

# $R_0$ from first principles

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(slides by Christophe Fraser, Jeffrey Eaton, and others...)

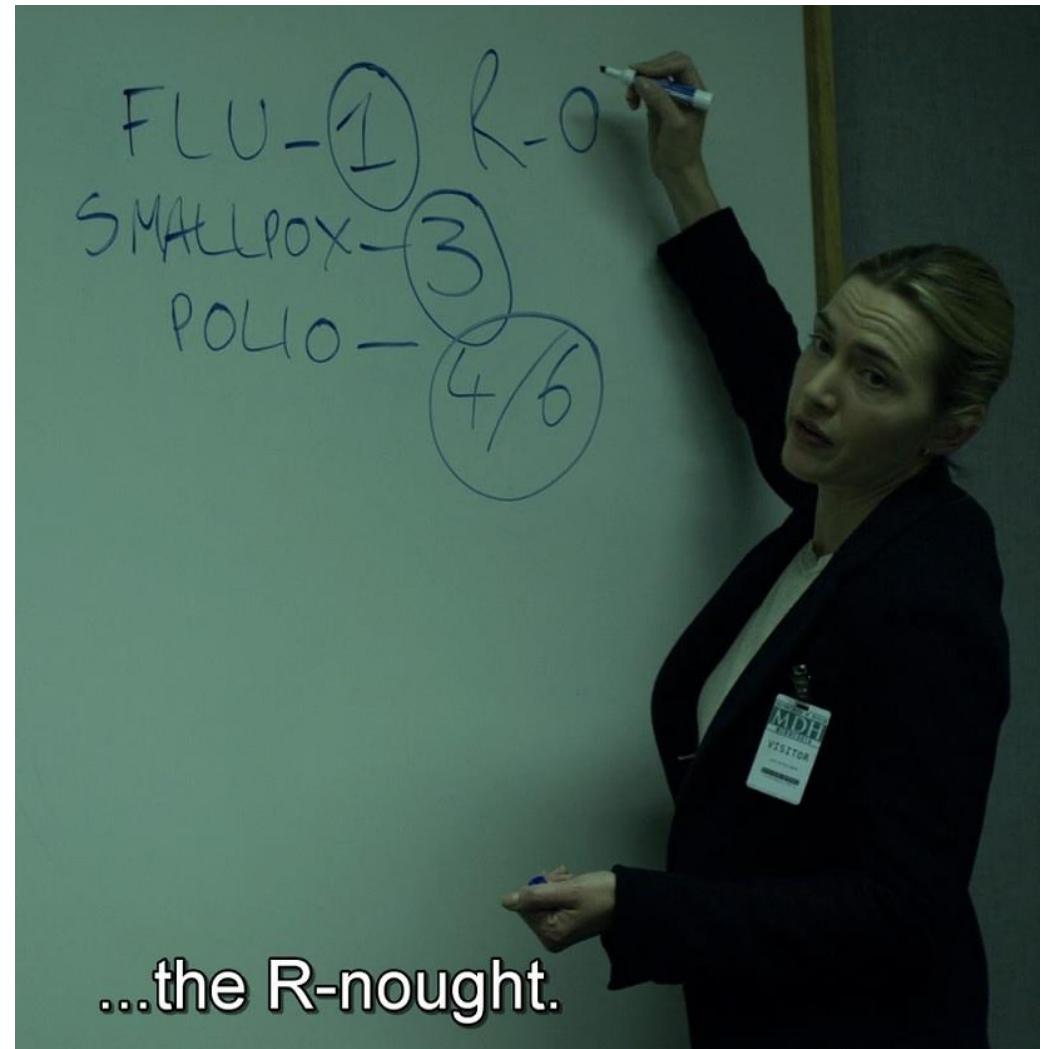
Oct. 2018

# Basic reproductive number, $R_0$

- It is the average number of secondary infections occurring from a typical infected individual in a totally susceptible population
- For an epidemic to occur requires that transmission from an infected individual causes on average more than one new infection (i.e.  $R_0 > 1$ ) so amplification occurs
- Measures how effectively infection spreads – higher  $R_0$  means harder to control

# Basic reproductive number, $R_0$

It's the “star” parameter of epidemic modelling!



“Contagion” (S.Soderbergh)  
IMDB rating = 6.6/10

# Using the $R_0$ formula

- We can derive the mathematical formula for  $R_0$  for a particular model
- Once we have the formula for  $R_0$  for the model we can use it in two ways:
  - if we know all of the parameter values then  $R_0$  can be directly estimated from them; or
  - if we know some of the parameter values and we can indirectly estimate  $R_0$  (e.g. from the rate of epidemic growth), then we can estimate the unknown parameter value(s) – or, at least, their 'aggregate' value without estimating each one independently

This afternoon: practical on flu  $R_0$  estimation (using indirect method)

# This lecture is in two parts

- Part 1: Estimating  $R_0$  from first principles
- Part 2: Deriving the mathematical formula for  $R_0$  for a particular model (for a homogeneous population)

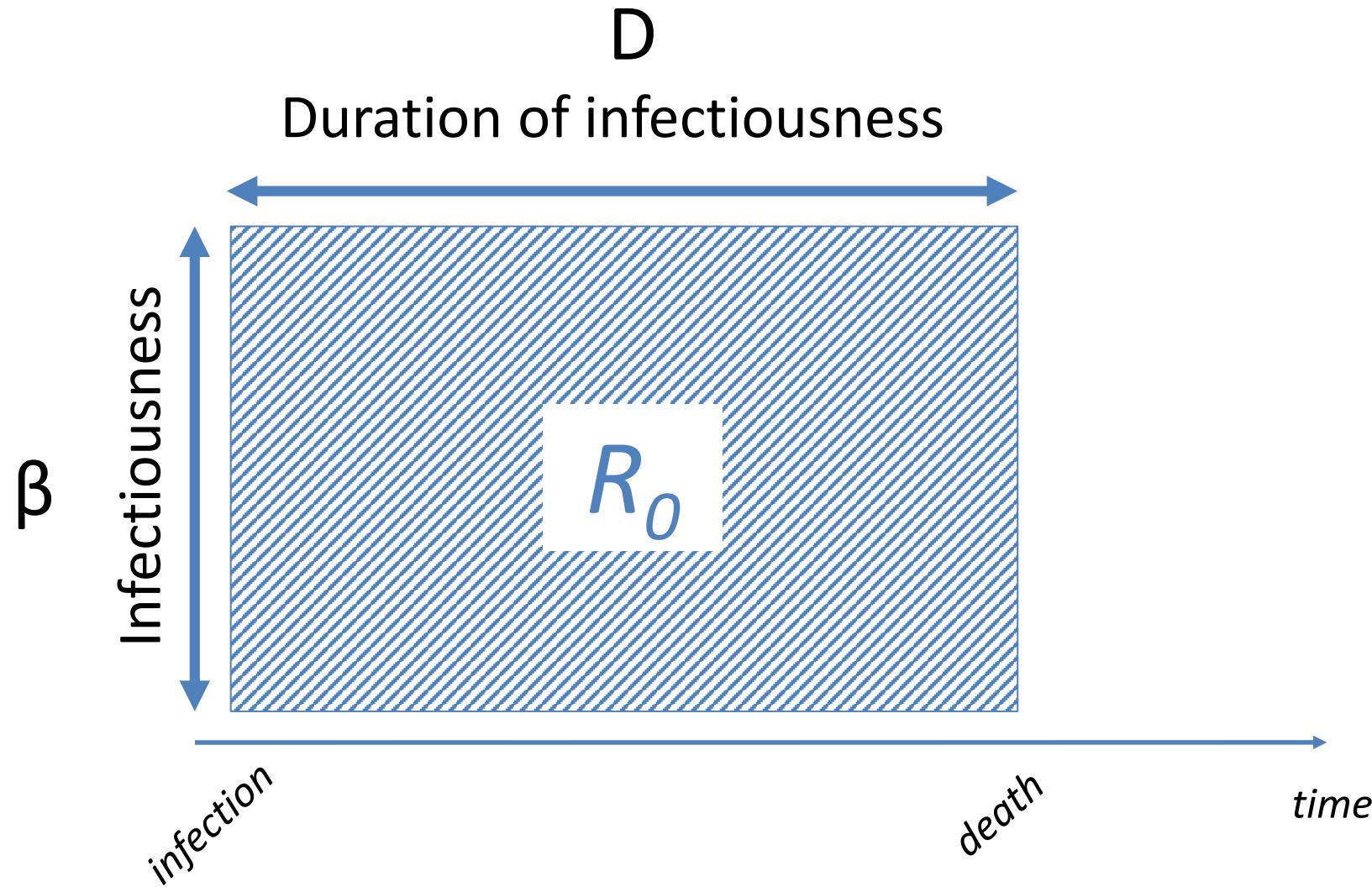
# **Part 1: Estimating $R_0$ from first principles**

# Estimating $R_0$

- Quantity defined in terms of model parameters (change in the model → change in  $R_0$  formula)
- Many different methods for estimation – direct and indirect
- Here, focus on most direct: estimation of component parameters
- This afternoon, indirect method (flu practical)

# $R_0$ from first principles: simple definition

Average number of secondary infections occurring from a typical infected individual in a totally susceptible population



# $R_0$ from first principles

$$R_0 = \beta D = p c D$$

Diagram illustrating the components of the basic reproduction number  $R_0$ :

- Transmission rate** ( $\beta$ ): Represented by a purple arrow pointing to the term  $\beta$ .
- Transmission probability per contact** ( $p$ ): Represented by a red arrow pointing to the term  $p$ .
- Contact rate** ( $c$ ): Represented by a green arrow pointing to the term  $c$ .
- Duration of infectiousness** ( $D$ ): Represented by a blue arrow pointing to the term  $D$ .

# $R_0$ from first principles

$$R_0 = \beta D = pcD$$

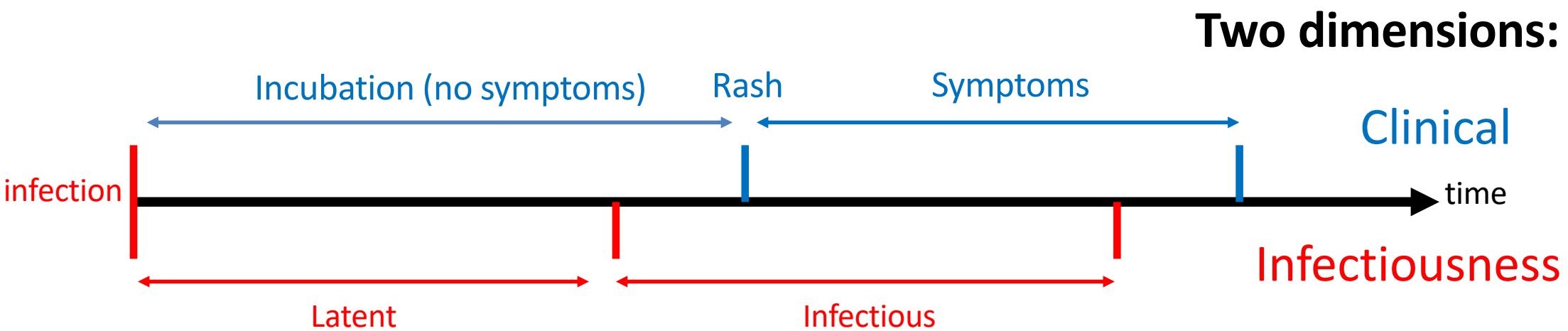
**Duration of infectiousness**

The equation  $R_0 = \beta D = pcD$  is displayed. The term  $\beta D$  is shown in gray, while  $pcD$  is shown in blue. Below the equation, the text "Duration of infectiousness" is written in blue, with two blue arrows pointing towards it from the terms  $D$  and  $cD$  respectively.

