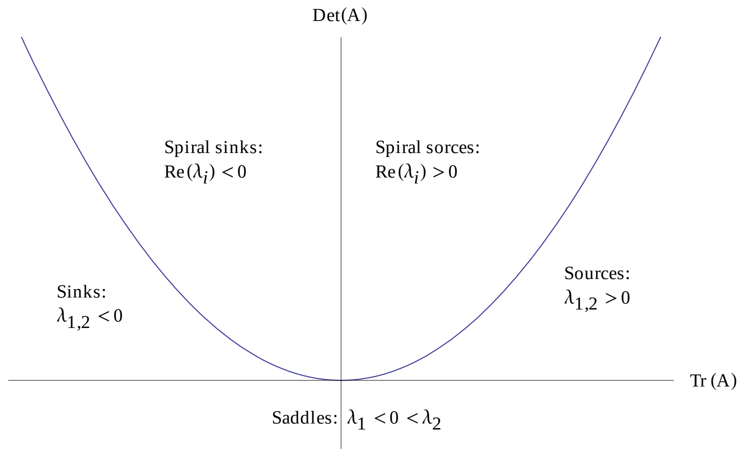


Figure 5: Trace-Determinant diagram of stability types of linear systems: $Y' = A \bullet Y$ with 2x2 matrix A

Analysis for SEIR

$$\frac{dS}{dt} = -\lambda + \rho R$$
$$\frac{dE}{dt} = \lambda - qE$$
$$\frac{dI}{dt} = qE - rI$$
$$\frac{dR}{dt} = rI - \rho R$$
$; \lambda = \beta IS$

S+E+I+R=1 - prevalences

BRN: $R_0 = \frac{\beta}{r}$

Endemic equilibrium

$$S^* = 1/R_0$$
$$E^* = \frac{(1-1/R_0)1/q}{(1/q + 1/r + 1/\rho)}$$
$$I^* = \frac{(1-1/R_0)1/r}{(1/q + 1/r + 1/\rho)}$$
$$R^* = \frac{(1-1/R_0)1/\rho}{(1/q + 1/r + 1/\rho)}$$

All fractions are ratios of mean durations of “latency”, “disease” and “immunity” over the combined period: “latency + disease + immunity”

SIR with population growth

We call SIR compartments X, Y, Z and write DS

$$\begin{aligned}\frac{dX}{dt} &= B-(\beta Y+\mu)X \\ \frac{dY}{dt} &= \beta XY-(r+\mu)Y \\ \frac{dZ}{dt} &= rY-\mu Z\end{aligned} \tag{7}$$

Here B – source (new-born or recruits), μ - natural mortality, β - transmission rate/infected host. For constant (steady) source total population: $\dot{N} = B-\mu N$, has equilibrium $N^* = B/\mu$. System (7) is reduced to 2D with $X+Y \le N^*$. It has BRN $R_0 = \frac{\beta N^*}{r+\mu}$, and 2 equilibria with stability types determined by R_0 (Figure 6:)

Table 3

Equilibrium	$I = (N^*, 0)$-eradication	$II = (X^*, Y^*) = \left(\frac{1}{R_0}, \frac{\mu(R_0-1)}{\beta}\right)$
Jacobian	$\begin{bmatrix} -\frac{1}{R_0(1+r/\mu)} & -1 \\ 0 & 1-1/R_0 \end{bmatrix}$	$\begin{bmatrix} -R_0 & -(1+r/\mu) \\ R_0-1 & 0 \end{bmatrix}$

