Aspects of homogeneous vs. heterogeneous transmission

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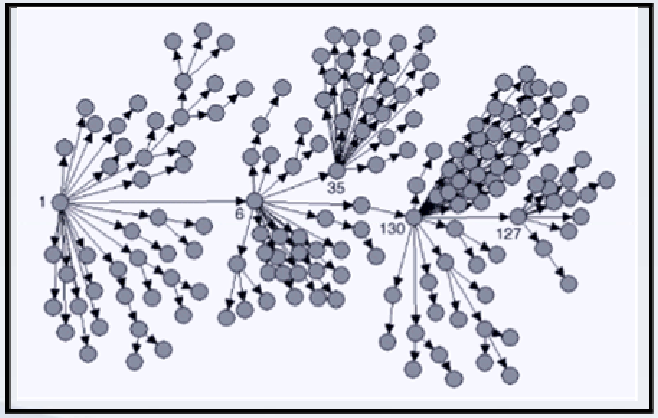
Topic 1

Heterogeneity: phenomenological observation

FIGURE 2. Probable cases of severe acute respiratory syndrome, by reported source of infection* — Singapore, February 25–April 30, 2003



Source: MMWR: 2003, 52 (18)

Superspreading SARS Events, Beijing, 2003

Zhiwang Shen,* Feng Ning,* Weiqong Zhou,†‡ Xiong He,* Chengying Lin,* Daniel P. Chin,† Zonghan Zhu,§ Anne Schuchat†‡

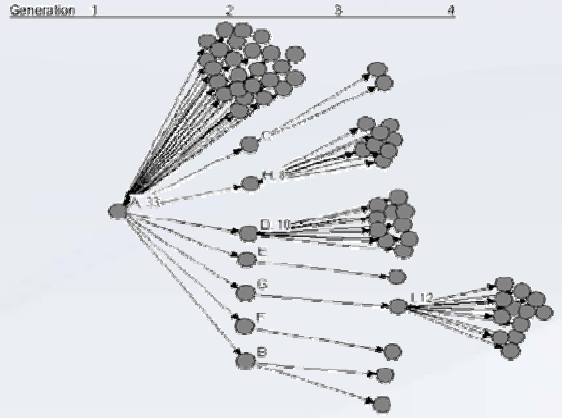


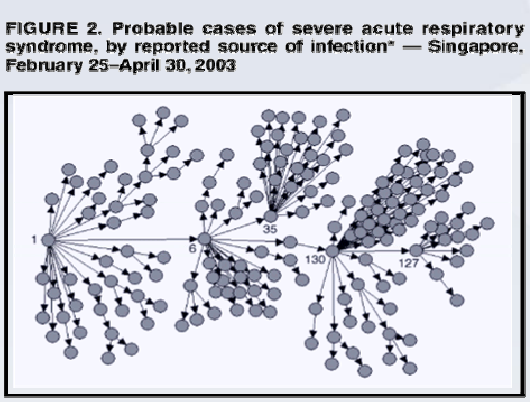
Figure 2. Probable cases of severe acute respiratory syndrome by source of transmission in chain of 77 cases in Beijing, 2003.
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 10, No. 2, February 2004

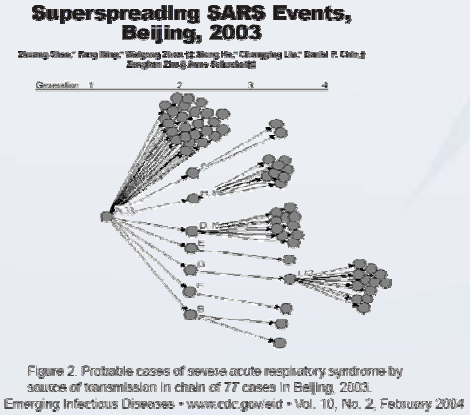
"A picture is worth 1000 words." --- really?

Heterogeneity: phenomenological observation

R_0 = average # of infections produced during ones entire infectious period
as one infectious individual ***seeded*** in an infinitely large susceptible population,

- *but some infect many and some infect a few. R_0 is about the mean.*





Source: MMWR: 2003, 52 (18)

- Heterogeneity, in a phenomenological sense, is about the variance.

In addition, # secondary infections one typical infected individual produces through ones entire infectious period depends on

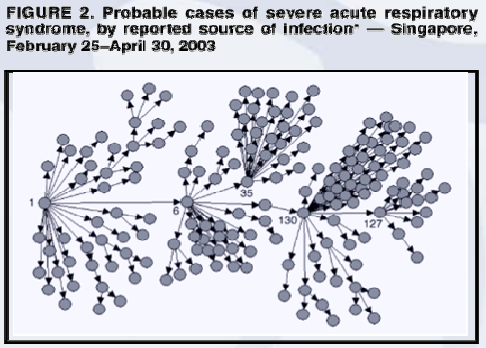
- the size of the susceptible population (if not infinity)
- whether this individual is at the beginning of, the middle of, or near the end of the epidemic.

Heterogeneity: phenomenological observation

As phenomenon, heterogeneity is about the variance.

In models assuming homogeneous transmission, one expects to see the distribution of the secondary transmissions being:

- No random variation : variance = 0
- Poisson distribution: variance = mean
- Geometric distribution: variance = mean + mean^2



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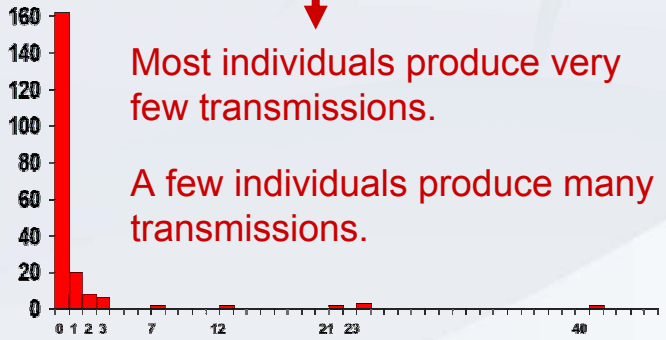


Most individuals produce very few transmissions.

A few individuals produce many transmissions.

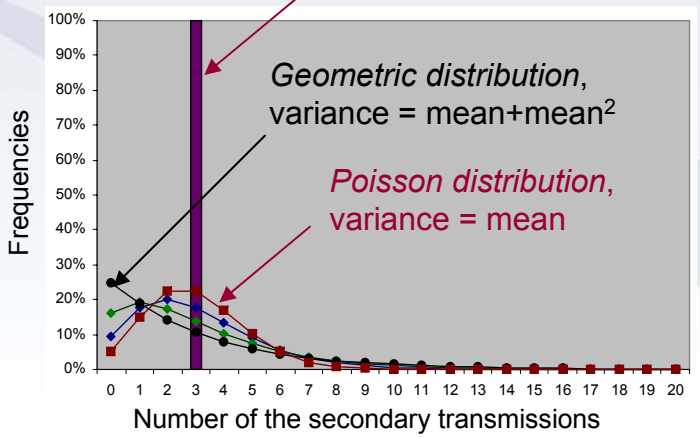
Loosely speaking,

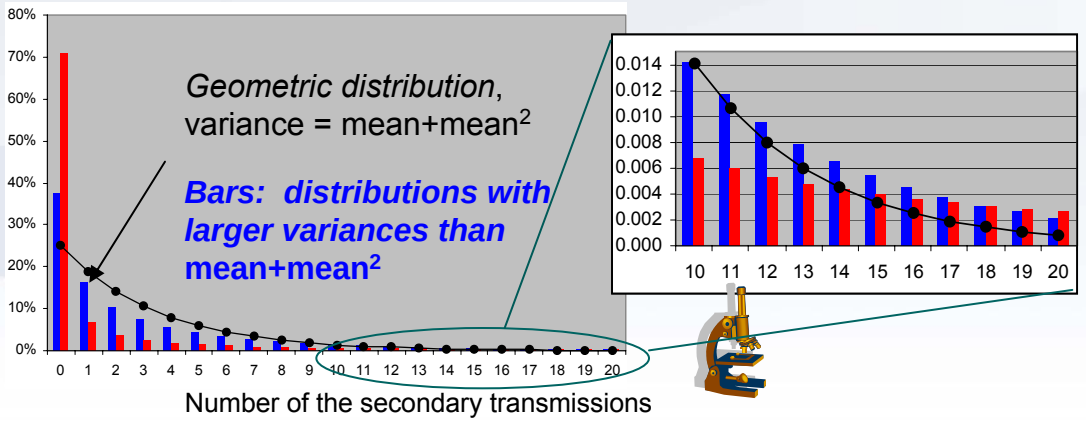
Homogeneous: variance ≤ mean+mean^2

Heterogeneous: variance > mean+mean^2

Illustration assuming $R_0 = 3$

Homogeneity in extreme sense: no variation





Heterogeneity: phenomenological observation

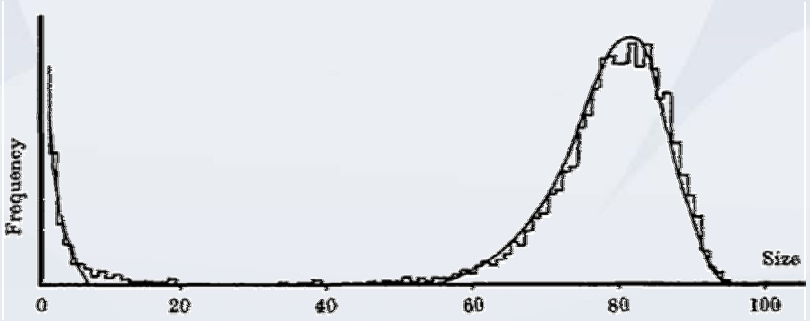
As phenomenon, heterogeneity is about the variance.

Important questions that can be addressed by the phenomenon:

Small outbreaks and large outbreaks

From Anderson and Watson (1980):
simulation based on n=100 individuals.

Bi-modal distribution with one mode at zero, and another mode around 0.8.



Sometimes: a small outbreak:

- a handful cases followed by extinction.
- The expected number of infected individuals by the end of the outbreak is finite even if the population size can be infinitely large:

$\frac{C(\infty)}{n} \to 0, \text{as } n \to \infty$ where $C(\infty)$ is the expected cumulative number of infected individuals as $t \to \infty$.