# Duration of infectiousness

Average period during which an infected individual is **infectious**

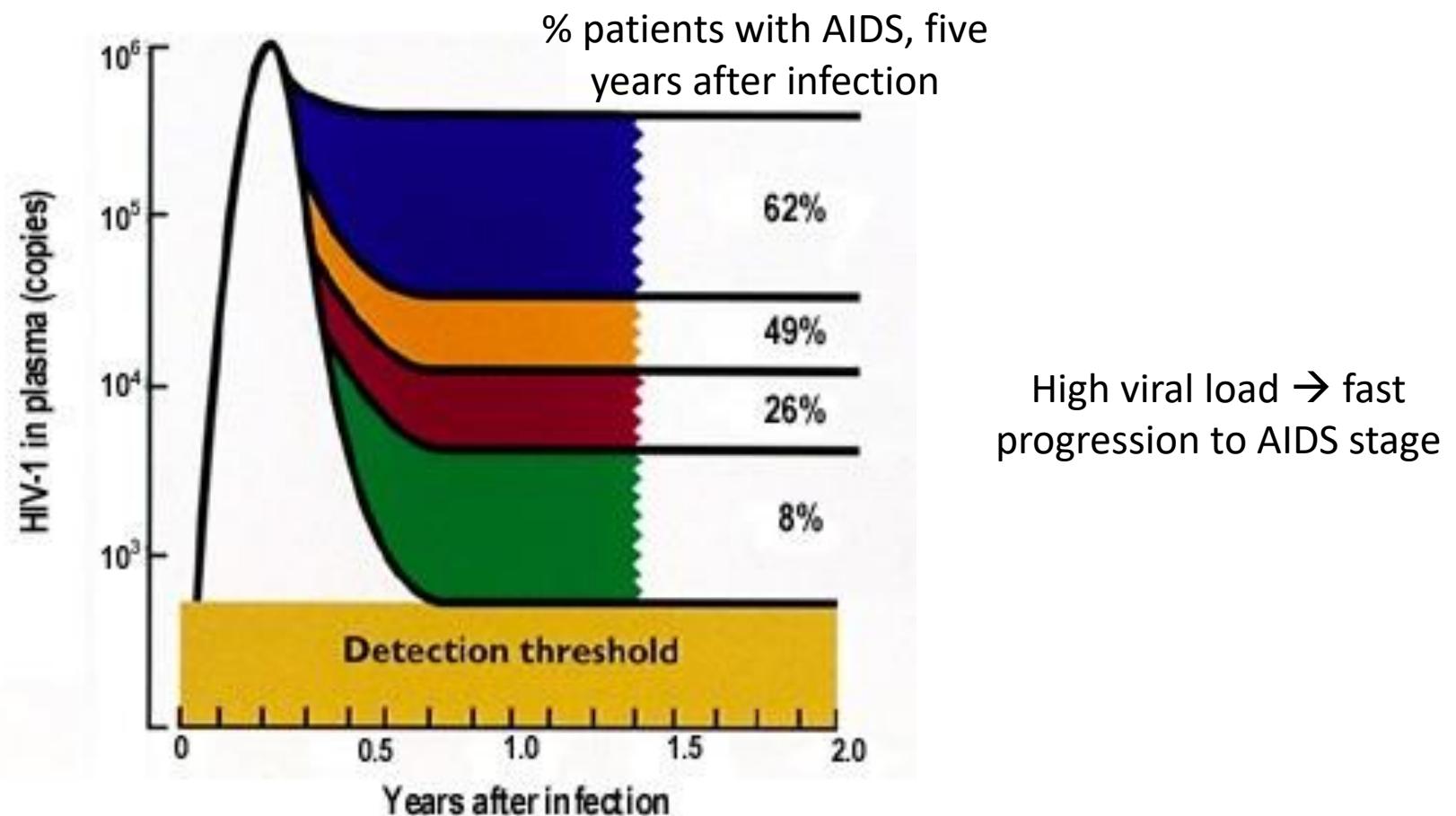
- Chicken Pox (VZV)
  - Incubation: 7-21 days
  - Infectious period: a few days before the rash until the last spot or blister has formed a scab



Mathematical models focus on the durations related to individual infectivity, not symptoms (**but** they can be related, e.g. a complex VZV model might represent school exclusion after the rash appears)

# HIV: Variability in progression

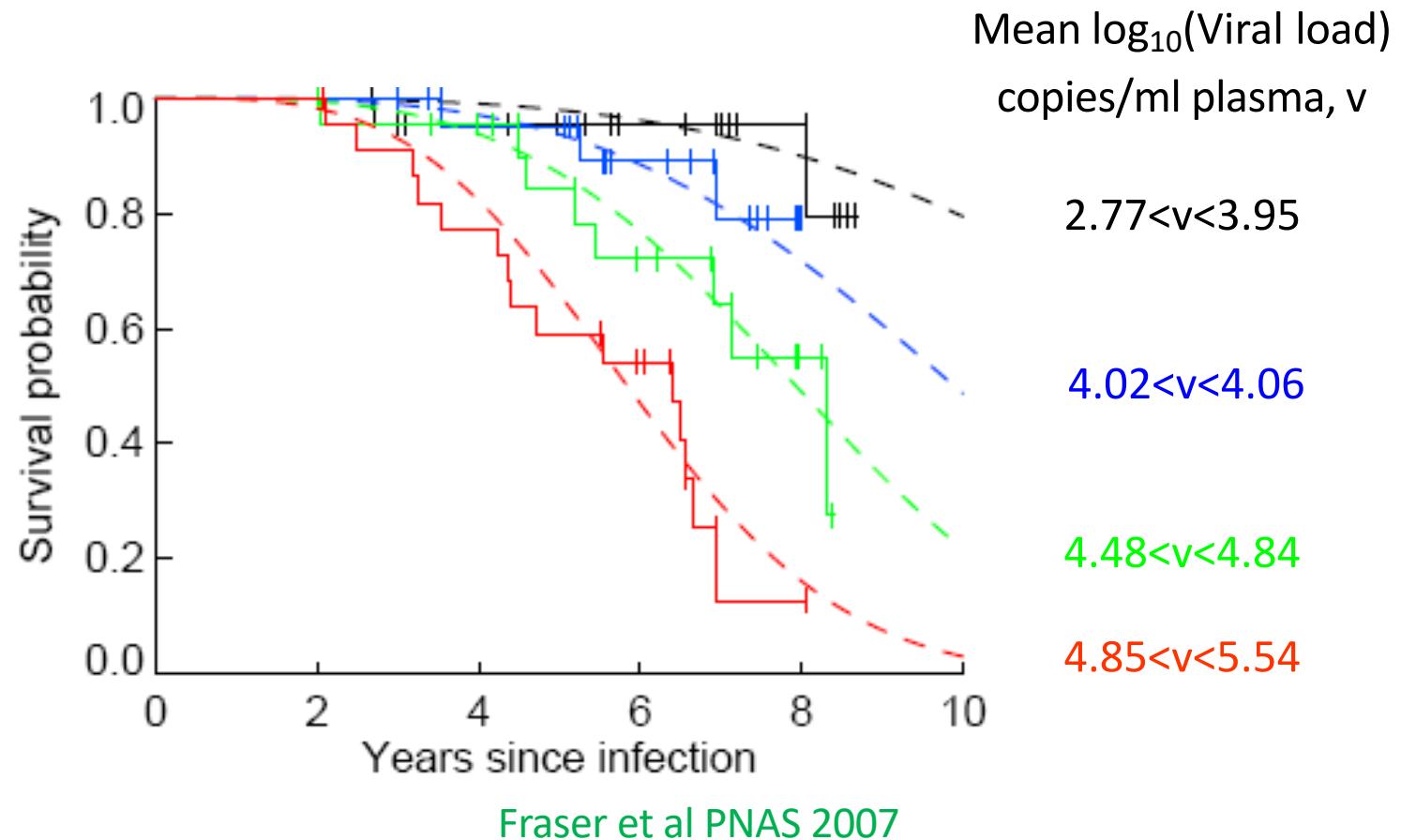
- Viral load is correlated with progression to AIDS



Ho, Science 1996

# HIV: Duration of infection

Weibull survival curve,  
dependent on mean  
viral load, fitted to  
Amsterdam  
Seroconvertors Cohort  
data pre-HAART.  
Shown for quartiles of  
mean viral load (n=23  
in each quartile)