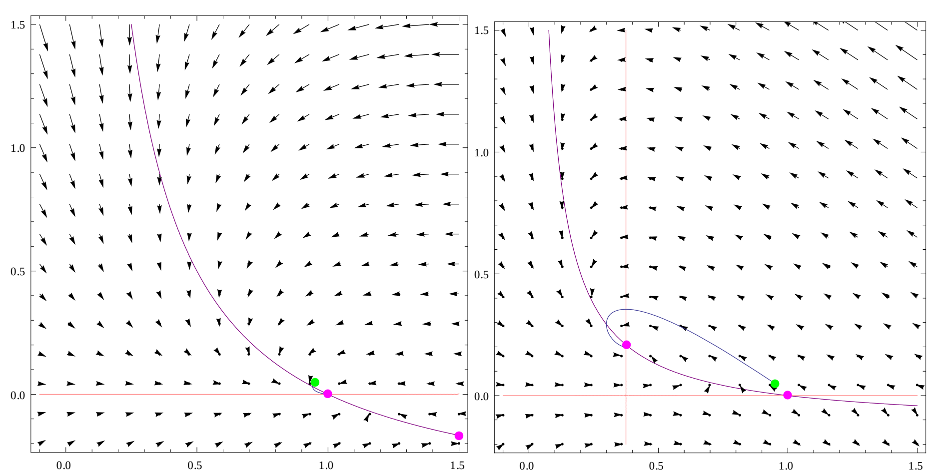


Figure 6: Phase-plane of system (7) with $R_0 < 1$ (left), and $R_0 > 1$ (right)

As R_0 changes from <1 to >1, the system undergoes transcritical bifurcation: "stable I" (eradication) to "stable II" (endemic).

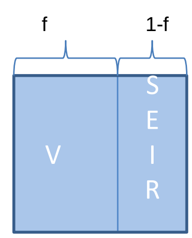
BRN: its meaning and implications

- ***(SIR with life-long immunity):*** R_0 determines whether outbreak occurs (R_0 >1), or infection dies out (R_0 <1)
- BRN is related to initial infection growth : as $e^{(R_0-1)} \approx R_0$, R_0 approximately measures "# secondary cases/per single infected" over "time range " r t=1
- BRN (R_0 >1) determines infection peak and timing, depending on initial state I_0
- For ***SIR with immune loss*** sets apart: (i) endemic equilibrium state (R_0 >1), or waning of infection (R_0 <1)

Prevention and control

I. Vaccination and Herd immunity:

vaccinating fraction *f* of population we decrease fraction of infectious contacts, and S,E,I prevalences by factor (1-f).



$$\omega \to (1-f)\omega$$

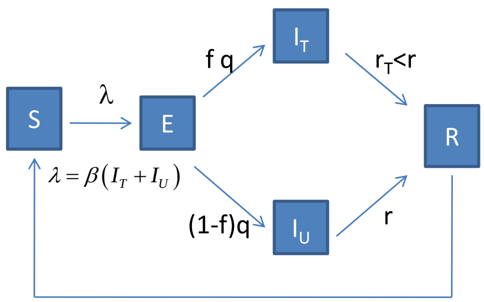
BRN	$(1-f)R_0$
S	$(1-f)S^*$
E	$(1-f)E^*$
I	...

Hence vaccination fraction *f>1-1/R*$_0$ (critical level) can prevents outbreak, eradicate infection.

Demographics: increased population density N drives up $R_0 = \beta N/r$ (enhanced outbreaks, higher endemicity)

Transmission prevention: Lower β decreases R_0

Drug treatment and transmission prevention



Exercise: Show that $R_0 = \beta\left(\frac{f}{r_T} + \frac{1-f}{r}\right)$ and find endemic equilibrium

$$\begin{pmatrix} E \\ I \\ R \end{pmatrix} = \frac{(1-R_0)}{a+b+c}\begin{pmatrix} a \\ b \\ c \end{pmatrix}$$

- in terms of "mean duration" a- "latency", c – "immunity", $b=f/r_T + (1-f)/r$ - disease

Conclusions

•Efficient drug ($\beta/r_T < 1 < \beta/r$), can bring $R_0 < 1$, eradication (find the appropriate cover fraction f).

• Reduced transmission /contacts β can also make $R_0 < 1$

•Quarantine or culling have similar effect by removing a fraction of infectious population

Parameter estimation

Goal: Develop and estimate SEI model for this outbreak ?