Other times: a large outbreak:

- The expected cumulative number of infected individuals scales linearly with the size of the susceptible population:

$$\frac{C(\infty)}{n} \to \eta > 0, \text{as } n \to \infty$$

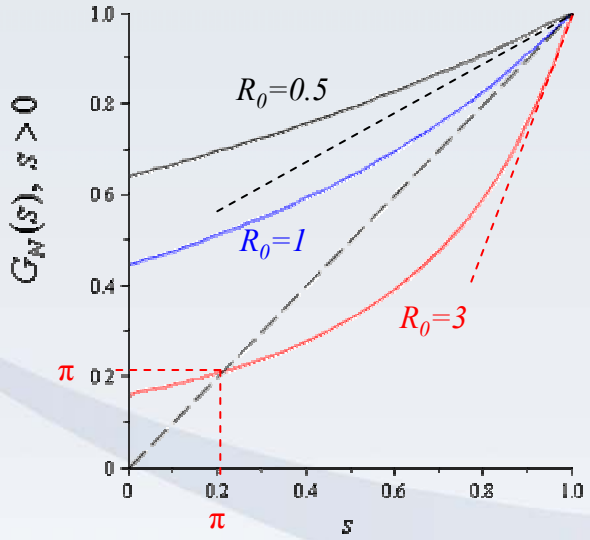
Heterogeneity: phenomenological observation

R_0 is about the mean. Heterogeneity, as phenomenon, is about variance.

N = # of infections produced during ones entire infectious period as an infectious individual seeded in infinite susceptible population. *N* is a random variable, $R_0 = E[N]$

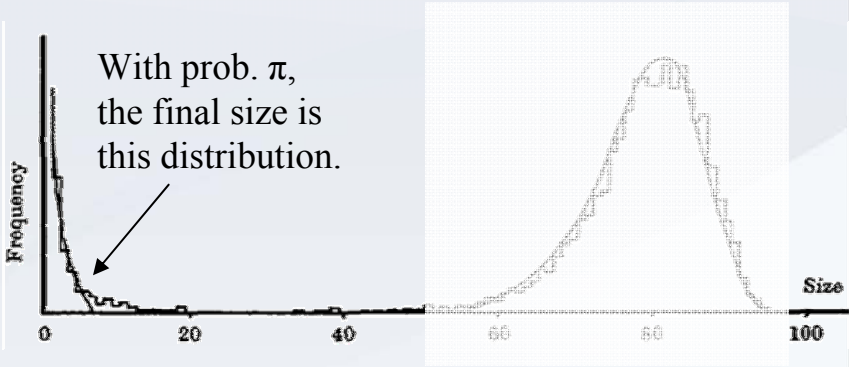
The distribution of *N* is uniquely determined by its *probability generating function* $G_N(s),\ s>0$

$$G_N(0)=\Pr\{N=0\},\ G_N(1)=1,\ \frac{d}{ds}G_N(s)>0,\ \frac{d^2}{ds^2}G_N(s)>0.$$



$$R_0 = \frac{d}{ds}G_N(s)\Big|_{s=1}$$

A small versus a large outbreak



1. What is the risk of a large outbreak: $1-\pi = ?$

π is the smallest root of the fixed-point equation

$$G_N(s)=s$$

If $R_0 \le 1$, then $\pi = 1$, with certainty.

Zero risk of large outbreak.

If $R_0 > 1$, then $\pi < 1$.

The risk of large outbreak = $1-\pi$.

Heterogeneity: phenomenological observation

R_0 is about the mean. Heterogeneity, as phenomenon, is about variance.

1. *What is the risk of a large outbreak: $1-\pi = ?$*

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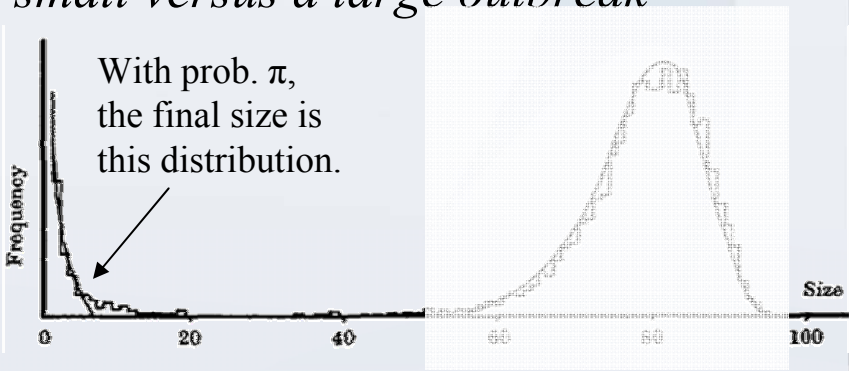
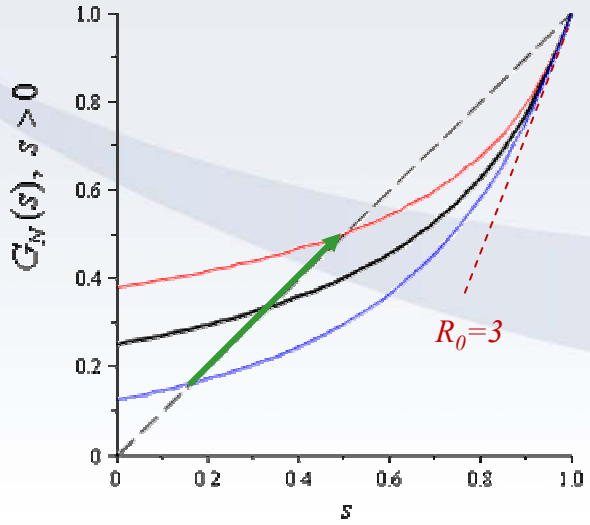
A small versus a large outbreak



2. *What does variance do to the risk of a large outbreak?*



$$\mathrm{var}[N] = \frac{d^2}{ds^2} G_N(s)\Big|_{s=1} + R_0 - R_0^{\,2}$$

Given the same R_0:

the larger the variance, the more convex is $G_N(s)\big|_{s=1}$.

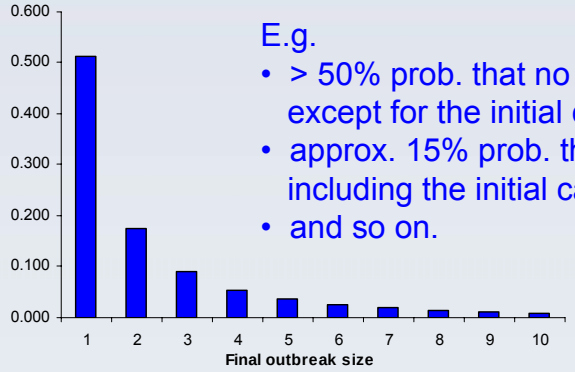
Statement

With some *ordering* assumption wrt. prob. generating functions, the larger the variance, the higher is the probability of a small outbreak and the less is the risk of a large outbreak.

Heterogeneity: phenomenological observation

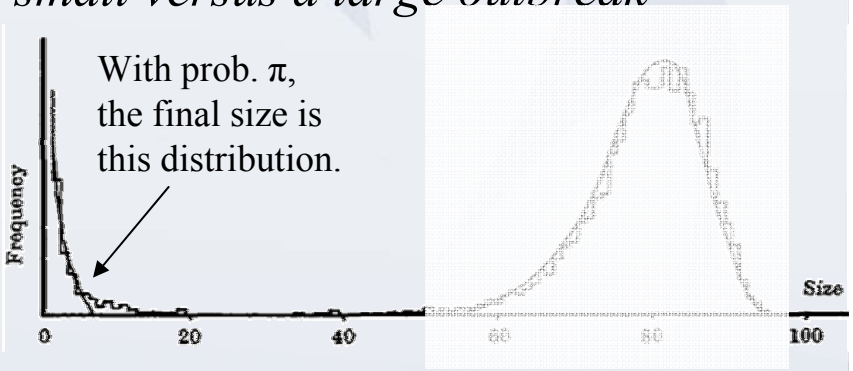
R_0 is about the mean. Heterogeneity, as phenomenon, is about variance.

3. *If a small outbreak, what is its final size?*



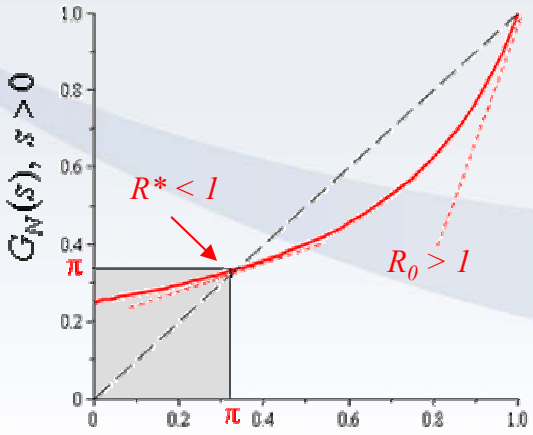
E.g.
- > 50% prob. that no transmission except for the initial case
- approx. 15% prob. that final size = 2 including the initial case,
- and so on.

A small versus a large outbreak



The final size distribution of a small outbreak can be precisely calculated via $G_N(s),\ s>0.$

To find the mean and variance of the final cumulative infections C(∞):



1. Find π by solving $G_N(s)=s.$
2. Define and evaluate $R^*=\dfrac{d}{ds}G_N(s)\Big|_{s=\pi}<1.$

Conditional mean

$$E[C(\infty)\,|\,\text{small outbreak}]=\frac{1}{1-R^*}$$

regardless how *N* is distributed.

If $R_0\le 1,\ \pi=1$ and $R^*=R_0.$

If $R_0>1,\ \pi<1$ and $R^*<1.$

Conditional variance is large if *var[N]* is large.

Heterogeneity: phenomenological observation

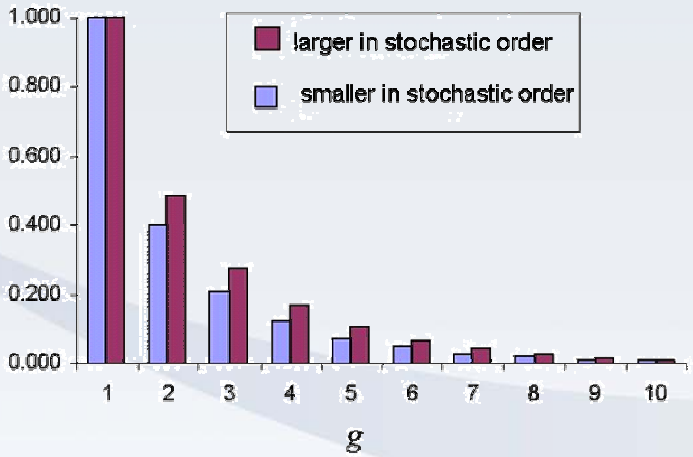
R_0 is about the mean. Heterogeneity, as phenomenon, is about variance.