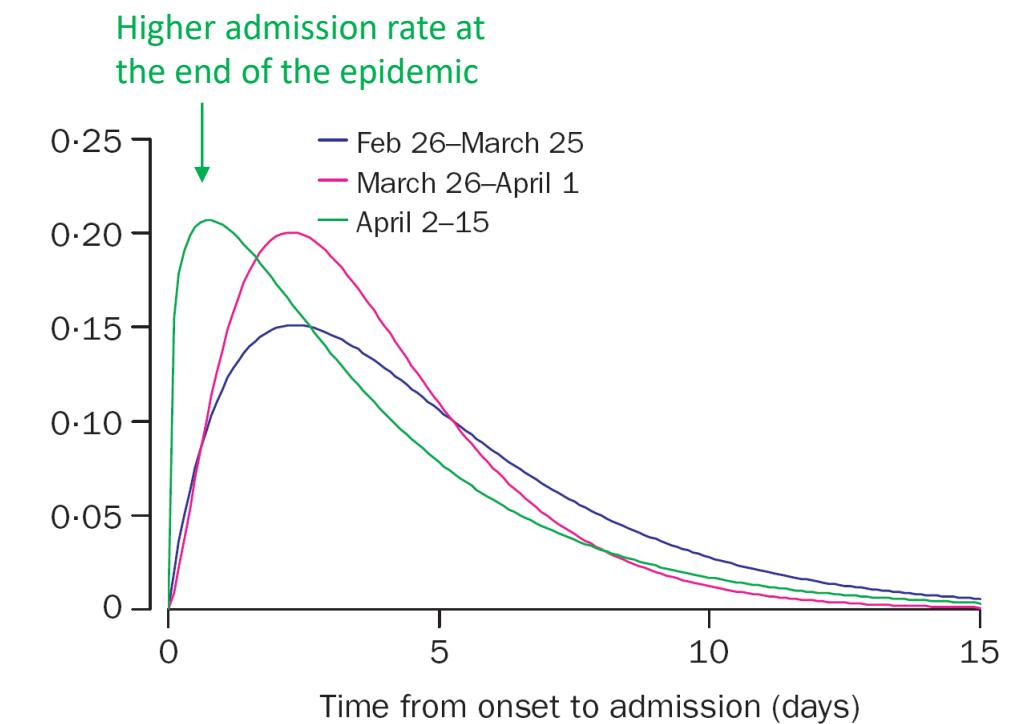
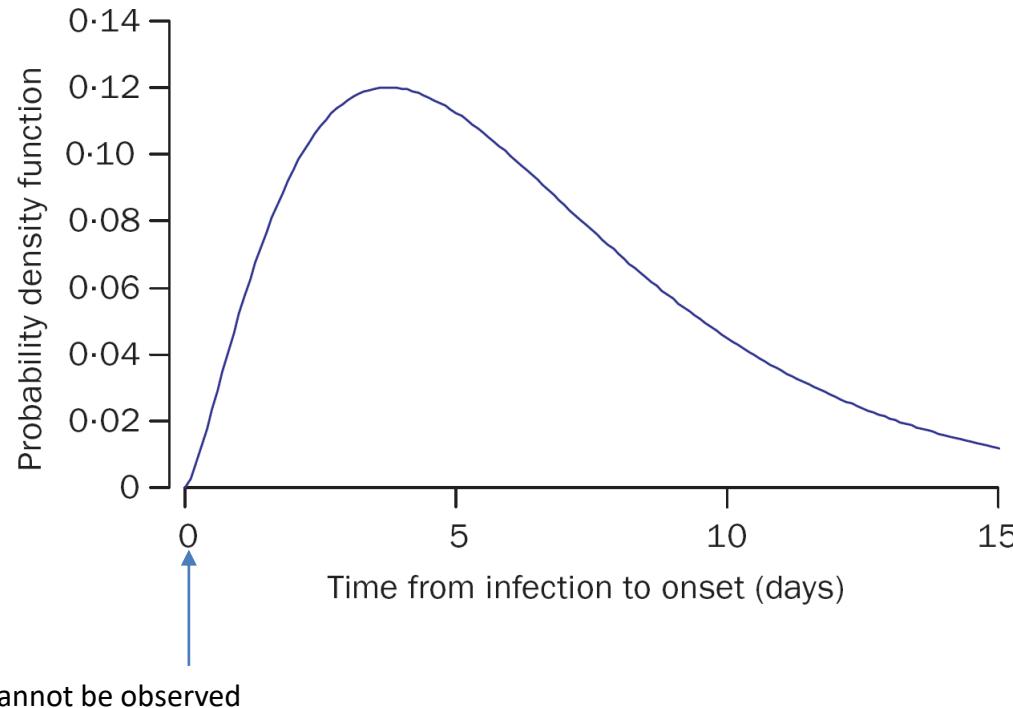


High viral loads ~ shorter lifetime

$\beta$  and D are rarely independent  $\rightarrow \text{mean}(R_0) \neq \text{mean}(\beta) \times \text{mean}(D)$

# Duration of infectiousness

- Variability between patients during the SARS epidemic



Donnelly *et al Lancet* 2003

$$R_0 = \beta D = pcD$$

Transmission

rate

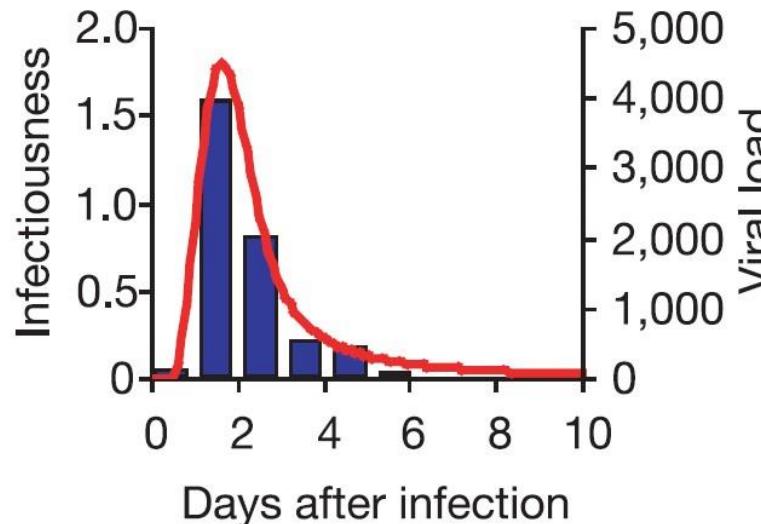


# Transmission rate

- Transmission rate  $\beta$ 
  - Rate at which infection is transmitted over time
  - Very difficult to estimate
  - Changes over course of infection

# Flu transmission rates

- Viral shedding and infectiousness
  - Infectiousness from household study
  - Shedding from challenge study



Ferguson *et al* Nature 2005



- Symptoms may not be a good marker for infectivity
  - Meta-analysis of volunteer studies

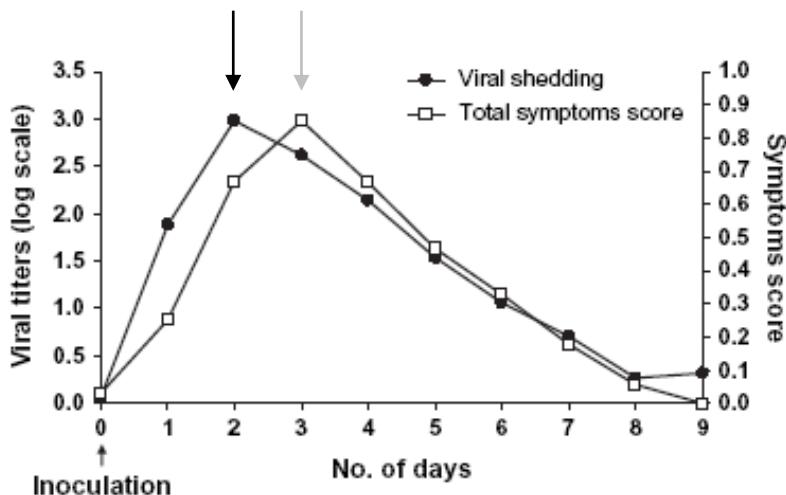


FIGURE 5. Summary curves of viral shedding and total symptoms scores in experimental influenza virus infection. Thirteen curves were used for viral shedding (refer to figure 2 legend), and 17 curves were used for total symptoms scores (refer to figure 3 legend).

Carrat *et al* Am J Epi 2008

$$R_0 = \beta D = p c D$$

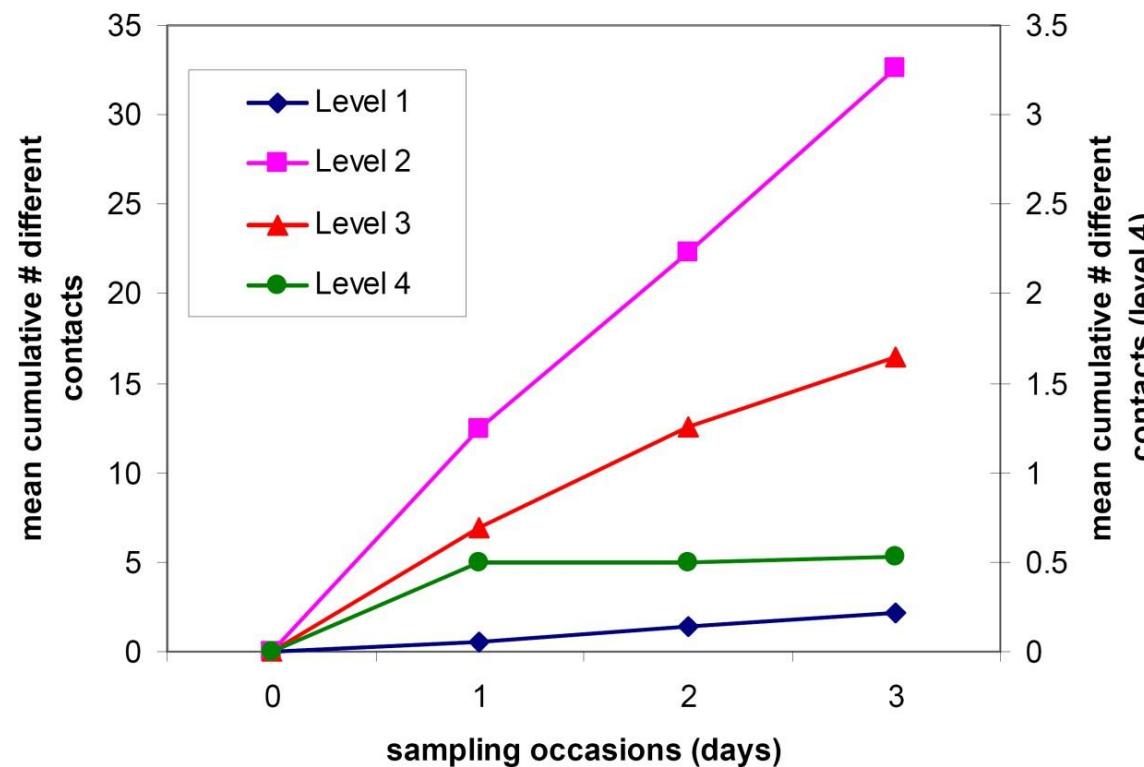
Contact rate



# A 'contact'

- What is a 'contact'?
- Who contacts who?
- Airborne diseases
  - Sitting on same bus/train for 10 minutes?
  - Having a conversation?
  - Sitting in a lecture room for 2 weeks?