Method:

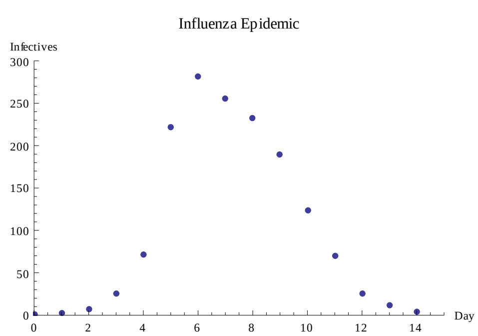
i) Produce SEI solution *I(t,b,r)*

ii) Find parameters *b,r* (transmission, recovery), that "best fit" the data

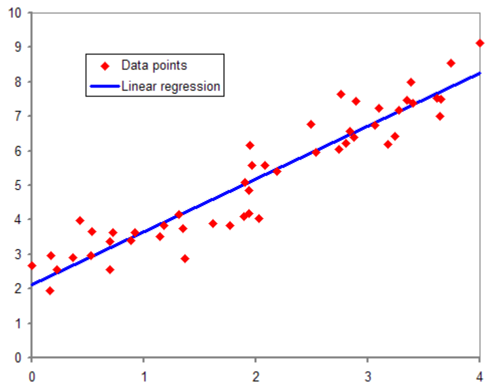
iii) Test (validate) the "best fit" model

Example: flu outbreak

Data (British Medical Journal, March 4 1978, p. 587)



Example of "best fit": Linear Regression by Least Squares



Estimating beta (the slope)

We use the summary statistics above to calculate $\widehat{\beta}$, the estimate of β.

$$\widehat{\beta} = \frac{nS_{XY} - S_X S_Y}{nS_{XX} - S_X S_X}.$$

Estimating alpha (the intercept)

We use the estimate of β and the other statistics to estimate α by:

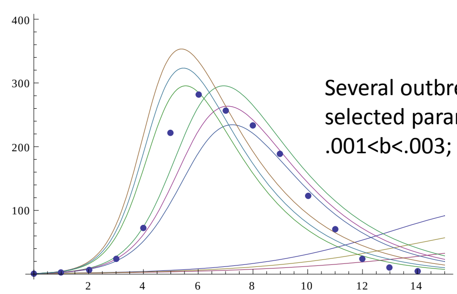
$$\widehat{\alpha} = \frac{S_Y - \widehat{\beta} S_X}{n}.$$

SEI solutions vs. data

Unlike "linear regression" SEI/SIR

(i) Have no ***analytic solution*** S(t),I(t)

(ii) Parameter dependence *S(t,**b**,**r**), I(t,**b**,**r**)* is highly ***nonlinear*** and ***implicit***



Several outbreak histories for selected parameter values: .001<b<.003; .4<r<.6

Which "parameter choice" is "best"?

Age structured SIR

Here all populations X,Y,Z are functions of time and age, with age-specific mortality $\mu=\mu(a)$, survival $\sigma(a)=\exp\left[-\int_0^a \mu(s)ds\right]$ and (newborn) source $B(t)$. They obey a 1st order PDS

$$\begin{aligned}
&\partial X/\partial t+\partial X/\partial a=-(\lambda+\mu)X(a,t)\\
&\partial Y/\partial t+\partial Y/\partial a=\lambda X-(\mu+r)Y(a,t)\\
&\partial Z/\partial t+\partial Z/\partial a=rY-\mu Z(a,t)\\
&N=X+Y+Z-\text{total}
\end{aligned} \tag{8}$$

System (8) is supplemented with boundary condition (at $a=0$)

$$\begin{aligned}
X(0)=N(0)=B\\
Y(0)=Z(0)=0
\end{aligned} \tag{9}$$

And initial state (at t=0) $X(a,0);Y(a,0);Z(a,0)$. The per capita force of infection λ can prescribed, which is appropriate for a population subgroup, or cohort subjected to external transmission environment (e.g. biting by infectious insects), or as shown later for stationary age-independent demographics. More generally, λ should itself depend on the state of infected group $Y(a,t)$, and transmission patterns within the community.