4. If a small outbreak, how many generations it takes to become extinct?

The distribution of generation-to-extinction of a small outbreak can be calculated via $G_N(s),\ s>0.$

Let $T_g = 1,2,\ldots$ be the number of generations to extinction, conditioning (with prob. *π)* conditioning (with prob. *π)* on being a small outbreak.

$\Pr\{T_g \geq g\}$: the survivor function



If two random variables $T_g^{(1)}$ and $T_g^{(2)}$ such that

$$\Pr\{T_g^{(1)} \geq g\} > \Pr\{T_g^{(2)} \geq g\}, \text{ for all } g,$$

we say that they are ranked in stochastic order.

Statement

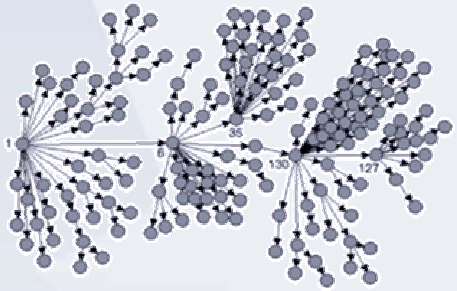
Large *var[N] makes the generation-to-extinction smaller in stochastic order.*

The mean generation = $\sum_g \Pr(T_g \geq g).$

Heterogeneity as large *var[N]* : Not only lowers the risk of large outbreak $1-\pi$, but also that should extinction occur, it happens more quickly with fewer generations.

Heterogeneity: beyond phenomenological observation

Different aspects of heterogeneity may produce the same phenomenon.



1. Likely due lack of homogeneity in the environment. The "super-spreading events" tend to occur in small "local population", e.g. hospital wards.

2. For the term "super-spreaders", the lack of homogeneity was either assigned to the infected host, or to the agent (viruses with different infectivity).

3. The same phenomenon can be re-produced under all the homogeneity criteria for the environment and hosts, by allowing the infectious period within host having very large variance.

When it becomes a large outbreak, these aspects have different impacts on transmission dynamics.

Food for thoughts: Is the 2003 SARS outbreak a large outbreak?

Topic 2

Homogeneity / Heterogeneity regarding

Agent: same infectiousness (Yes / No)

Host:

All susceptible individuals are the same (Yes / No)

All infectious individuals are the same (Yes / No)

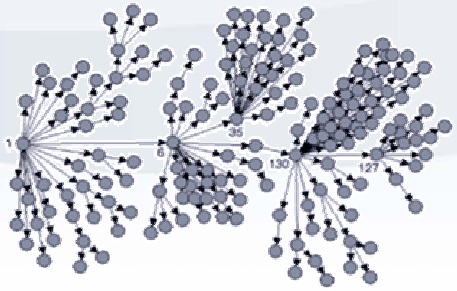
Equally infectiousness during infectious period (Yes / No)

Environment: homogeneous mixing (Yes / No)

Which parts of the outcomes of an outbreak are critically determined by these criteria ?

Which individual criterion, if violated, will change which part of the outcome, in which way?

Different aspects of heterogeneity may produce the same phenomenon.



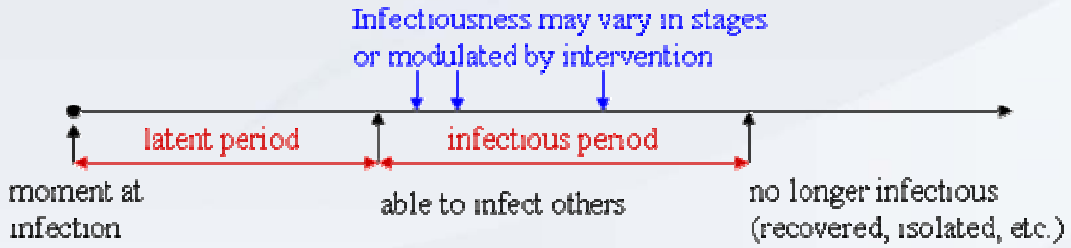
Conceptual assumptions vs. tactical assumptions

Example of conceptual assumptions

1. The force of infection onto *a susceptible individual* $\propto \frac{I(t)}{n(t)}$: % infectious individuals

2. The instantaneous rate of passing the infection from *a typical infectious individual* to another $\propto \frac{S(t)}{n(t)}$: % of susceptible individuals

Example of tactical assumptions



1. *Is there a latent period? If yes, how long on average? How variable?*
2. *Besides the average infectious period μ_I , how variable is it distributed?*

Conceptual assumptions vs. tactical assumptions

Example of conceptual assumptions

1. The force of infection onto *a susceptible individual* $\propto \frac{I(t)}{n(t)}$: % infectious individuals

$$\rightarrow \quad \beta \frac{I(t)}{n(t)} S(t).$$

2. The instantaneous rate of passing the infection from *a typical infectious individual* to another $\propto \frac{S(t)}{n(t)}$: % of susceptible individuals

$$\rightarrow \quad \beta \frac{S(t)}{n(t)} I(t).$$

same β ?

In many deterministic models:

$$\frac{d}{dt} S(t) = -\beta \frac{S(t)I(t)}{n(t)} + (\text{susceptible replacement}) - (\text{non - disease related depletion})$$

In stochastic, Markov SIR model:

$$\Pr\left\{ \begin{pmatrix} S(t+dt) = s-1 \\ I(t+dt) = i+1 \end{pmatrix} \middle| \begin{matrix} S(t) = s \\ I(t) = i \end{matrix} \right\} = \beta \frac{S(t)I(t)}{n(t)} dt$$

same *β, and this is a hidden assumption* !

Homogeneity criteria in conceptual assumptions

same *β, and this is a hidden assumption* !

Agent: same infectiousness during the study period.

Host:

- All susceptible individuals are the same: equally susceptible.
- All infectious individuals are the same: equally infectious when infectious period starts.
- An infected individual remains equally infectious throughout its infectious period.

Environment (homogeneous mixing): an individual contacts with all other individuals in the population with equal probability. In an infinitely large population, the number of contacts made by a typical individual follows a stationary Poisson process.

→ $\beta = \lambda p = \text{contact freq.} \times \text{prob. of infection per contact}$

- independent of time
- Independent of which contact pair

→ a single parameter β for $\beta \frac{S(t)I(t)}{n(t)}$.

Homogeneity / Heterogeneity in conceptual assumptions

Agent: same infectiousness ($\surd$Yes / No)

Host:

All susceptible individuals are the same ($\surd$Yes / No)

All infectious individuals are the same ($\surd$Yes / No)

Equally infectiousness during infectious period ($\surd$Yes / No)

Environment: homogeneous mixing ($\surd$Yes / No)

If all the answers are "Yes", then we have the bilinear relationship $\beta \frac{S(t)I(t)}{n(t)}$.

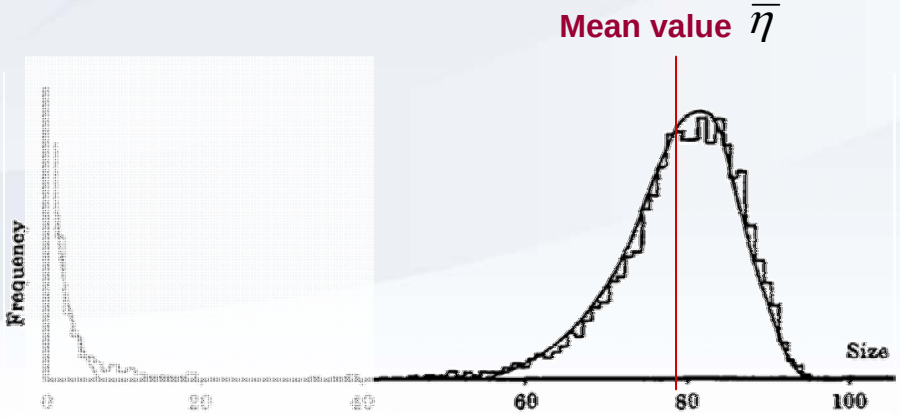
We also have the expression: $R_0 = \beta\mu_I$, where $\mu_I =$ average infectious period.

If the population is closed with size *n*, without replacement of susceptible individuals, the *final size* of the epidemic is meaningful:

$$\eta = \frac{C(\infty)}{n}, \text{ with mean } \overline{\eta} > 0.$$

where *C*(∞) is the cumulative number of infected individuals as $t \to \infty$.

The final size distribution of a large outbreak



Homogeneity / Heterogeneity in conceptual assumptions

Agent: same infectiousness (√Yes / No)

Host:

All susceptible individuals are the same (√Yes / No)

All infectious individuals are the same (√Yes / No)

Equally infectiousness during infectious period (√Yes / No)

Environment: homogeneous mixing (√Yes / No)

The very beginning:

As an infectious individual ***seeded*** in a large susceptible population, R_0 = ave. # of infections s/he produces during the entire infectious period.

$$R_0 = \beta\mu_I, \text{ where } \mu_I = \text{average infectious period.}$$

The end:

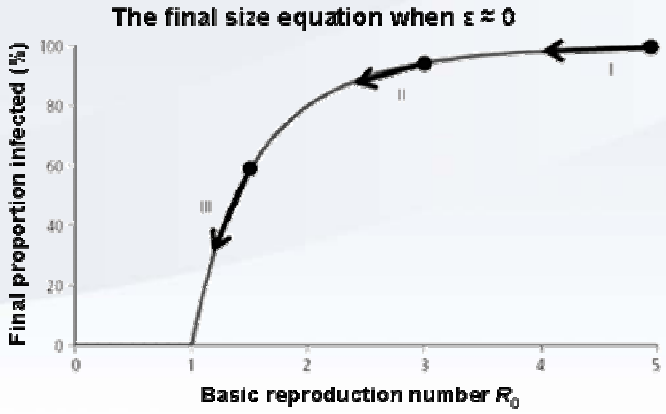
$$\eta = \frac{C(\infty)}{n}, \text{ with mean } \overline{\eta} > 0.$$

The very beginning transcends to the very end:

Expected proportion of final infections

$$1 - \overline{\eta} = (1 - \varepsilon)\exp(-R_0\overline{\eta})$$

Proportion of initial infectives



Homogeneity / Heterogeneity in conceptual assumptions

Agent: same infectiousness ($\surd$ Yes / No)

Host:

All susceptible individuals are the same (Yes / No ?)