# Contact patterns – level of contact

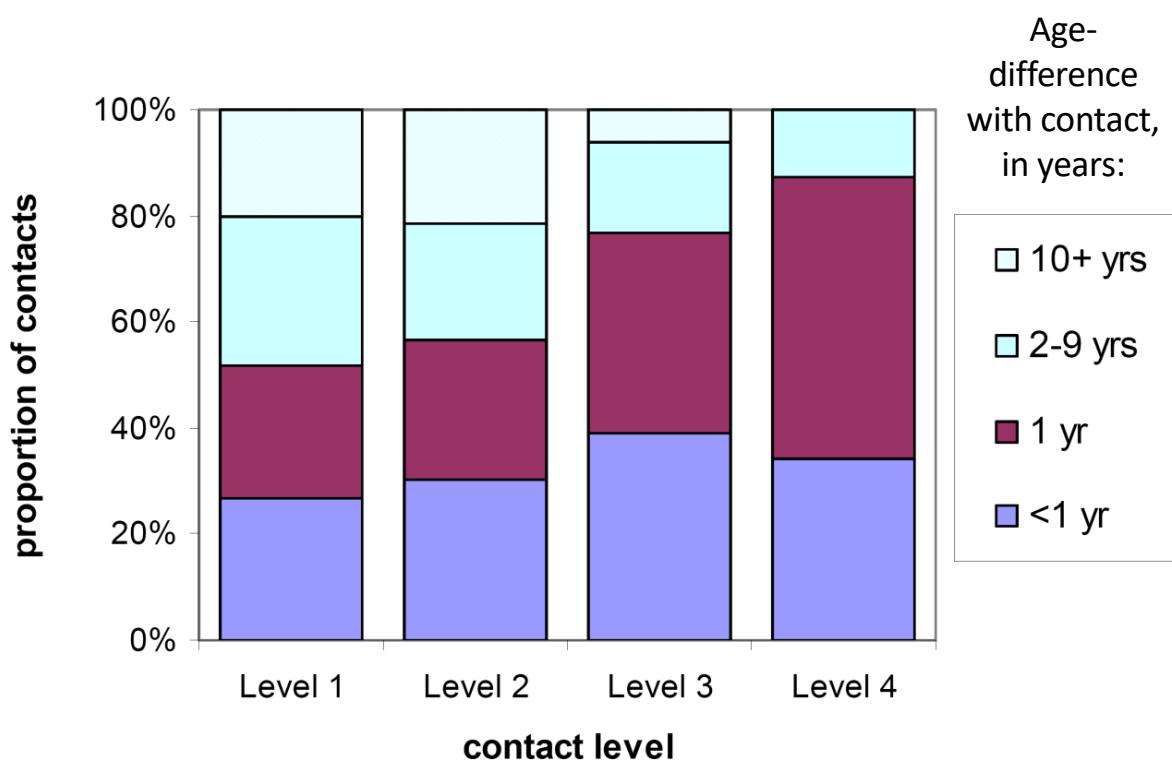


1. Physical, no conversation
2. Conversation, no physical
3. Conversation, non-sexual physical
4. Sexual contact, including kissing

Population:  
Warwick university students (volunteers)

Edmunds *et al* Emerging Themes  
in Epidemiology (2006)

# Contact patterns – age differences

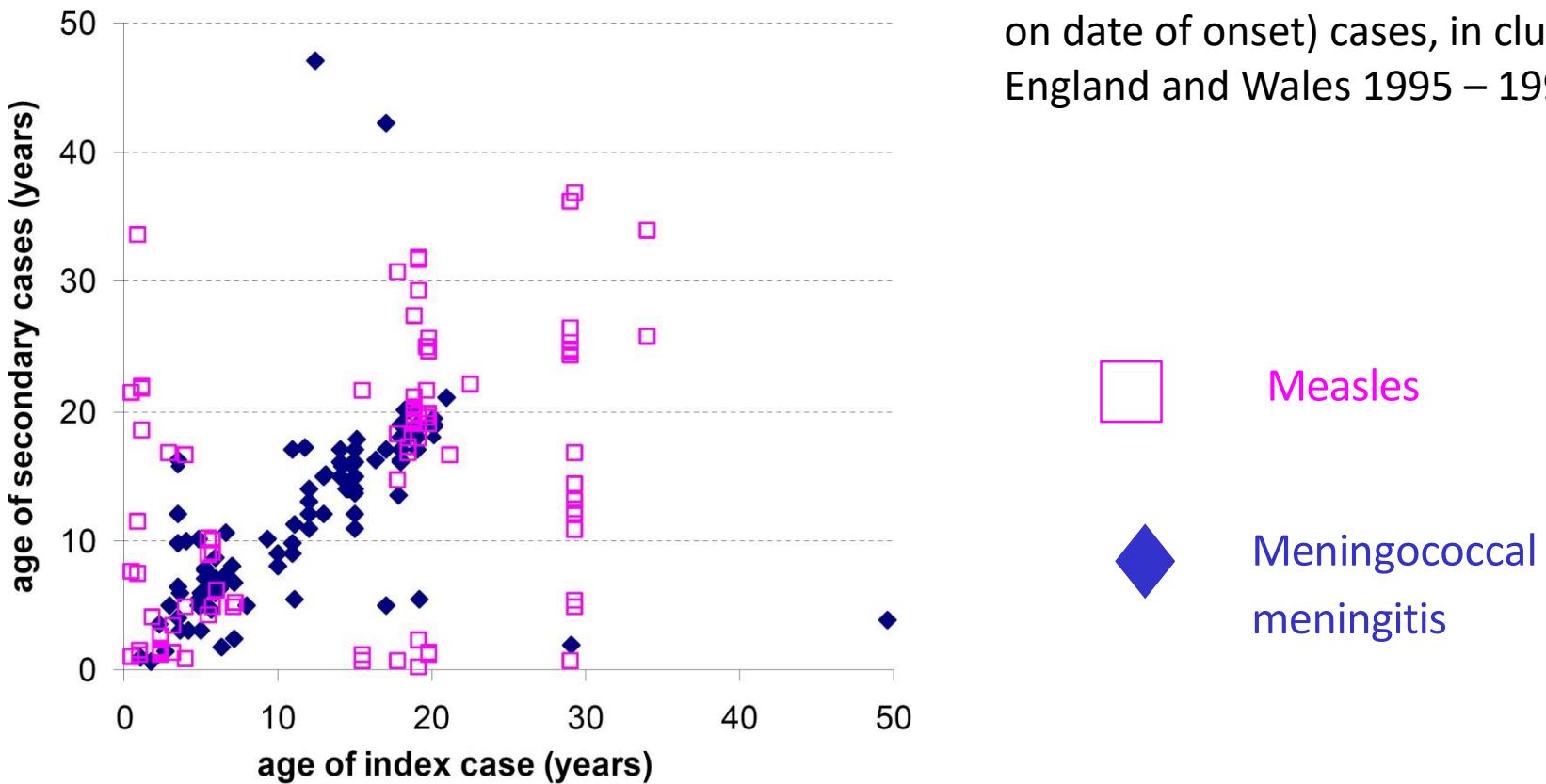


Contacts are increasingly assortative as intimacy increases

1. Physical, no conversation
2. Conversation, no physical
3. Conversation, non-sexual physical
4. Sexual contact, including kissing

Edmunds *et al* Emerging Themes in Epidemiology (2006)

# Contact patterns – age distribution

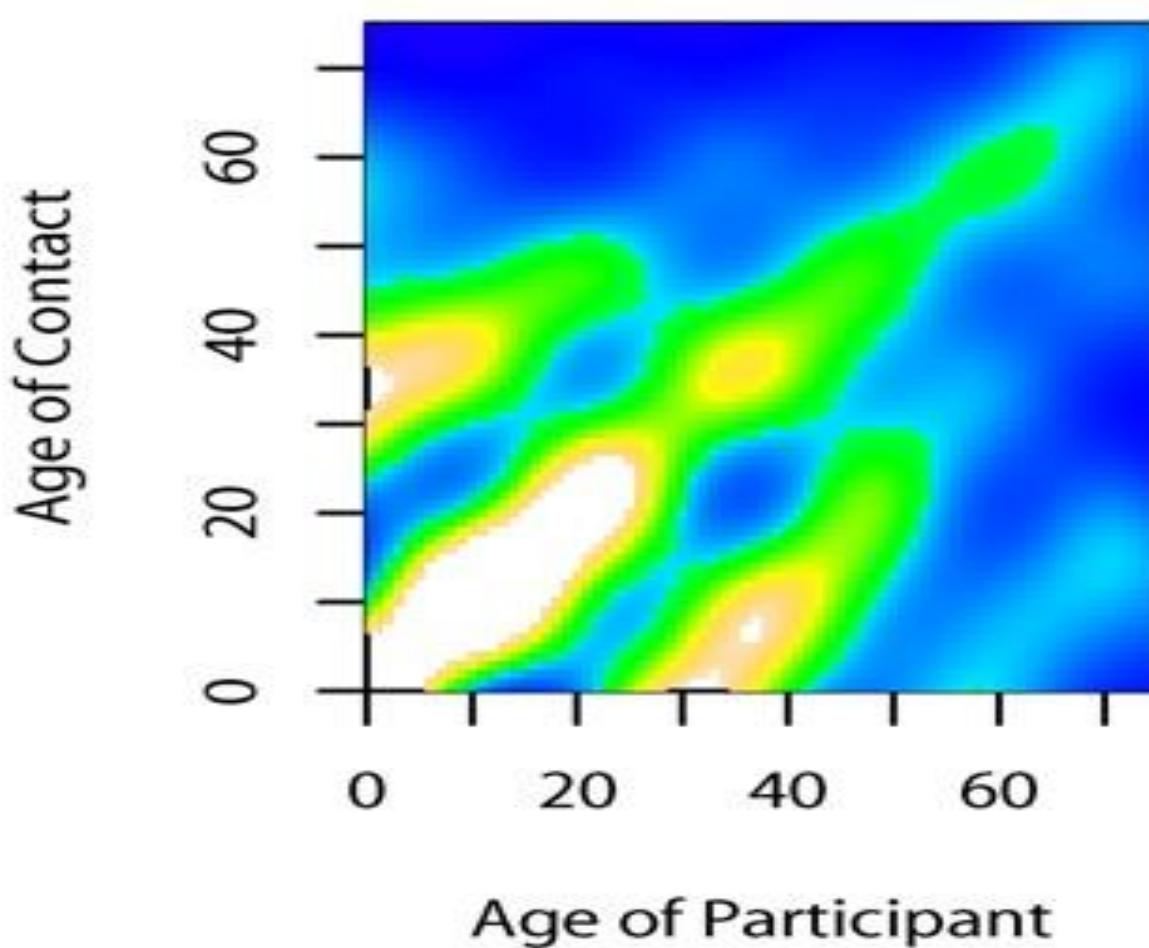


Diagonal: assortative (“like-with-like”) contacts

Edmunds *et al* Emerging Themes in Epidemiology (2006)