All rates λ,μ,r etc. can be age-dependent. Two important examples of such mortality are called Type I and Type II:

(I) $\mu(a)=\begin{cases}0; a<L\\ \infty; a>L\end{cases}$; (II) $\mu(a)=1/L$

Both cases have life span *L*. In (I) everyone lives through age L and then dies, in (II) the rate is constant over ages.

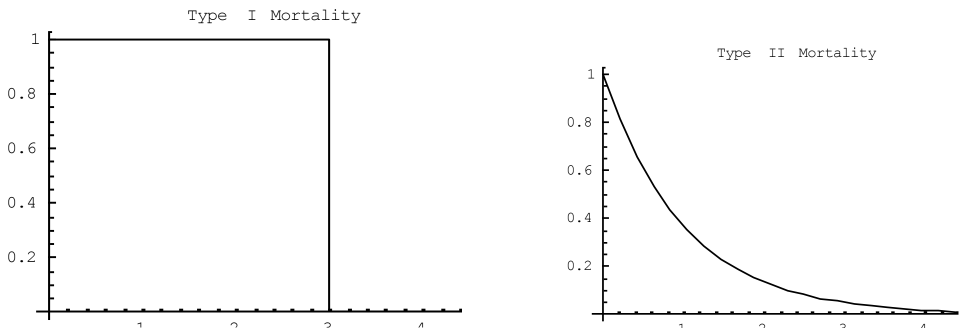


Figure 7: Survival functions $\sigma(a)$ for 2 types.

Similarly, mean recovery rate can change with age $r = r(a)$, but we'll fix it.

If we ignore disease mortality the total population obeys a "renewal" pde model

$$\begin{aligned}&\partial_t N + \partial_a N = -\mu N\\&N(0,t) = B(t)\end{aligned}$$

with suitable source.

We look for stationary solutions of (8)-(9), dropping ∂_t - terms. Then

$$\begin{aligned}&N(a) = N_0\sigma(a) = B\sigma(a)\\&X(a) = X_0 e^{-\int_0^a(\lambda+\mu)ds} = N(a)\left\{e^{-\int_0^a \lambda ds}\right\};\\&Y(a) = \int_0^a e^{-\int_{a-s}^a(r+\mu)}\lambda(s)X(s)ds = N(a)\left\{e^{-ra} * \left(\lambda e^{-\int_0^a \lambda ds}\right)\right\};\\&Z(a) = N(a)\left\{r\int_0^a\left[e^{-rs} * \left(\lambda e^{-\int_0^s \lambda}\right)\right]ds\right\}\end{aligned} \tag{10}$$

For constant force of infection λ integrals (10) can be computed explicitly

$$
\begin{aligned}
X(a) &= e^{-\lambda a} N(a); \\
Y(a) &= \lambda \left(\frac{e^{-ra} - e^{-\lambda a}}{\lambda - r} \right) N(a); \\
Z(a) &= \left(1 - \frac{\lambda e^{-ra} - r e^{-\lambda a}}{\lambda - r} \right) N(a);
\end{aligned}
\qquad (11)
$$