All infectious individuals are the same (Yes / No ?)

Equally infectiousness during infectious period (Yes / No ?)

Environment: homogeneous mixing (Yes / No ?)

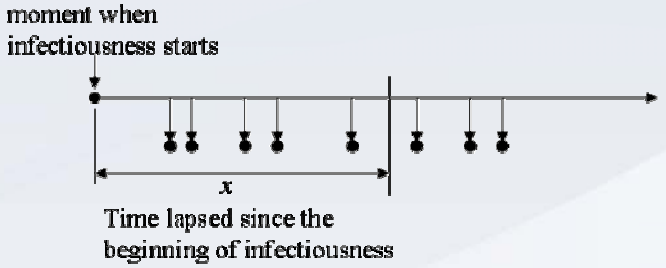
Mixed-Poisson Process

The prob. of transmission per contact may vary around a mean value and finite variance.

The contact process has extra-Poisson variation, but maintains the *stationary increment property* as explained below.

Relaxing homogeneity assumptions to the extent:

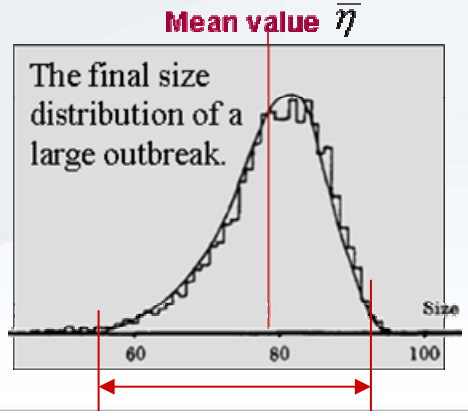
The expected number of transmissions by a typical infectious individual is proportional to the length of time during the infectious period.



Still true: $R_0 = \beta\mu_I$, where $\mu_I =$ average infectious period

Still true: $1-\overline{\eta} = (1-\varepsilon)\exp(-R_0\overline{\eta})$

- but η will have larger variance.



Homogeneity / Heterogeneity in conceptual assumptions

Agent: same infectiousness (√Yes / No)

Host:

All susceptible individuals are the same (Yes / No ?)

All infectious individuals are the same (Yes / No ?)

Equally infectiousness during infectious period (Yes / No ?)

Environment: homogeneous mixing (Yes / No ?)

Mixed-Poisson Process

The prob. of transmission per contact may vary around a mean value and finite variance.

The contact process has extra-Poisson variation, but maintains the *stationary increment property*

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ORIGINAL ARTICLE

Generality of the Final Size Formula for an Epidemic of a Newly Invading Infectious Disease

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valid. We show that the final size formula is unchanged any number of distinct infectious stages and/or a stage e isolated (the durations of each stage can be drawn from any integrable distribution). We also consider the possibility that the transmission rates of infectious individuals are arbitrarily distributed—allowing, in particular, for the existence of super-spreaders—and prove that this potential complexity has no impact on the final size formula. Finally, we show that the final size formula is unchanged even for a general class of spatial contact structures. We conclude that whenever a new respiratory pathogen emerges, an estimate of the expected

Homogeneity / Heterogeneity in conceptual assumptions

Agent: same infectiousness (√Yes / No)

Host:

All susceptible individuals are the same (√Yes / No)

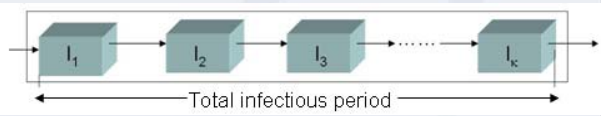
All infectious individuals are the same (√Yes / No)

Equal infectiousness during infectious period (Yes / X No)

Environment: homogeneous mixing (√ Yes / No)

Staging

Staged infectious period with different infectiousness.



$\beta \frac{S(t)I(t)}{n(t)}$ becomes $\frac{S(t)}{n(t)}(\beta_1 I_1(t) + \cdots + \beta_k I_k(t))$

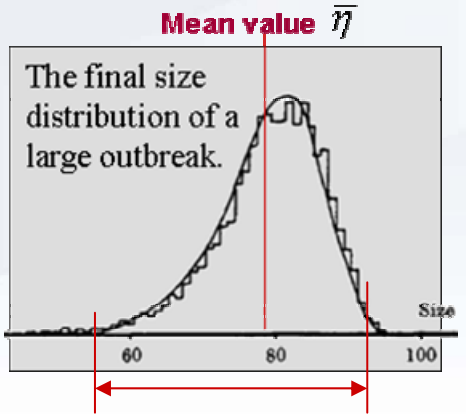
where $I_j(t)$ represents the numbers of infectious individuals in stage $j = 1, \ldots, k$.

$R_0 = \beta\mu_I$ becomes $R_0 = \beta_1\mu_I^{(1)} + \cdots \beta_k\mu_I^{(k)}$

where $\mu_I^{(j)}$ = average time of the j^{th} stage of the infectious period

Still true: $1-\overline{\eta} = (1-\varepsilon)\exp(-R_0\overline{\eta})$

- if the variation for β is small, the more the staging, the smaller is the variance for the final size η.



Homogeneity / Heterogeneity in conceptual assumptions

	Structured population
Agent: same infectiousness (√Yes / No)	
Host:	
All susceptible individuals are the same (Yes / XNo)	multiple types of susectptibles
All infectious individuals are the same (Yes / XNo)	multiple types of infectives
Equal infectiousness during infectious period (√Yes / No)	
Environment: homogeneous mixing (√ Yes / No)	

The next generation matrix:

a square matrix in which the *ij*th element is the expected number of secondary infections of type *i* caused by a single infected individual of type *j*, assuming that the population of type *i* is entirely susceptible.

Expression of R_0:

the dominant eigen-value (spectral radius) of the second generation matrix.

This is a straightforward generalization of the single type population in which

$R_0 = \beta\mu_I$, where $\mu_I =$ average infectious period

Homogeneity / Heterogeneity in conceptual assumptions

Agent: same infectiousness (√Yes / No)

Host:

All susceptible individuals are the same (Yes / XNo)

All infectious individuals are the same (Yes / XNo)

Equal infectiousness during infectious period (√Yes / No)

Environment: homogeneous mixing (√ Yes / No)

Structured population

multiple types of susectptibles

multiple types of infectives

Expression of R_0:

the dominant eigen-value (spectral radius) of the second generation matrix.

The final size equation: $1-\overline{\eta} = (1-\varepsilon)\exp(-R_0\overline{\eta})$

holds for single type of susceptibles and single type of infectives.

For structured populations, it is still true that the very beginning transcends to the very end.

Analogous relationships can be developed, although complicated.

(Ludwig, 1975; Scalia-Tomba, 1986; Ball, 1986; Addy, Longini, et al. 1991; and many others.)

Homogeneity / Heterogeneity in conceptual assumptions

Agent:

Same infectiousness (√Yes / No)

Host:

All susceptible individuals are the same (√Yes / No)
All infectious individuals are the same (√Yes / No)
Equally infectiousness during infectious period (√Yes / No)

Environment (homogeneous mixing): In an infinitely large population, the number of contacts made by a typical individual follows a stationary Poisson process. (Yes / X No)

Some relaxation:

Variable contact probability with finite variance. In an infinitely large population, the number of contacts follows a process with extra-Poisson variation but maintains *stationary increment* (i.e. expected # contacts in a time interval proportional to the length of the interval).

In terms of mean values, still $R_0 = \beta\mu_I$, where $\mu_I =$ average infectious period.

$$1-\overline{\eta} = (1-\varepsilon)\exp(-R_0\overline{\eta}).$$

Heterogeneous mixing as "scale-free" networks:

If with *preferential attachment* : the more one attracts others, the larger the probability of making more new connections, the contact process loses the stationary increment property. The # contacts (in any time interval) follows highly skewed distributions (Yule, Waring, power-law, etc.). The variance becomes infinitely large. Both the R_0 expression and the final size relationship break down.

Homogeneity / Heterogeneity in conceptual assumptions

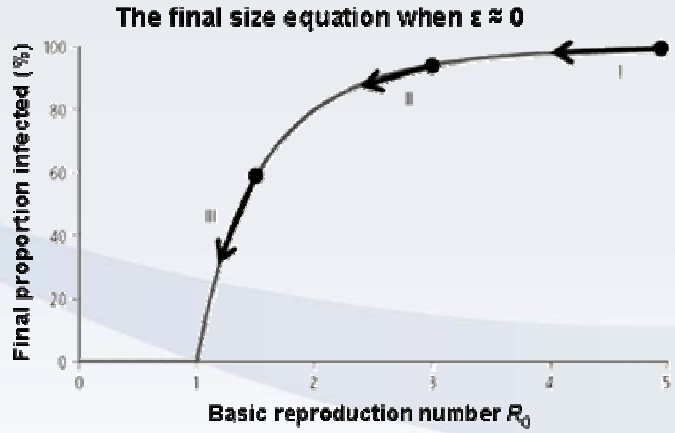
Partial summary:

1. The relationship $\beta \frac{S(t)I(t)}{n(t)}$ requires homogeneity in agent-host-environment.

2. Heterogeneous hosts (multiple types) invalidate the simple expression $R_0 = \beta\mu_I$, but there is a generalization as the spectral radius of the second generation matrix.

3. In many heterogeneous transmission situations, how people interact and transmit at the beginning of the epidemic determines the final size, as the "escape probability" of susceptible individuals, with or without a simple equation.

4. In many cases, a simple equation $1-\overline{\eta} = (1-\varepsilon)\exp(-R_0\overline{\eta})$ holds. It is extremely useful.