## Large scale POLYMOD study

GB

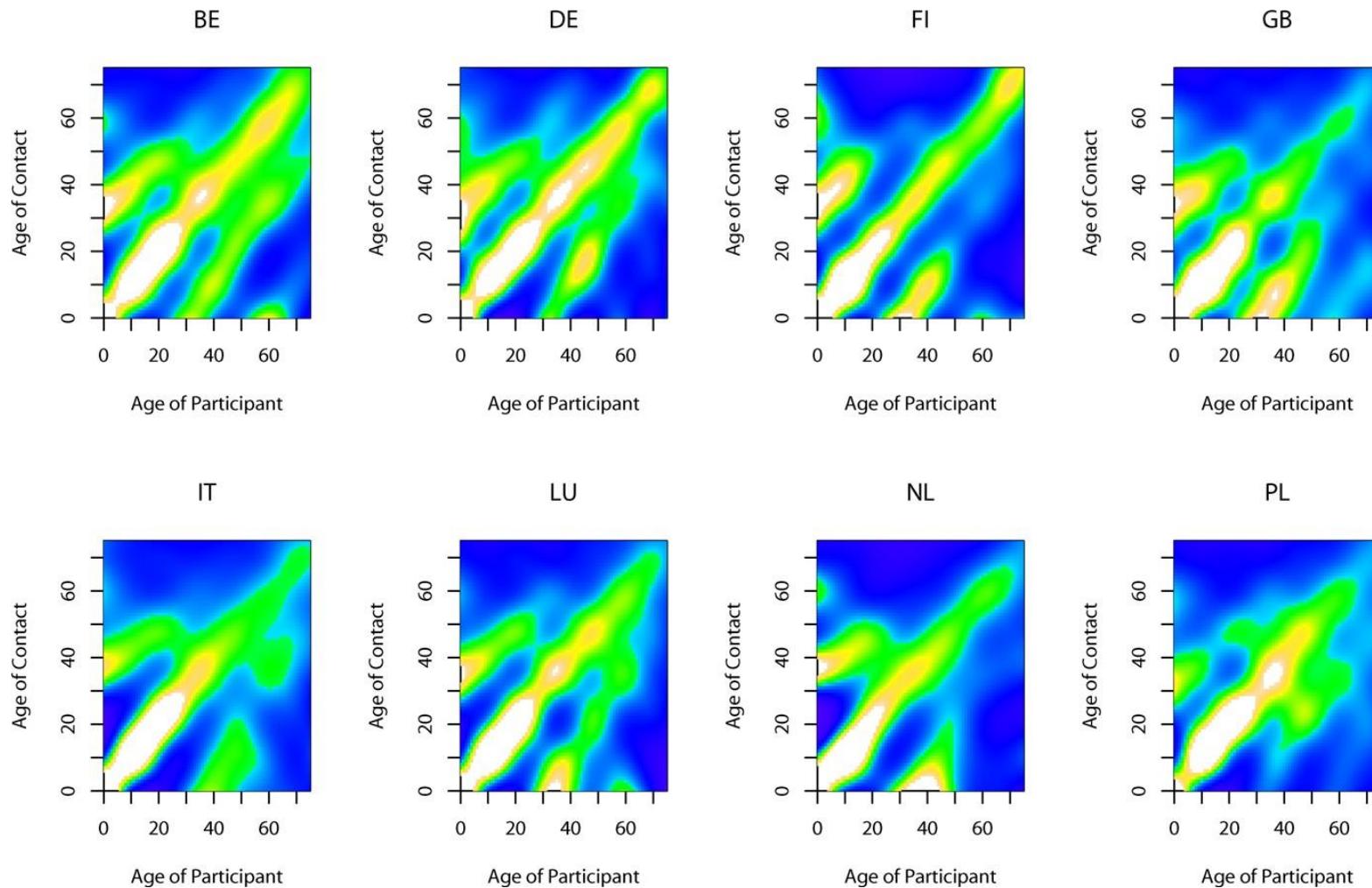


Assortative mixing +  
contacts within the  
household

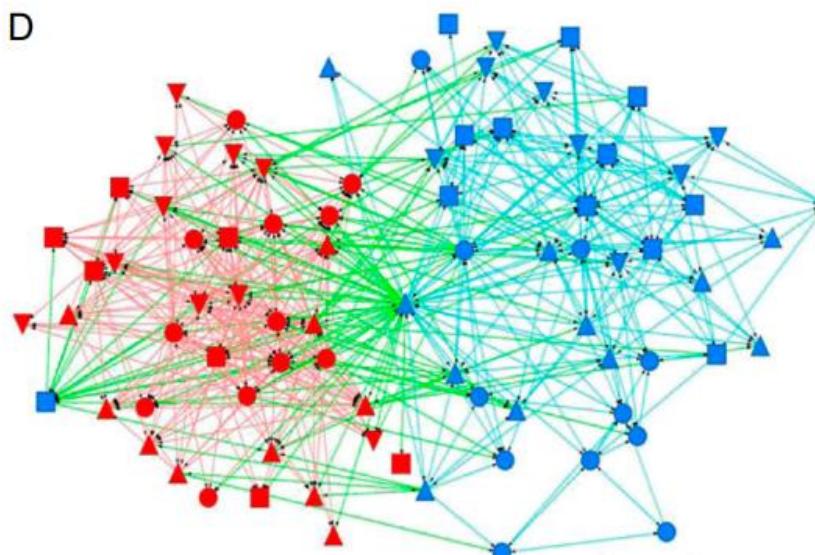
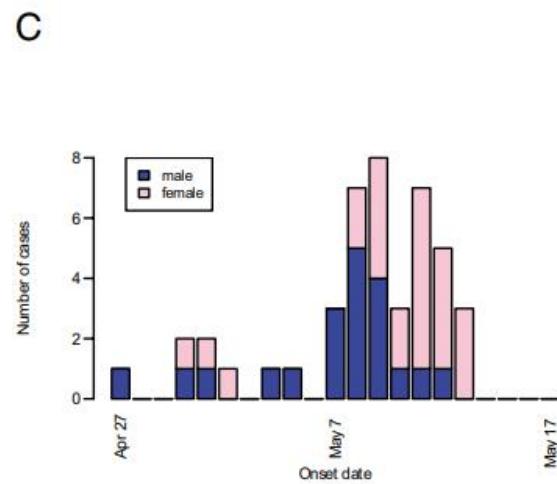
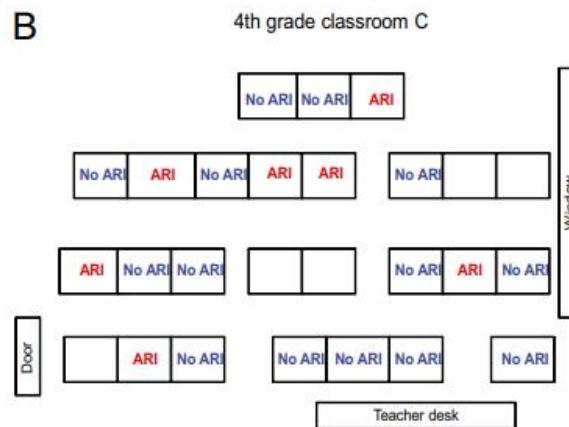
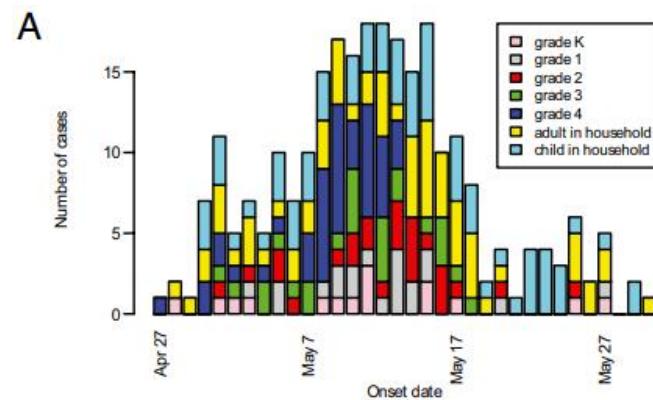
2<sup>nd</sup> Nov. “2. More complex  
models” module

Mossong et al, Plos Med, 2008

# Large scale POLYMOD study



# Contact patterns – role of social networks



Cauchemez *et al* PNAS (2011)

Community outbreak  
of 2009 H1N1  
pandemic influenza  
(Pennsylvania)  
(ARI = acute  
respiratory illness)

Panel B) Sitting next to a case or being the playmate of a case did not significantly increase the risk of infection. The structuring of the school into classes and grades strongly affected spread.

Panel D) There was evidence that boys were more likely to transmit influenza to other boys than to girls (and vice versa)

# Airborne diseases: other contacts

Flu can be transmitted via multiple surfaces, including banknotes!

APPLIED AND ENVIRONMENTAL MICROBIOLOGY, May 2008, p. 3002–3007  
0099-2240/08/\$08.00+0 doi:10.1128/AEM.00076-08  
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## Survival of Influenza Virus on Banknotes<sup>▽</sup>

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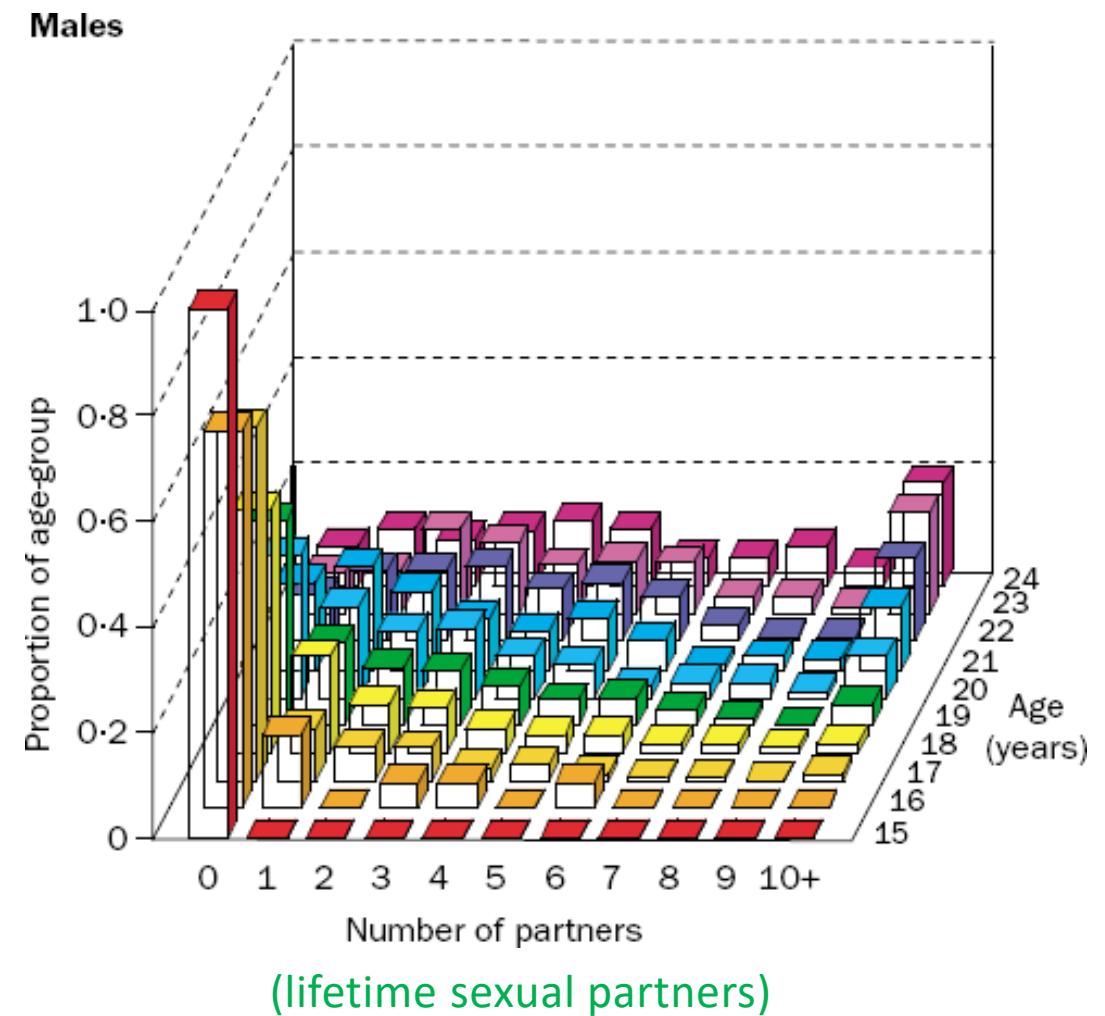
# A 'contact'

- What is a 'contact'?
- Who contacts who?
- *Airborne diseases*
  - *Sitting on same bus/train for 10 minutes?*
  - *Having a conversation?*
  - *Sitting in a lecture room for 2 weeks?*
- Sexually Transmitted Infections (STI's)
  - A 'sex act'?
  - A 'relationship'?