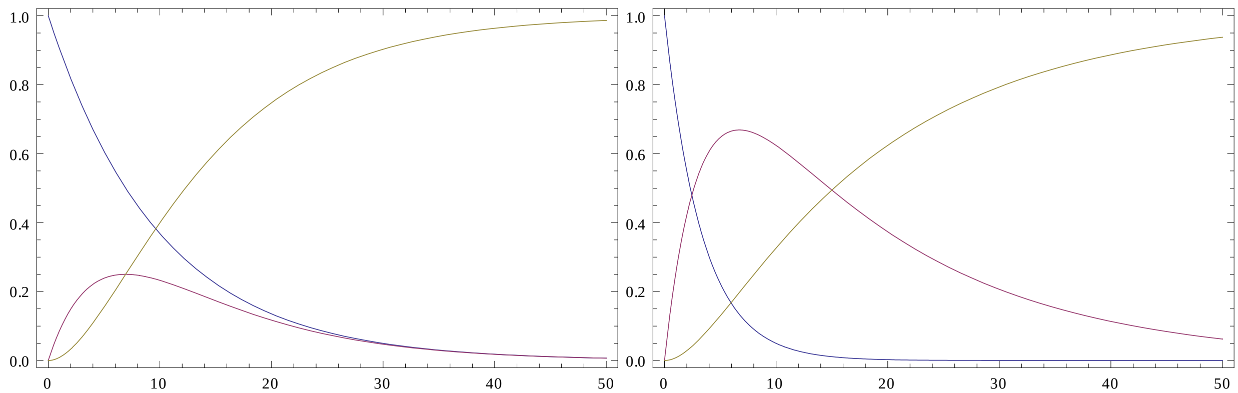


Figure 8: Age-distribution of SIR prevalences $\left\{ \frac{X}{N}; \frac{Y}{N}; \frac{Z}{N} \right\}$ in cases: $\lambda < r$ (left) and $\lambda > r$ (right)

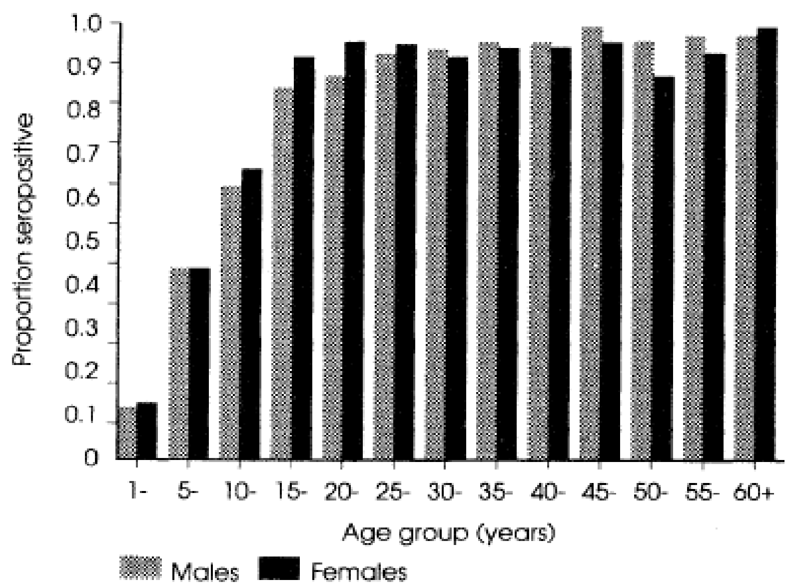


Fig. 4.2. Serological profile for rubella antibodies in a sample of sera collected in southeast England over the period 1980–4, which is stratified by sex and age (from Nokes *et al.* 1986).

Figure from Anderson-May "Infectious diseases of humans".

BRN

At the equilibrium, the rate of infection is balanced against recruitment of new susceptibles.

So each infection will on average produce exactly one secondary infection. If x^* is the susceptible fraction at equilibrium, then replication factor $R = R_0 x^* = 1$, so we define BRN as $R_0 = 1/x^*$

To compute it we need to total populations of all groups:

$$\bar{N} = B\left(\int_0^\infty \sigma da\right); \bar{X} = B\left(\int_0^\infty e^{-\lambda a}\sigma da\right); \ldots \tag{12}$$

etc, as well as mean age of infection

$$A = \frac{\int a\lambda X(a)da}{\int \lambda X(a)da} \tag{13}$$

$\lambda X(a)$ - age dependent incidence of infection. We summarize results for type I-II mortalities in the Table 4 (bar designate cumulative populations – sum over all ages)