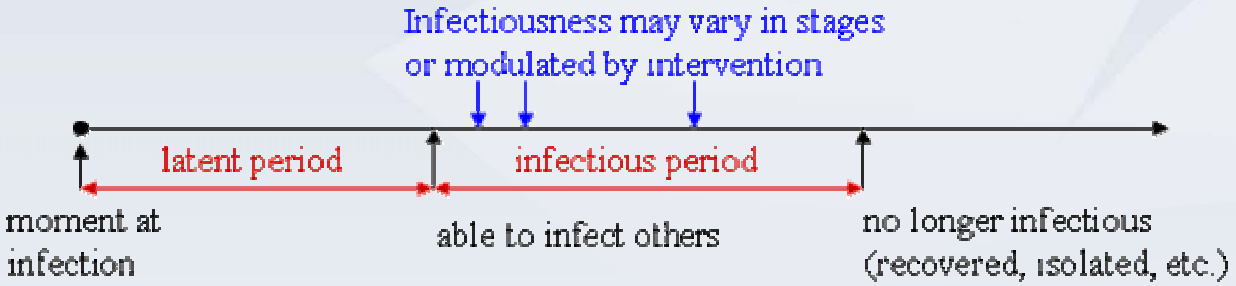


I. R_0 = 5: 20% reduction of R_0, 1% reduction of final size
II. R_0 = 3: 20% reduction of R_0, 6% reduction of final size
III. R_0 =1.5: 20% reduction of R_0, 27% reduction of final size

5. In extremely heterogeneous environment (e.g. scale-free network), R_0, as mathematical expectation, may not exist, not to mention the relationship between R_0 and the final size.

Topic 3

Homogeneity vs. variability in tactical assumptions



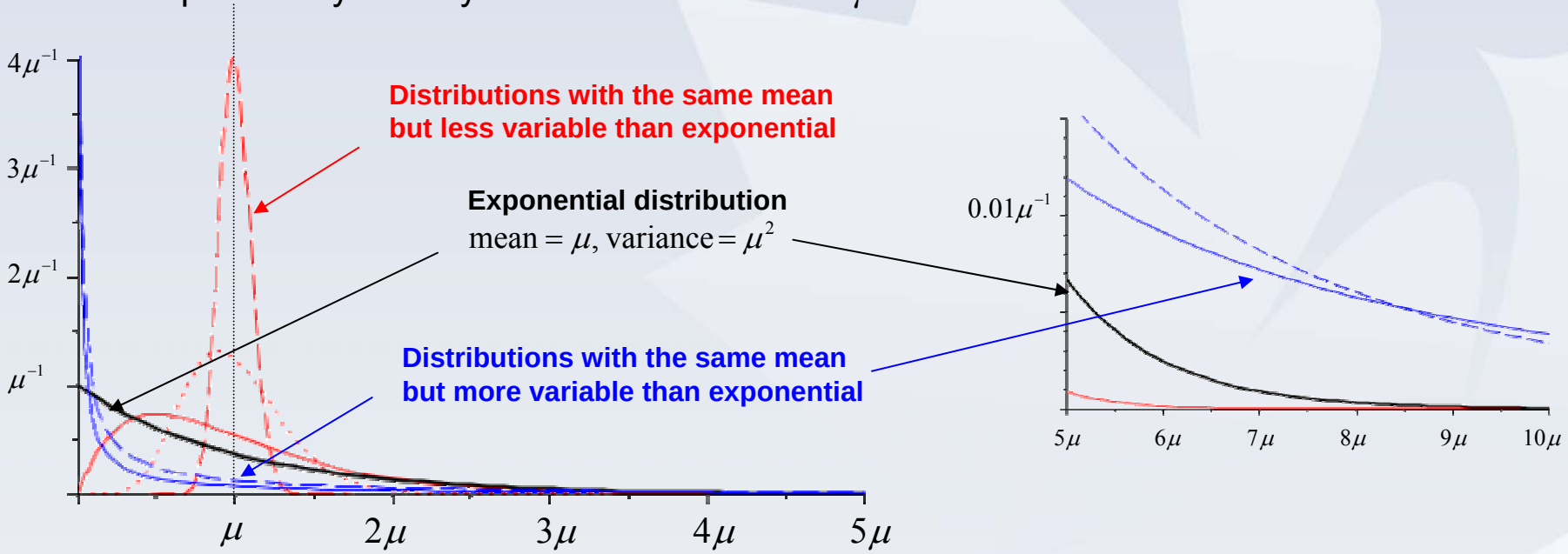
What will the presence of a latent period make a difference to the transmission dynamics over time and effectiveness of control measures ?

What will the variations of the latent period make a difference to the above questions?

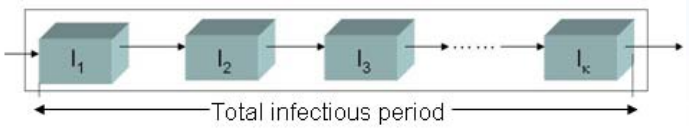
Given the same average infectious period, what do large or small variations do to the transmission dynamics over time and to the effectiveness of control measures?

Variability of random variables for time durations

Plots of probability density functions with mean $= \mu$

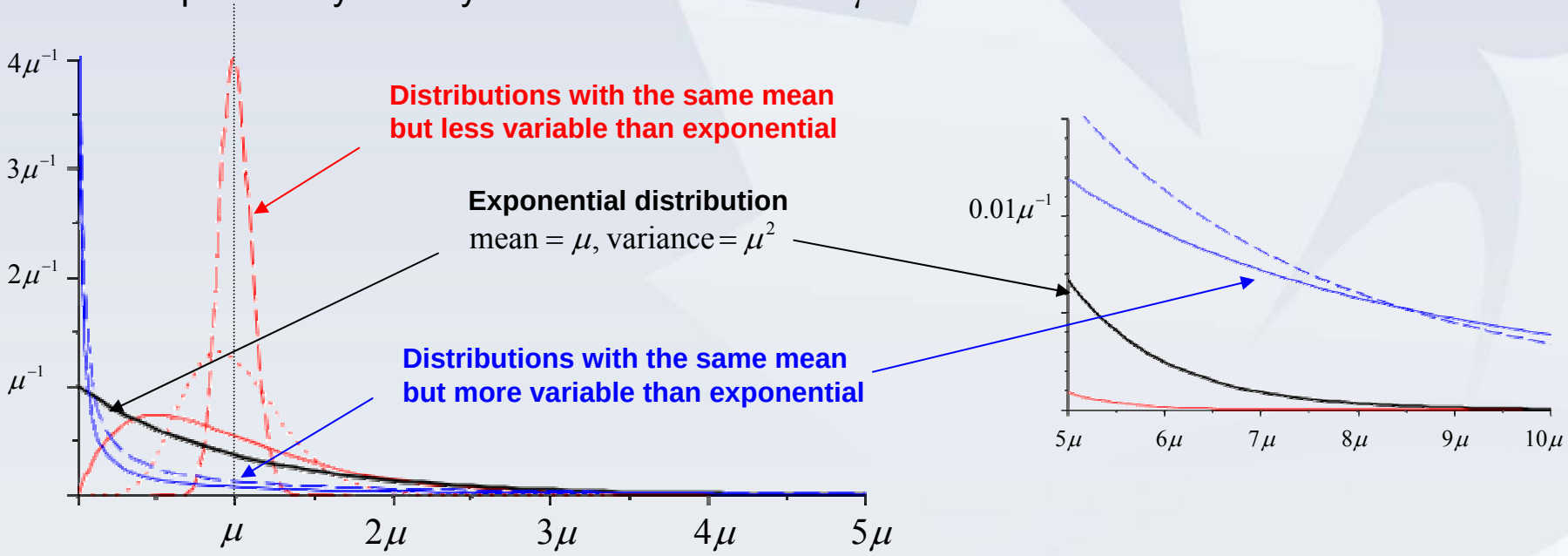


- Some models assume that the latent and the infectious periods are constants (no variation).
- SEIR models: ODEs or Markov process, assume that the latent and the infectious periods are distributed exponentially (variance = mean^2).
- If the infectious period is staged (k – stages), with each stage being exponential ($mean = \frac{\mu}{k}$), the infectious period still has mean = μ but with smaller than exponential variation.



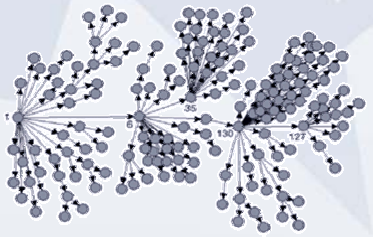
Variability of random variables for time durations

Plots of probability density functions with mean $= \mu$



Conveniently, *homogeneity* can be regarded as distributions with variations equal to or smaller than that of the exponential distribution (as in most models in the literature).

Variability of random variables for time durations

How does variability of infectious period do to  ?

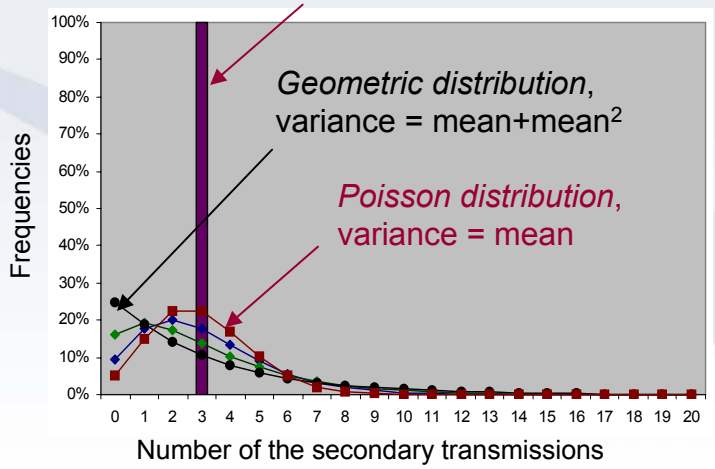
Assuming all the homogeneity criteria for agent-host-environment so that $R_0 = \beta\mu_I$, the larger the variance of the infectious period, the larger is the variance of *N*.

$$\mathrm{var}[N] = \beta\mu_I + \beta^2\,\mathrm{var}[\text{infectious period}]$$ (This can be proven using probability generating functions.)

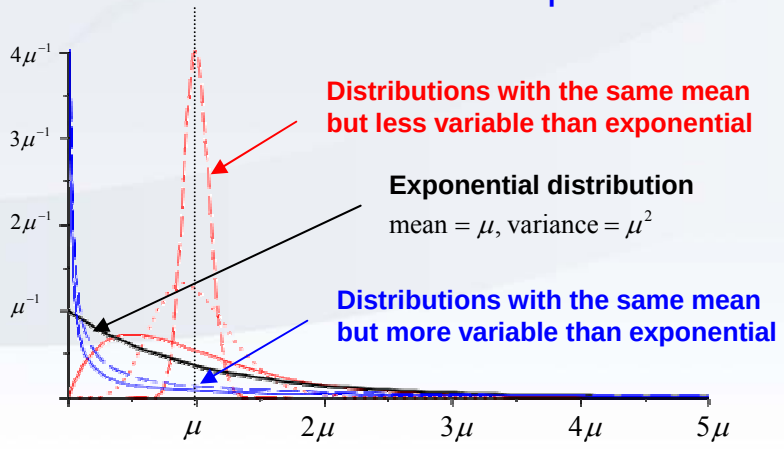
The shape of the (discrete) probability distribution of *N*, the secondary transmissions (by a typical infectious individual), resembles the probability density function of the infectious period.