# Sexual contacts

- Information gathered by surveys
  - Sensitive information
  - Difficult to interpret

Gregson *et al Lancet* 2002



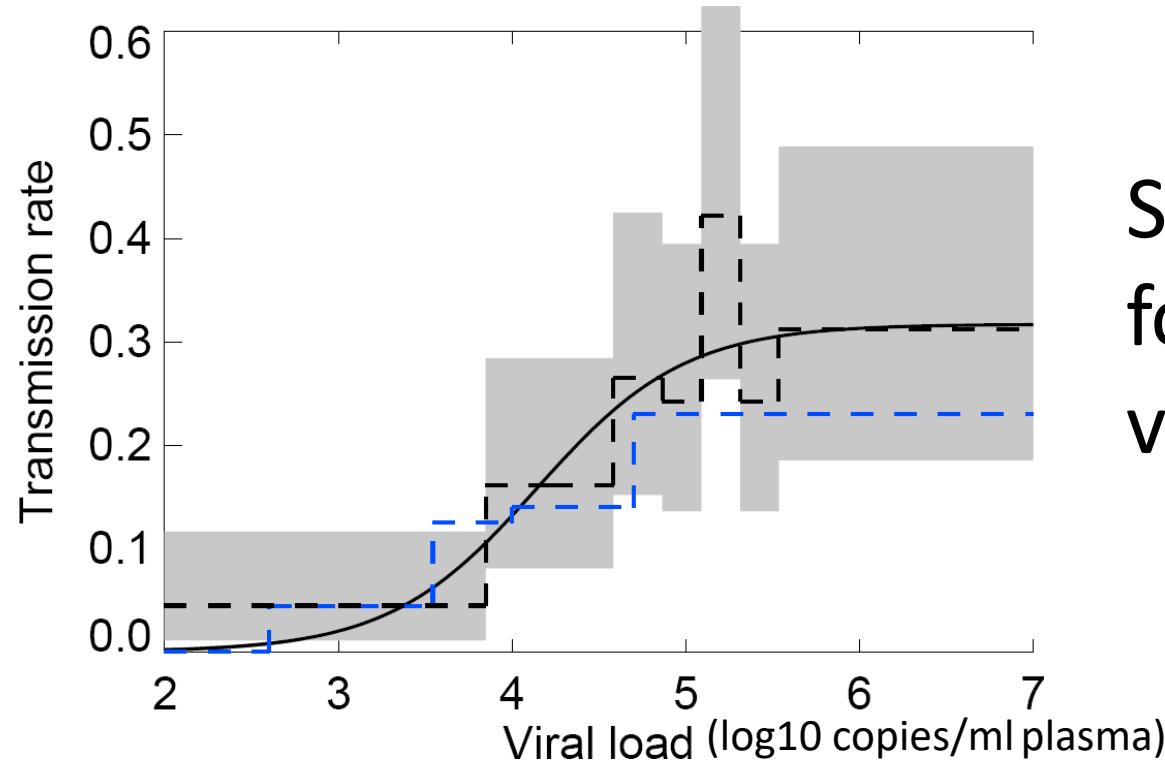
$$R_0 = \beta D = p^{cD}$$

Transmission  
probability  
per contact

# Probability of transmission

- Probability that disease is transmitted per contact
- Very difficult to study unless have detailed data
- STI's: discordant couples studies
  - One individual infected and observe the other individual in the relationship
- Will depend on multiple factors

# HIV: Transmission as a function of viral load

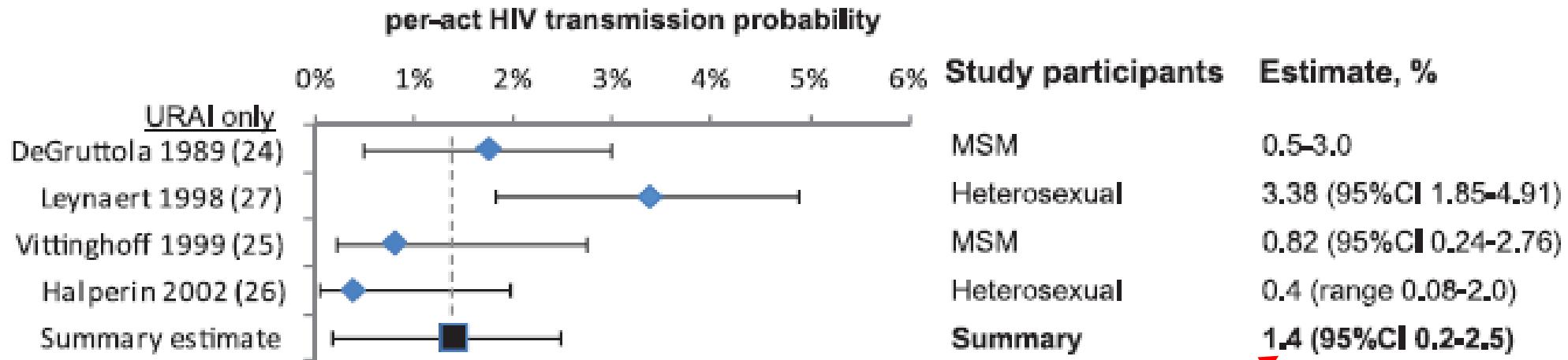


- Logistic regression of data from Fideli *et al* (2001) AIDS 17:901-910
- Data from Quinn *et al* (2002) New England Journal Medicine 342:921-292
- Proportion of transmitters in Fideli *et al* data septiles, 95% Conf Inter

Fraser *et al* (2007)

# HIV probability of infection during one receptive anal intercourse

(a)



Up to 18 times the probability of HIV transmission during one receptive vaginal intercourse

Baggaley *et al* (2010)  
Boily *et al* (2009)

But data on the number of such contacts is very difficult to collect

$$R_0 = \beta D = p c D$$

Transmission rate →  $\beta$

Transmission probability per contact →  $p$

Contact rate →  $c$

Duration of infectiousness →  $D$

# Estimates of $R_0$ for HIV

Extremely variable

Source	Location	Time Period	Estimate
Anderson and May (1991)	England and Wales (male homosexuals)	1981-5	2-5
	Nairobi, Kenya (female sex workers)	1981-5	11-12
	Kampala, Uganda (heterosexuals)	1985-7	10-11
Salemi et al <i>J Molecular Evolution</i> (2005)	Brazil (mixed population)	1992-2001	3-9
Williams et al <i>PLOS Med</i> (2006)	South Africa	1990-8	$6.4 \pm 1.6$
Eaton and Hallett <i>PNAS</i> (2014)	South Africa	1990: 2012:	4.9 (3.8-6.2) 3.5 (2.4–5.0)

# **Part 2: Deriving $R_0$ for compartmental models with homogeneous mixing**

11am practical: “ $R_0$  for compartmental models with homogeneous mixing”

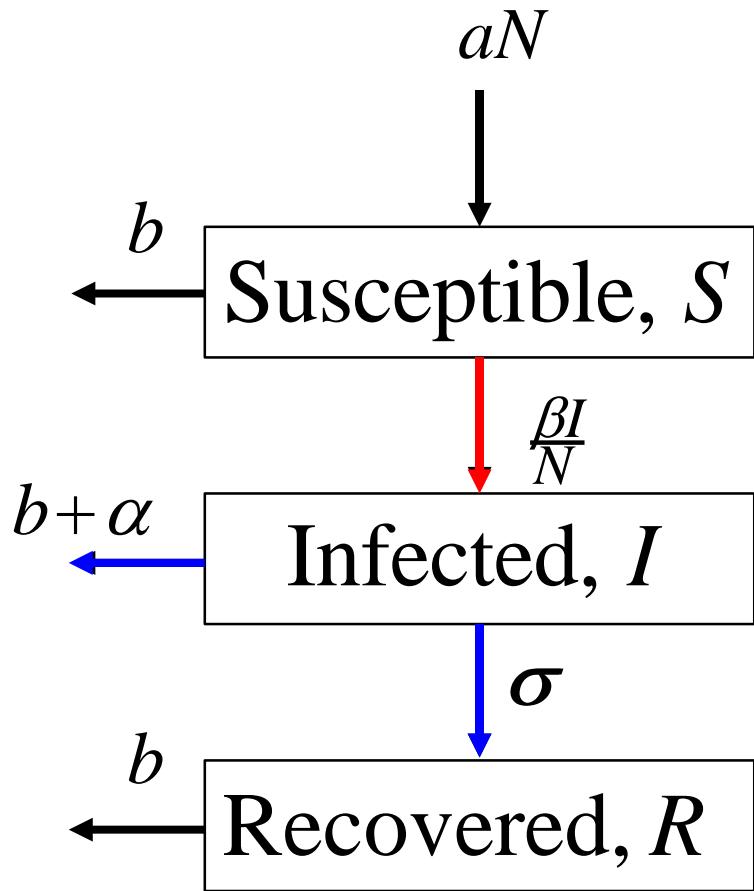
# Relationship between $R_0$ and parameters

- This part of the lecture will show how we derive the mathematical formula for  $R_0$  for a particular model (for a homogeneous population)
- **If we change the model then we (usually) change the formula for  $R_0$ !**
- But remember,  $R_0$  is a real quantity and can (in principle) be measured
  - Different candidate models for an infection → different  $R_0$  formulae and different parameter values, but we require those models to reproduce real-world behaviour and to estimate the real value of  $R_0$  correctly (model fitting)