Table 4

	Type I	Type II
$\bar{N}$	BL	BL
$\bar{X}$	$\frac{\bar{N}\left(1-e^{-\lambda L}\right)}{\lambda L}$	$\frac{\bar{N}}{1+\lambda L}$
$\bar{Y}$	$\frac{\bar{N}}{rL}\left(1-\frac{\lambda e^{-rL}-re^{-\lambda L}}{\lambda - r}\right)$	$\frac{\bar{N} * \lambda L}{(1+\lambda L)(1+rL)}$
$\bar{Z}$		$\frac{\bar{N} * \lambda L * rL}{(1+\lambda L)(1+rL)}$
Age A	$\frac{1-(1+\lambda L)e^{-\lambda L}}{\lambda\left(1-e^{-\lambda L}\right)} \approx \frac{1}{\lambda}$	$\frac{1}{\lambda+\mu} = \frac{L}{1+\lambda L}$
$R_0 = \frac{\bar{N}}{\bar{X}}$	$\frac{\lambda L}{1-e^{-\lambda L}}$	$1+\lambda L$

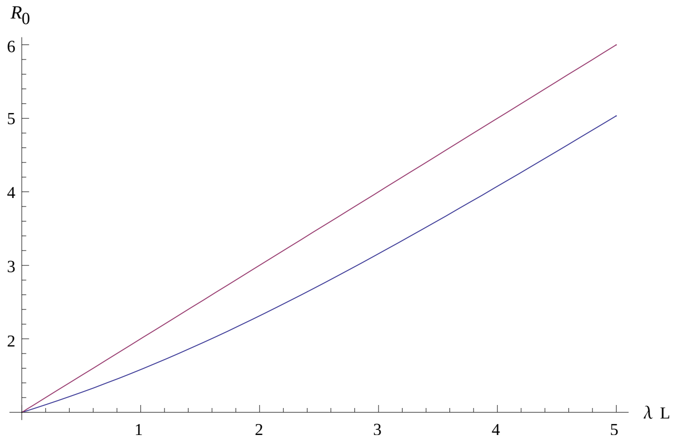


Figure 9: BRN as function of λL

Force of infection in a closed community

Prescribed force of infection λ of previous section can be appropriate for a cohort subjected to external force from a larger community and environment.

Having a closed community stratified by age, the force of infection should depend on contacts among various age groups

$$\lambda(a) = \int_0^\infty \beta(a,a') \frac{Y(a')}{N(a')} da'$$

$Y(a)/N(a)$ - infectious fraction of contacts. When substituted in the original (or equilibrium) system (8) it gives nonlinear integro-differential system for $\{X(a), Y(a)\}$. BRN should correspond to largest eigenvalue of linear integro-differential operator (Jacobian of (8)) at the "infection-free" equilibrium $\{N(a), 0\}$. It simplifies assuming equal transmission rates among strata $\beta(a,a') = \bar{\beta}$. Then

$$\lambda = \bar{\beta} \int_0^\infty \frac{Y(a)}{N(a)} da \tag{14}$$

Such λ is no more fixed, but is itself a linear functional of $Y(a)$. So formula (11) and Table 1 don't apply.

One can reduce, the problem to a homogeneous population case (of section Simple SIR and SEIR) by integrating out densities: $\bar{X}(t)=\int_0^\infty X(a,t)da$, etc. Then PDS (8) turns into a system

$$\begin{aligned}\frac{d\bar{X}}{dt}&=B-\int_0^\infty(\lambda+\mu)X(a)\,da\\ \frac{d\bar{Y}}{dt}&=\int_0^\infty(\lambda+\mu)X(a)\,da-\int_0^\infty(r+\mu)Y(a)\,da\end{aligned}$$

We can close it for $\bar{X},\bar{Y}$ using constant (age-independent) μ, r and force of infection (14). Then assuming type I survival (constant N) we get standard SIR

$$\begin{aligned}\frac{d\bar{X}}{dt}&=B-\beta\frac{\bar{Y}}{\bar{N}}\bar{X}\\ \frac{d\bar{Y}}{dt}&=\beta\frac{\bar{Y}}{\bar{N}}\bar{X}-r\bar{Y}\end{aligned}$$

with transmission $\beta=\bar{\beta}L$, analyzed above. Its BRN $R_0=\frac{\beta}{r}$ is approximately equal to BRN of Table 1, $R_0\approx\lambda L=\frac{\bar{\beta}L}{r}$.