(The theory behind is given by Lynch, J.,*Scan. J. Stat*. 1988).

Distribution of N:



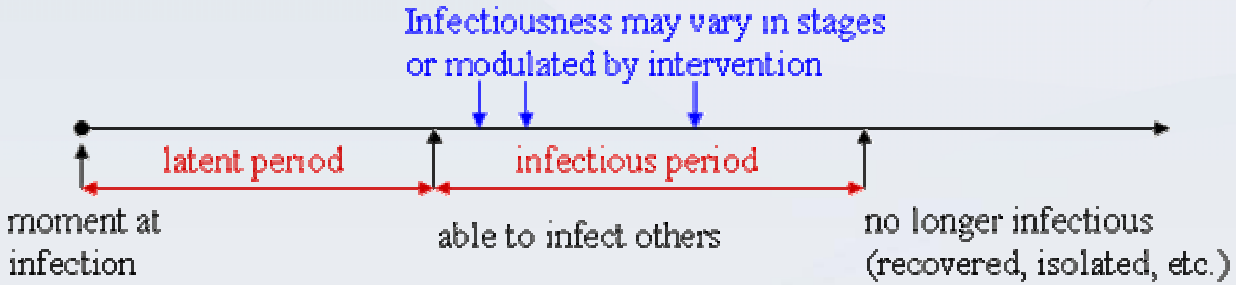
Distribution of the infectious period:



Variability orders of random variables for time durations

We rank distributions with the same mean value, according to their *variability orders.*

We show how variability orders for the latent period and the infectious period change the transmission dynamics and affect control measure effectiveness.



Variability orders of random variables for time durations

The most common measure for variability is the variance $\text{var}[X] = E\left[(X-\mu)^2\right]$

where X stands for the random variable, $E[X]=\mu$ is the mean value.

A generalization is the *dilation order:*

X_1 is smaller than X_2 in dilation order, denoted as $X_1 \le_{dil} X_2$

if $E[\Phi(X_1-\mu_1)] \le E[\Phi(X_2-\mu_2)]$ for all convex function $\Phi(x)$.

Fagiuoli, et al. (1999): dilation order is location independent.

→ If $\mu_1 = \mu_2 = \mu$, $X_1 \le_{dil} X_2 \Leftrightarrow E[\Phi(X_1)] \le E[\Phi(X_2)]$ for all convex function $\Phi(x)$,

denoted as $X_1 \le_{cx} X_2$

X_1 is smaller than X_2 in *Laplace transform order*, $X_1 \le_{Lt} X_2$, if $E[e^{-rX_1}] \ge E[e^{-rX_2}], r>0.$

The *Laplace transform* order is an alternative to *variance* for comparing variability.

The former is a convenient tool in mathematical models. The latter is an useful statistical measure.

If $\mu_1 = \mu_2 = \mu$,

$$X_1 \le_{dil} X_2 \quad \Leftrightarrow \quad X_1 \le_{cx} X_2 \quad \Rightarrow \quad X_1 \ge_{Lt} X_2$$
$$\Downarrow$$
$$\text{var}[X_1] \le \text{var}[X_2]$$

Variability of the latent / infectious periods and dynamics

Homogeneity in conceptual assumptions

How people interact and transmit at the beginning transcendentally determines the final size.

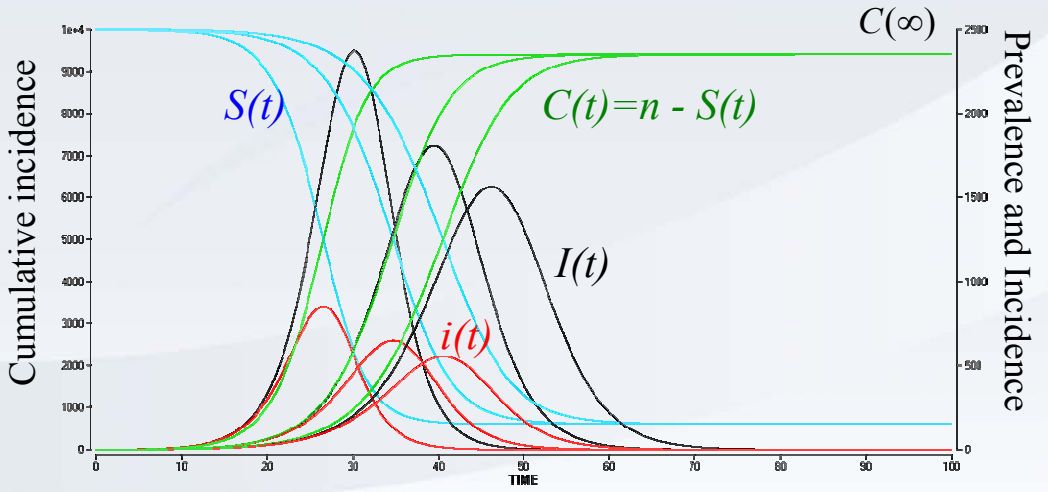
Typical outputs of models:

- *prevalence = # individuals in a "state": S(t), I(t).*
- *(instantaneous) incidence i(t) = instantaneous infection*
- *cumulative incidence* $C(t) = \int_0^t i(u)du.$ If the population is closed (size *n*), $C(\infty) = n\eta.$

The roles of latent/infectious periods: • growth, peak incidence & prevalence, duration

1. Same total area $C(\infty) = \int_0^\infty i(t)dt,$
   different paths for *i(t): incidence.*

2. Same total area
   $\int_0^\infty I(t)dt = \mu_I \times \int_0^\infty i(t)dt = \mu_I \times C(\infty)$
   different paths for *I(t): prevalence*

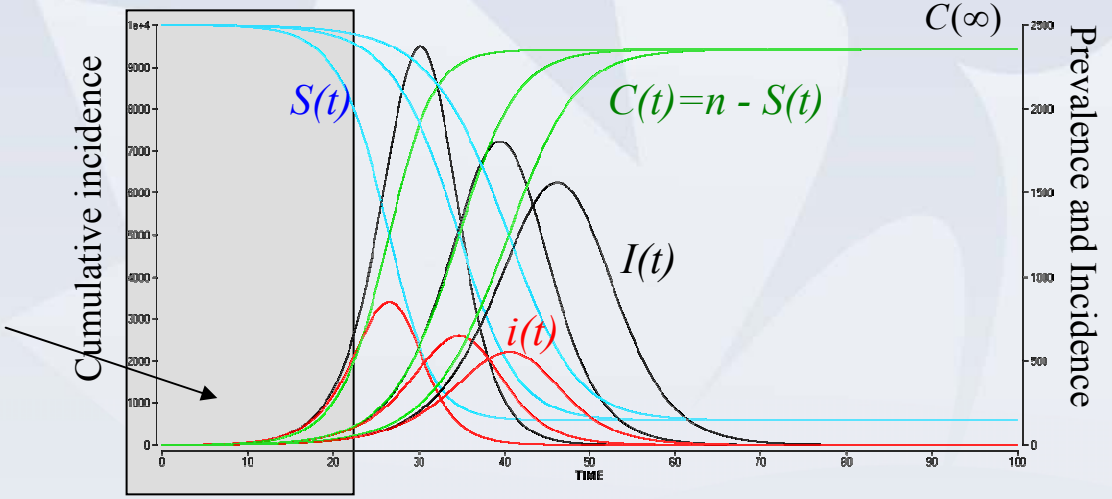


$\int_0^\infty I(t)dt$ is the "value" of the epidemic, as the total person-time of infectiousness.

Variability of the latent / infectious periods and dynamics

The early phase of an epidemic

1. When depletion of susceptibles *S(t)* is negligible .
2. If it turns out to be a large outbreak, *C(t)* grows exponentially.
3. Denote the exponential growth rate ρ: the Malthusian number.



Under suitable homogeneity assumptions for agent-host-environment, so that $\beta \frac{S(t)I(t)}{n(t)}$

Statement

The Malthusian number is separately determined (ranked) according to the Laplace transform orders of the latent and the infectious periods, via

$$\frac{\beta}{\rho} L_{Latent}(\rho)\left[1 - L_{Infectious}(\rho)\right] = 1$$

Yan (*J. of Theoretical Biology*, 2008)

where $L_{Latent}(\rho) = \int_0^\infty e^{-\rho x} dF_{Latent}(x), L_{Infectious}(\rho) = \int_0^\infty e^{-\rho x} dF_{Infectious}(x)$ are the Laplace transform functions for the latent and the infectious periods evaluated at ρ .

Variability of the latent / infectious periods and dynamics

The early phase of an epidemic

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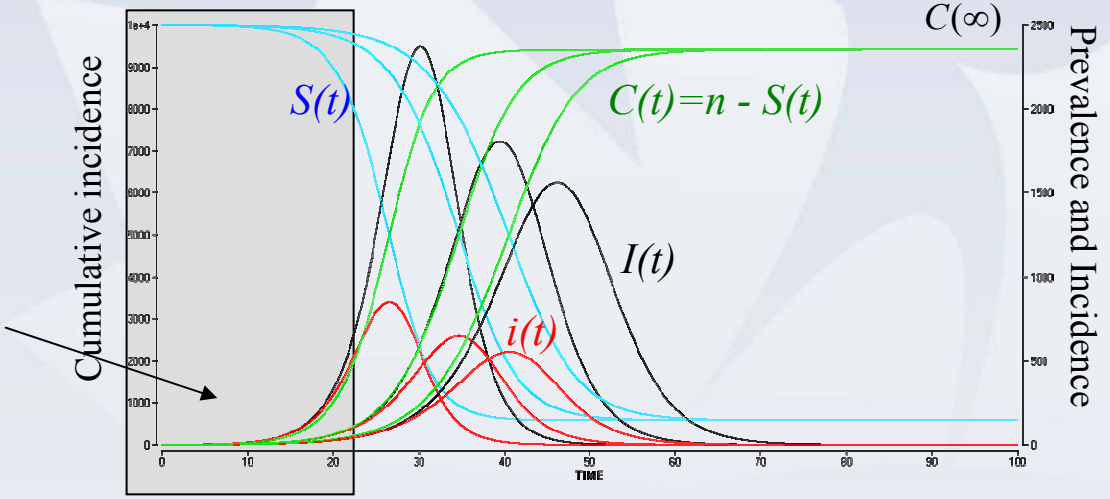

Under suitable homogeneity assumptions for agent-host-environment, so that $\beta \frac{S(t)I(t)}{n(t)}$

Statement

$$\frac{\beta}{\rho} L_{Latent}(\rho)\left[1 - L_{Infectious}(\rho)\right] = 1$$

Yan (*J. of Theoretical Biology*, 2008)

→ 1. When β and the infectious period distribution is given, the larger the latent period in Laplace transform order, the smaller is the Malthusian number ρ.