# Estimating $R_0$

- Fundamentally,  $R_0$  depends upon:
  - transmission rate: how rapidly individuals transmit infection:  $\beta = p$  (transmission probability)  $\times c$  (contact rate)
  - average infectious period: how long individuals are infectious for:  $D$

# SIR model



$$\frac{dS}{dt} = aN - \frac{\beta SI}{N} - bS$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - (b + \alpha + \sigma)I$$

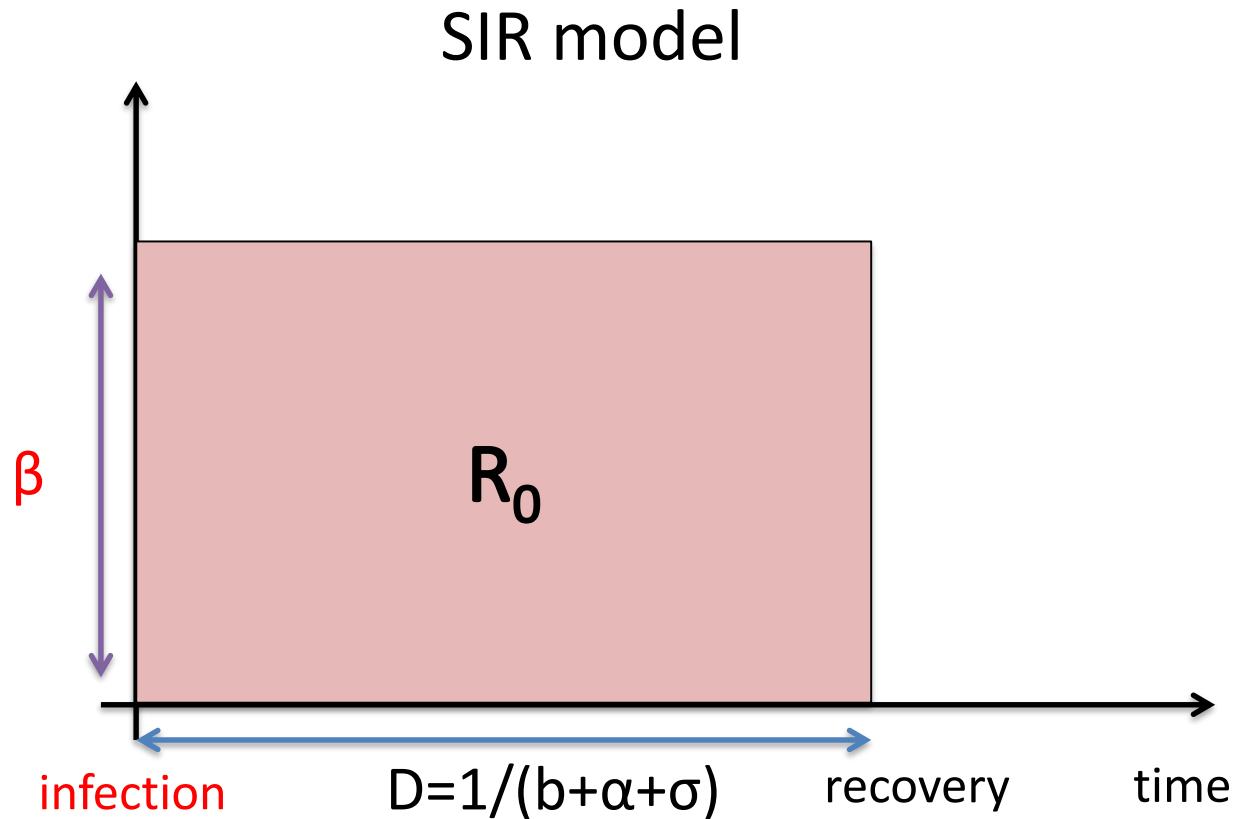
$$\frac{dR}{dt} = \sigma I - bR$$

$$N = S + I + R$$

Overall transmission rate      ‘Loss’ rate of infecteds

# Calculating $R_0$ for a simple SIR model

Mean infectious period  
= 1 / 'Loss' rate of infecteds

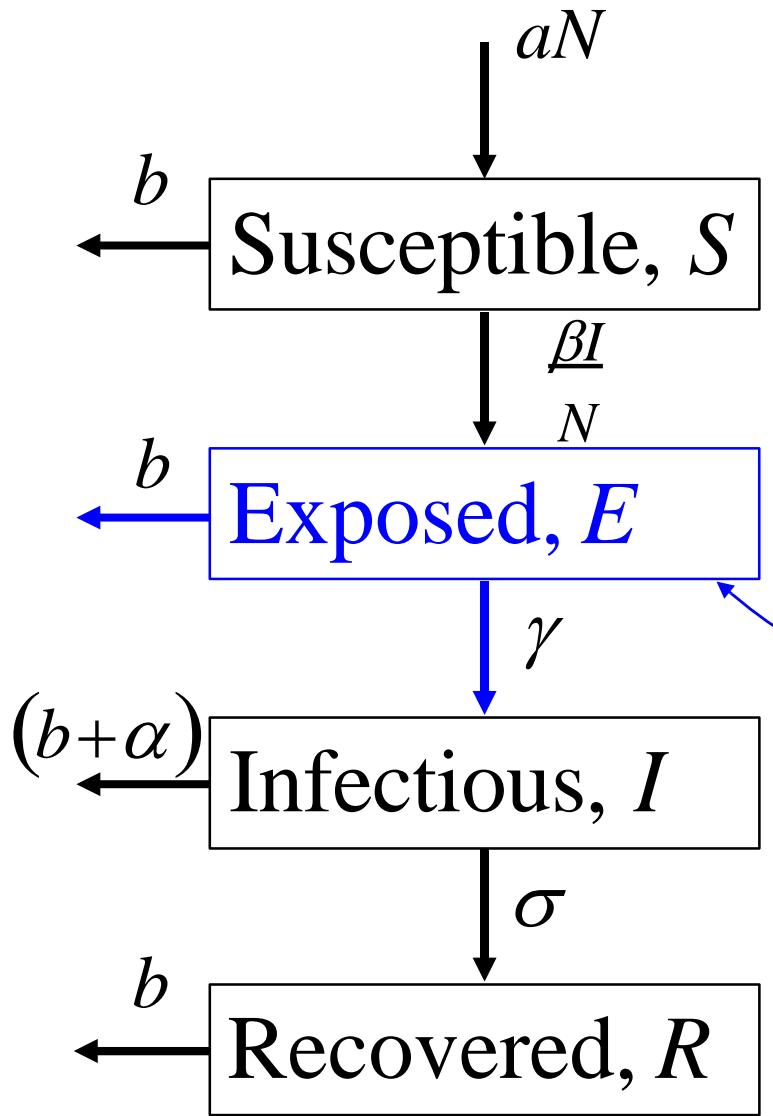


$$R_0 = \beta \times D = \frac{\beta}{b + \alpha + \sigma}$$

# SEIR model

- Let's modify the model to add a latent ("exposed") stage – a delay between becoming infected and becoming infectious
- How does this change the  $R_0$  formula?

# SEIR model



$$\frac{dS}{dt} = aN - \frac{\beta SI}{N} - bS$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - (b + \gamma)E$$

$$\frac{dI}{dt} = \gamma E - (b + \alpha + \sigma)I$$

Infected but not infectious

$$\frac{dR}{dt} = \sigma I - bR$$

$$N = S + E + I + R$$

# SEIR model

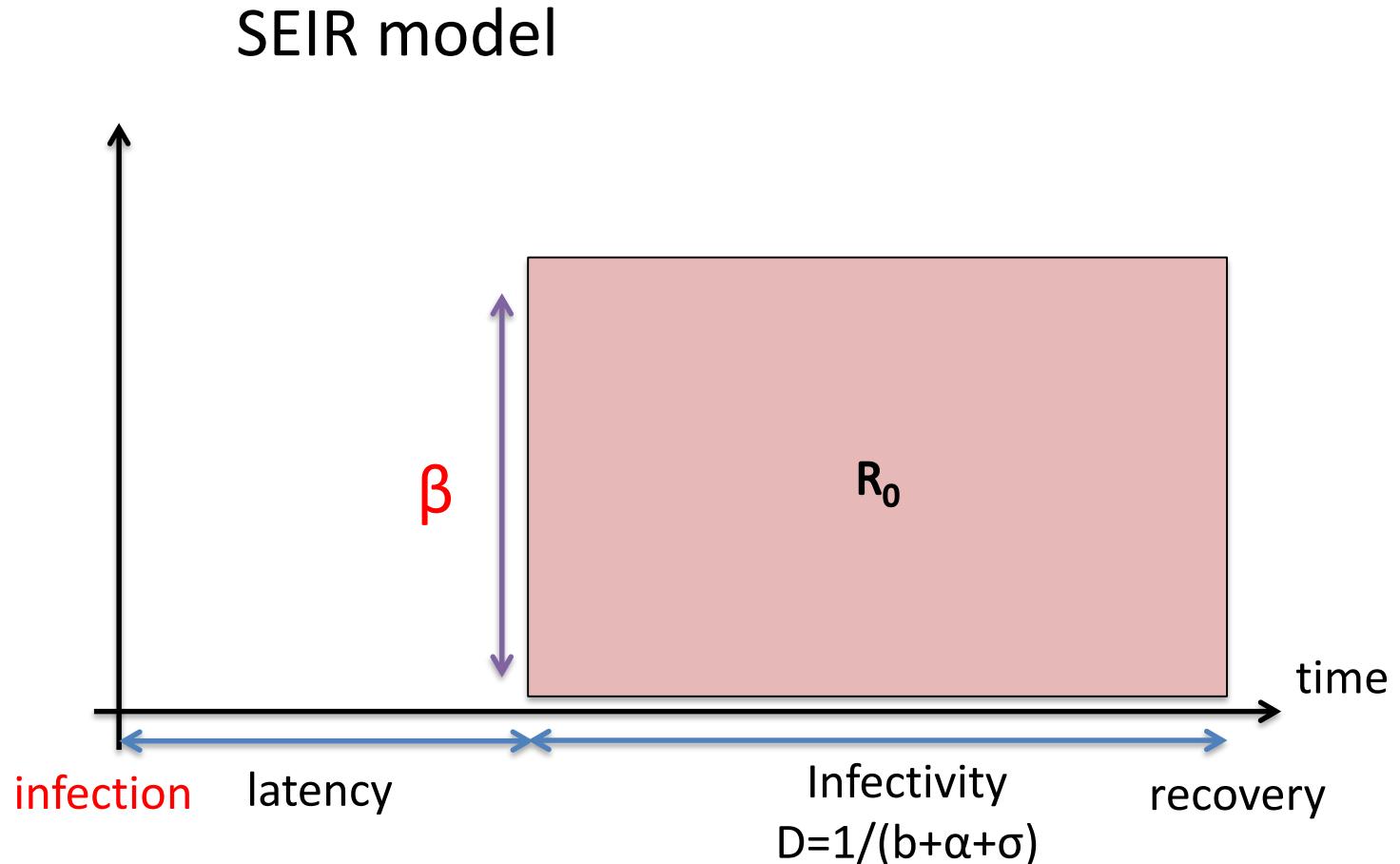
- Since there is background mortality, some *Exposed* individuals will die before they become infectious...
- ... so we need to consider the proportion of those who survive until the infectious stage