Stationary system with constant fertility/birth, death, transmission

We fix age-independent demographic parameters: $\mu=\mu(a); b=b(a)$- per capita fertility rate, and transmission $\beta(a,a')=\beta$. To maintain stationary population the birth and death rates should be equal $\mu=b$. So we get stationary form of system (8)

$$\begin{aligned}&\partial_a x=-\lambda x-bx=-\beta(Y+b)x(a); && x(0)=bN\\ &\partial_a y=\lambda x-(r+b)y=\beta Yx(a)-(r+b)y(a); && y(0)=0\\ &\partial_a z=ry(a)-bz(a); && z(0)=0\end{aligned} \tag{15}$$

with per capita force of infection $\lambda=\beta Y$. As above capital letters designate total population of each group

$$X=\int_0^\infty x(a)da; Y=\int_0^\infty y(a)da;\ldots; N=X+Y+Z$$

Solution of (15) comes from equilibrium SIR equations for X, Y, Z (by integrating over all ages *a*)

$$bN = \beta(Y+b)X; \qquad X^* = \frac{r+b}{\beta} = \frac{N}{R_0}$$

$$0 = \beta YX - (r+b)Y \quad \Rightarrow \quad Y^* = N\left(1-\frac{1}{R_0}\right)\frac{b}{r+b}$$

$$0 = rY - bZ; \qquad Z^* = N\left(1-\frac{1}{R_0}\right)\frac{r}{r+b}$$

The age distribution of x, y, z is given by formulae (11) with $\lambda = \beta Y$,

$$x(a) = bNe^{-(\lambda+b)a}$$

$$y(a) = bN\lambda\left[\frac{e^{-(\lambda+b)a} - e^{-(r+b)a}}{r-\lambda}\right]; \lambda = b(R_0 - 1)$$

$$z(a) = bNe^{-ba} - x(a) - y(a)$$

The age of infection (13) computed in Table 4 is given by

$$A = \frac{1}{\lambda+b} = \frac{1}{bR_0}$$

Age of infection can be measured in many places, and it gives an estimate of BRN $R_0 = \frac{L}{A}$ - "life expectancy/age of infection". Vaccination (fraction *p*<1) decreases BRN to $(1-p)R_0$, hence extends the age of infection to $A' = A/(1-p)$. It can be used for public health control and planning of vaccination (e.g. rubella).

Bernoulli small-pox model (1766)

Population cohort - n(a) with age-specific mortality - μ(a), force of infection - λ; fatality rate – ν

1**) No infection**:

$$\frac{dn}{da} = -\mu(a)n;\ n(0) = n_0$$

Solution for: $n_0 = 1$

$$n(a) = e^{-\int_0^a \mu dt} = \Phi(a) \text{ - survival function}$$

$L_0 = \int_0^\infty \Phi(a)\,da$ - life expectancy

Case $\mu = \text{const} \Rightarrow$

$\Phi(a) = e^{-\mu a};\ L_0 = 1/\mu$

Bernoulli estimates:

FI: $\lambda = 1/8$ year;

Disease mortality: $\nu = 1/8$;

Observed life-span: $L_S \approx 26.5$ years

2) **Small pox infection**: n(a) –total; X(a) - susceptible

$$\frac{dn}{da} = -\mu n - \nu\lambda X;\ n(0) = 1$$

$$\frac{dX}{da} = -(\mu+\lambda)X;\ X(0) = 1$$

Solution: $X(a) = e^{-\int_0^a (\mu+\lambda)dt}$

$n(a) = \Phi(a)\left[1 - \int_0^a \frac{X(t)}{\Phi(t)}dt\right]$ - survival

For $\mu, \lambda - \text{const}$

survival: $\Phi_S(a) = e^{-\mu a}(1-\nu) + \nu e^{-(\mu+\lambda)a}$

Life expectancy: $L_S = \frac{1-\nu}{\mu} + \frac{\nu}{\mu+\lambda} \approx 26.5$

$\Rightarrow L_0 = 1/\mu \approx 28.9$ year

Gain = 2.5 years!!

Issues:

- inoculation mortality
- other ???