→ 2. When β and the latent period distribution is given, the larger the infectious period in Laplace transform order, the larger is the Malthusian number ρ.

Variability of the latent / infectious periods and dynamics

The early phase of an epidemic

1. When depletion of susceptibles *S(t)* is negligible .
2. If it turns out to be a large outbreak, *C(t)* grows exponentially.
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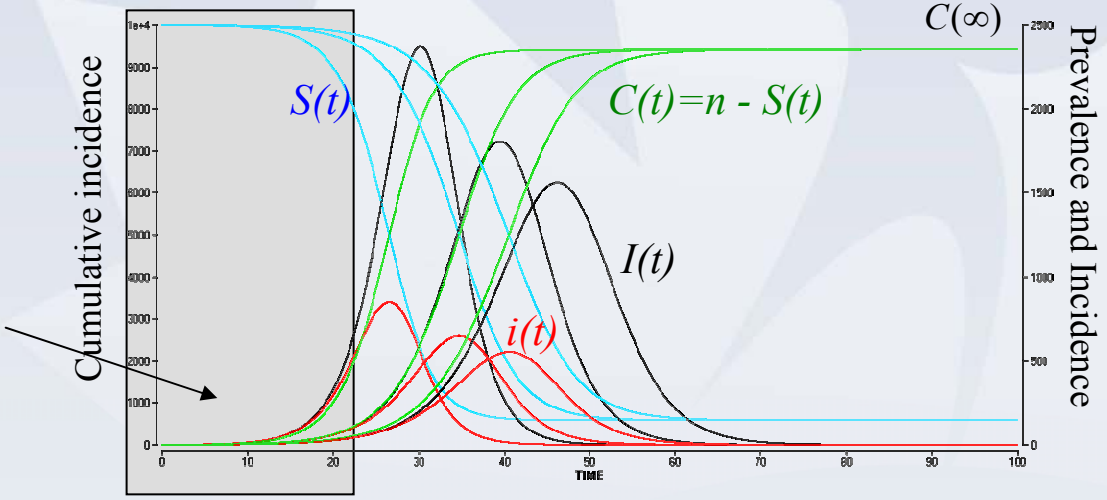

In most commonly used probability models, $\text{var}[X_1] \le \text{var}[X_2] \Leftrightarrow X_1 \ge_{Lt} X_2$.

1. When β and the infectious period distribution is given, the larger the latent period in Laplace transform order, the smaller is the Malthusian number ρ.

→ *"Comparing with models without a latent period, a latent period slows the initial growth. Of latent periods of equal mean values, the smaller the variance (homogeneous), the smaller is the initial growth rate ρ."*

2. When β and the latent period distribution is given, the larger the infectious period in Laplace transform order, the larger is the Malthusian number ρ.

→ *"Of the infectious periods of equal mean values, the smaller the variance (homogeneous), the larger is the initial growth rate ρ."*

Variability of the latent / infectious periods and dynamics

The early phase of an epidemic

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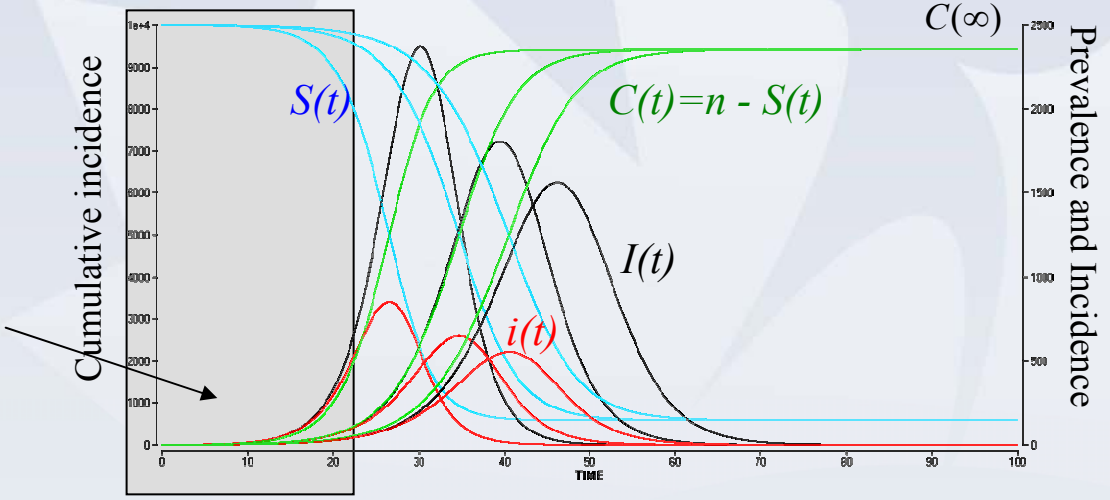


In most commonly used probability models, $\text{var}[X_1] \le \text{var}[X_2] \Leftrightarrow X_1 \ge_{Lt} X_2$.

→ *"Comparing with models without a latent period, a latent period slows the initial growth. Of latent periods of equal mean values, the smaller the variance (homogeneous), the smaller is the initial growth rate ρ."*

Conjecture *also later peak, longer duration of the epidemic.*

→ *"Of the infectious periods of equal mean values, the smaller the variance (homogeneous), the larger is the initial growth rate ρ."*

Conjecture *also earlier peak, shorter duration of the epidemic.*

Variability of the latent / infectious periods and dynamics

What have been discussed: given the same R_0

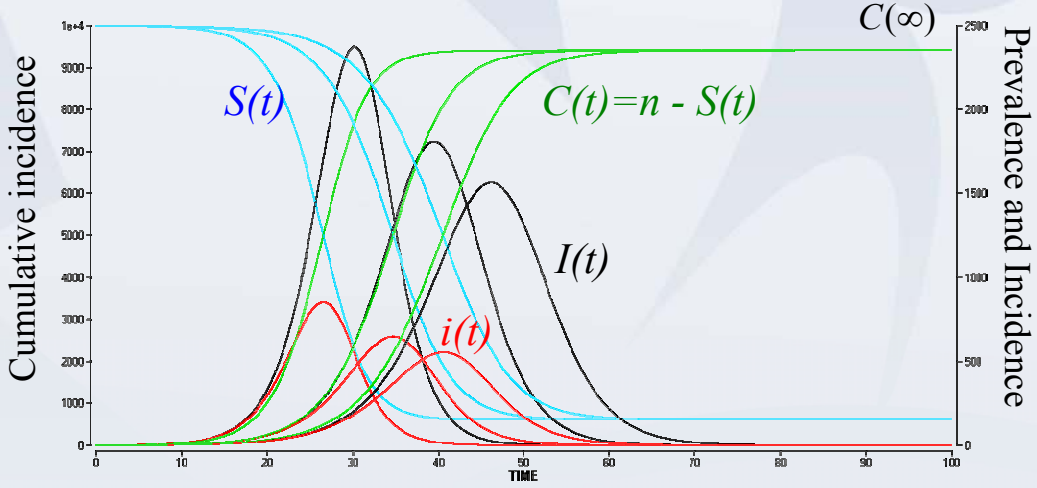
1. Same total area $C(\infty) = \int_0^\infty i(t)dt,$

   different paths for *i(t): incidence.*

2. Same total area

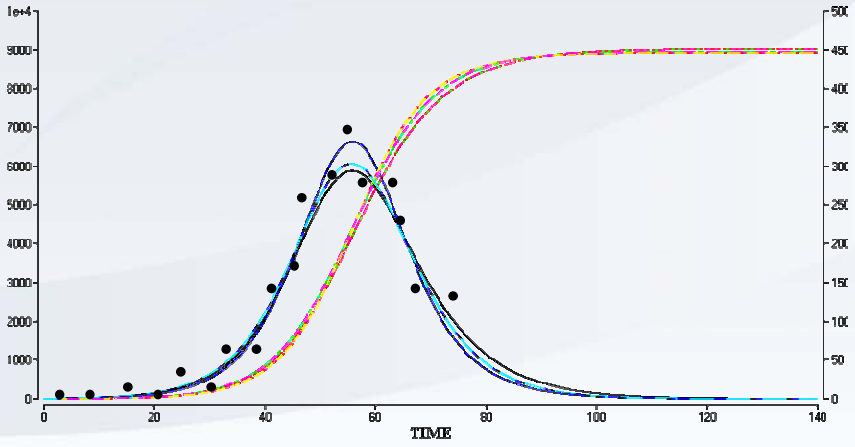
   $\int_0^\infty I(t)dt = \mu_I \times \int_0^\infty i(t)dt = \mu_I \times C(\infty)$

   different paths for *I(t): prevalence*



Conversely, for very different R_0s:

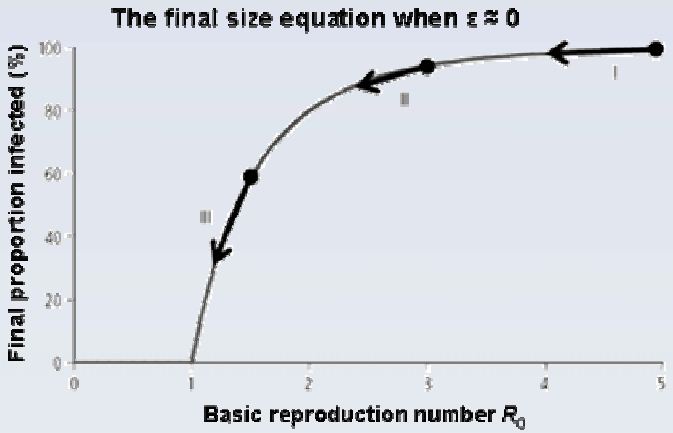
Different distributions for the latent and infectious period (even if the mean infectious period is fixed but the variance is assumed differently), can produce the same or very similar curves for *i(t)* or *I(t).*



Caution on curve fitting models to data to estimate important transmission parameters.