# Calculating $R_0$ for a SEIR model

Proportion (or probability) of *Exposed* becoming *Infectious* ( $E \rightarrow I$ )

$$= \frac{\gamma}{b + \gamma}$$

Mean infectious period  
= 1 / 'Loss' rate of infectious individuals  
(same as SIR model)



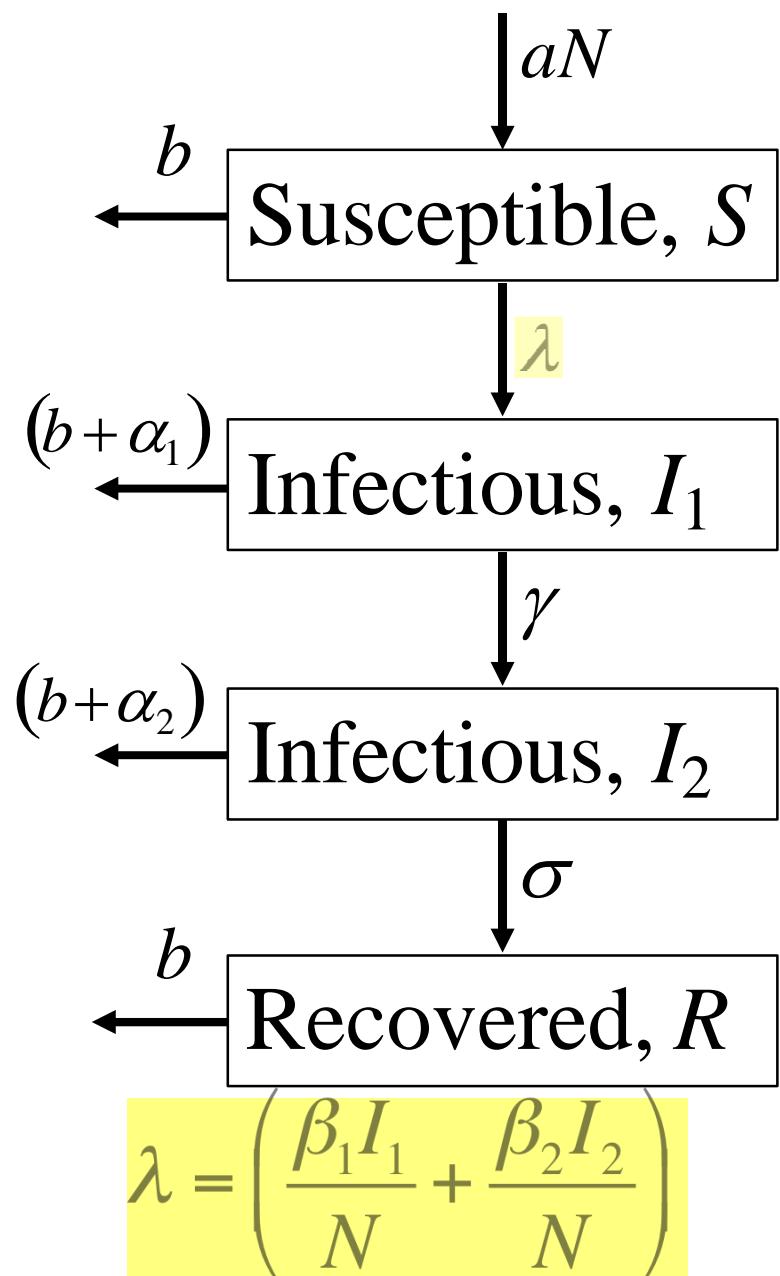
$$R_0 = \frac{\beta}{b + \alpha + \sigma} \times \frac{\gamma}{b + \gamma}$$

Transmission rate       $E \rightarrow I$

# Multiple infectious stages

- There may be different infectious stages (e.g. HIV)
- We need to consider
  - the proportion of those who are infected who reach each stage,
  - how long they spend in each stage (on average), and
  - their infectiousness in each stage

# SI<sub>1</sub>I<sub>2</sub>R model



Overall transmission rate now noted  $\lambda$

$$\frac{dS}{dt} = aN - \lambda S - bS$$

$$\frac{dI_1}{dt} = \lambda S - (b + \alpha_1 + \gamma)I_1$$

$$\frac{dI_2}{dt} = \gamma I_1 - (b + \alpha_2 + \sigma)I_2$$

$$\frac{dR}{dt} = \sigma I_2 - bR$$

$$N = S + I_1 + I_2 + R$$

# SI<sub>1</sub>I<sub>2</sub>R model

	I <sub>1</sub>	I <sub>2</sub>
Infectious stage		
Prop. of infected entering stage	1	$\gamma / (b + \alpha_1 + \gamma)$
Transmission rate	$\beta_1$	$\beta_2$
Mean duration	$1 / (b + \alpha_1 + \gamma)$	$1 / (b + \alpha_2 + \sigma)$

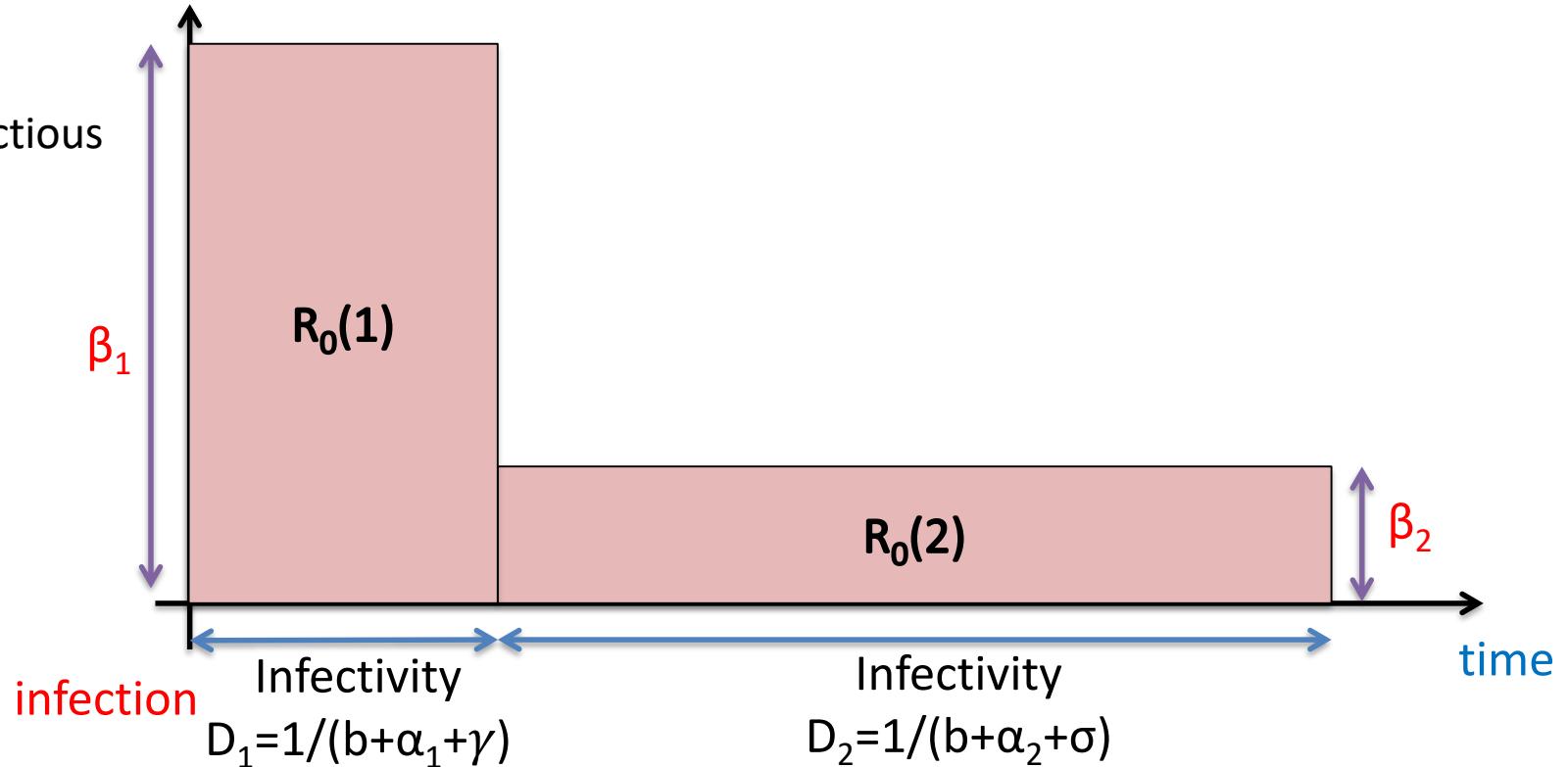
$$R_0 = \frac{\overbrace{\beta_1}^{\beta_1}}{(b + \alpha_1 + \gamma)} + \frac{\overbrace{\gamma}^{\gamma}}{(b + \alpha_1 + \gamma)} \frac{\overbrace{\beta_2}^{\beta_2}}{(b + \alpha_2 + \sigma)}$$

# Calculating $R_0$ for a $SI_1I_2R$ model

## $SI_1I_2R$ model

Proportion of *Infected* entering the second Infectious stage ( $I_1 \rightarrow I_2$ )

$$= \frac{\gamma}{b + \alpha_1 + \gamma}$$



$$R_0 = \frac{\beta_1}{(b + \alpha_1 + \gamma)} + \frac{\gamma}{(b + \alpha_1 + \gamma)} \frac{\beta_2}{(b + \alpha_2 + \sigma)}$$

# Summary

- Measurement of  $R_0$ 
  - Variability should be accounted for
    - Biological
    - Behavioural
    - Environmental
      - Humidity affects influenza transmission (Shaman et al PNAS 2009), temperature affects Zika transmission (Tesla, Proc. R. Soc. B 2018)
    - Offspring distributions –  $R_0$  is not constant, but variable (Grassly and Fraser, Nature Rev Microb 2008 (excellent review))
  - Partially observed
  - Infectivity not the same as symptoms!!
- Calculation of  $R_0$ 
  - Define ‘average’ or ‘typical’ infected person
  - Duration of infection and transmission rate rarely independent, so need to account for covariance

Calculating  $R_0$  from first principles requires good, detailed data, under controlled conditions

For overall estimates, it is usually preferable to estimate  $R_0$  indirectly (this afternoon)

‘First principles’ estimation useful to understand contributions of different factors to  $R_0$