Variability of the latent / infectious periods and control measures

Recall: The final size equation $1-\overline{\eta} = (1-\varepsilon)\exp(-R_0\overline{\eta})$

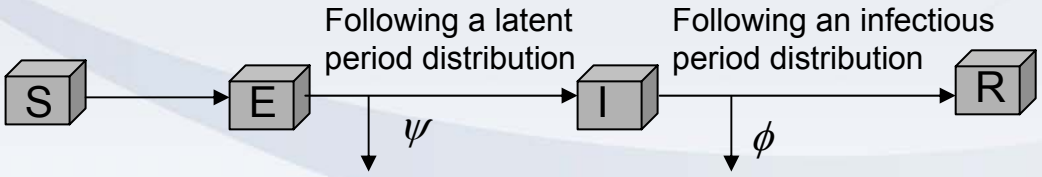


I. **R_0 = 5: 20% reduction of R_0, 1% reduction of final size**
II. **R_0 = 3: 20% reduction of R_0, 6% reduction of final size**
III. **R_0 =1.5: 20% reduction of R_0, 27% reduction of final size**

To reduce the final size, the same % reduction of R_0 may or may not be very effective, depending on the magnitude of R_0 before intervention.

Control measures can be pharmaceutical or non-pharmaceutical.

They can be applied to susceptible individuals (e.g. vaccine), or to infected individuals in either latent or infectious periods.

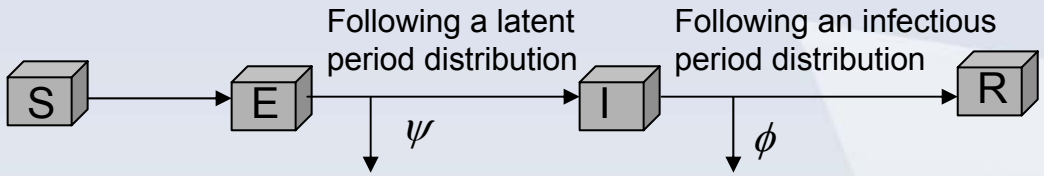


A. Removing from circulation before being able to transmit the virus

B. Removing from circulation so that no longer able to contact other susceptibles

To reduce the reproduction number, from R_0 to R_c, for some control measures, the effectiveness is determined by the variability of the latent and the infectious period.

Variability of the latent / infectious periods and control measures



A. Removing from circulation before being able to transmit the virus

B. Removing from circulation so that no longer able to contact other susceptibles

To reduce the reproduction number, from R_0 to R_c, the effectiveness is determined by the variability of the latent and the infectious period.

Under suitable homogeneity assumptions for agent-host-environment, so that $\beta \frac{S(t)I(t)}{n(t)}$

Statement

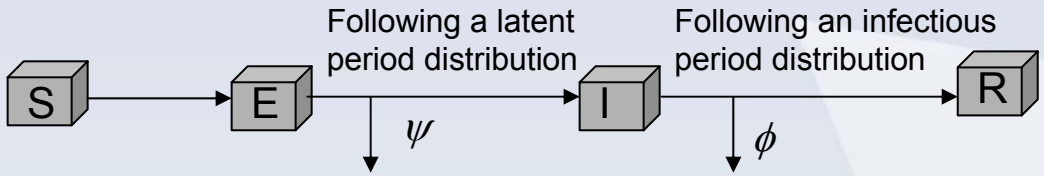
Assuming both actions are "perfect" (100% success), the controlled reproduction number depends on the distributions of both periods and is ranked separately according to their Laplace transform orders.

$$R_c(\psi,\phi) = \frac{\beta}{\phi} L_{Latent}(\psi)\left[1 - L_{Infectious}(\phi)\right]$$

Yan and Feng (*Mathematical Biosciences*, 2010)

Unlike $R_0 = \beta\mu_I$, which does not depend on the latent period and depends on the infectious period only by its mean value.

Variability of the latent / infectious periods and control measures



A. Removing from circulation before being able to transmit the virus

B. Removing from circulation so that no longer able to contact other susceptibles

To reduce the reproduction number, from R_0 to R_c, the effectiveness is determined by the variability of the latent and the infectious period.

Statement

$$R_c(\psi,\phi) = \frac{\beta}{\phi} L_{Latent}(\psi)\left[1 - L_{Infectious}(\phi)\right]$$

Yan and Feng (*Mathematical Biosciences*, 2010)

$L_{Latent}(\psi) =$ the proportion of latent individuals that eventually escape from being removed (under constant rate ψ) and become infectious.

→ The larger the latent period in Laplace transform order (~ smaller variance), the larger is the probability for latent individuals to be removed, and the easier it is to use A. to control the epidemic.

$\frac{1 - L_{Infectious}(\phi)}{\phi} =$ the average duration of infectious individuals in the I-class before either recovers naturally or removed by control measure (under constant rate ϕ).

→ The larger the infectious period in Laplace transform order (~ smaller variance), the longer is the average duration of infectiousness, and the harder it is to use B. to control the epidemic.

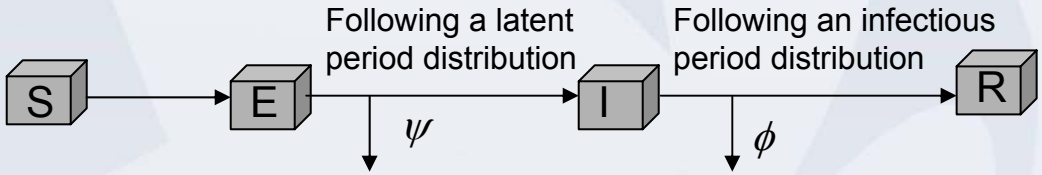
Variability of the latent / infectious periods and control measures

Statement

$$R_c(\psi,\phi)=\frac{\beta}{\phi}L_{Latent}(\psi)\left[1-L_{Infectious}(\phi)\right]$$

assuming both actions are "perfect" (100% success)

Extension to "leaky situations":



A. Removing from circulation before being able to transmit the virus

B. Removing from circulation so that no longer able to contact other susceptibles

1. For action B, infected individuals may be put into "leaky isolation", with reduced transmissibility $(1-\sigma_I)\beta$.

2. For action A, latent individuals may be put into "leaky isolation", and when they become infectious, they have reduced transmissibility $(1-\sigma_L)\beta$.

Quantitative:

$$R_c(\psi,\phi\,|\,\sigma_L,\sigma_I)=(1-\sigma_L)R_0+(\sigma_L-\sigma_I)L_{Latent}(\psi)R_0+\frac{\sigma_I\beta}{\phi}L_{Latent}(\psi)\left[1-L_{Infectious}(\phi)\right]$$

Yan and Feng (*Mathematical Biosciences*, 2010)

Qualitative statements on variability of the latent / infectious periods and control measures based on $R_c(\psi,\phi)=\frac{\beta}{\phi}L_{Latent}(\psi)\left[1-L_{Infectious}(\phi)\right]$ remain unchanged.

Variability of the latent / infectious periods and control measures

Qualitative discussions that are also applicable to other measures applied to individuals during their latent and infectious periods:

1. Certain control measures, such as contract tracing for exposed individuals with subsequent quarantine and/or pharmaceutical interventions (prophylaxis), work well if there is a significantly long latent period, and not so well if the latent period is very short.

   Add: Such measures work well if the latent period is a long and not very variable (homogeneous). They may not work well if there is large variation (heterogeneous), even if the latent period is long on average.

   For the same average latent period: homogeneous: good;
   heterogeneous: bad.

2. Isolating infectious individuals and/or treating them using antiviral drugs that may reduce transmission, work better if the natural infectious period is short.

   Add: Such measures work well if the infection period has large variation (heterogeneous), even when the infectious period is long on average.

   For the same average infectious period: homogeneous: bad;
   heterogeneous: good.

Final remarks: Connections

Under homogeneity assumptions for agent-host-environment, so that $\beta \frac{S(t)I(t)}{n(t)}$

$\frac{\beta}{\rho} L_{Latent}(\rho)\left[1 - L_{Infectious}(\rho)\right] = 1$: the initial (exponential) growth of a large outbreak is ranked by the Laplace transform orders of the latent and the infectious periods.

This connects to the question : *What is the risk of a large outbreak: $1-\pi = ?$*

Let *N* be the random variable so that $R_0 = E[N]$, *with probability generating function* $G_N(s),\ s > 0$

π is the smallest root of the fixed-point equation $G_N(s) = s$

In fact: $G_N(s) = L_{Infectious}(\beta(1-s)) \rightarrow L_{Infectious}(\beta(1-\pi)) = \pi$

If there is no latent period (SIR): $\frac{\beta}{\rho}\left[1 - L_{Infectious}(\rho)\right] = 1 \rightarrow 1 - \pi = \frac{\rho}{\beta}!$

If there is a latent period (SEIR): $\frac{\beta}{\rho} L_{Latent}(\rho)\left[1 - L_{Infectious}(\rho)\right] = 1 \rightarrow 1 - \pi > \frac{\rho}{\beta}.$

One can show that if $R_0 > 1$, it is always true that $\rho < \beta$.

One can use the observed initial growth rate in a large outbreak to provide a lower bound of the risk of a large outbreak in a similar community, under similar initial conditions.

Final remarks: Connections

Under homogeneity assumptions for agent-host-environment, so that $\beta \frac{S(t)I(t)}{n(t)}$

$\frac{\beta}{\rho} L_{Latent}(\rho)\left[1 - L_{Infectious}(\rho)\right] = 1:$ the initial (exponential) growth of a large outbreak is ranked by the Laplace transform orders of the latent and the infectious periods.

This also connects to : $R_c(\psi, \phi) = \frac{\beta}{\phi} L_{Latent}(\psi)\left[1 - L_{Infectious}(\phi)\right]$

If one can set control objectives $\psi \geq \psi_c$ and $\phi \geq \phi_c$ in order to achieve $R_c(\psi, \phi) \leq 1$,

then one can successfully prevent a large outbreak from taking place.

Ideally, it is achievable if $\psi_c = \phi_c = \rho.$

Lessons can be learned from observed initial growth rate in large outbreak that have happened elsewhere to set control targets to prevent a large outbreak from happening in a similar community, under similar initial conditions.