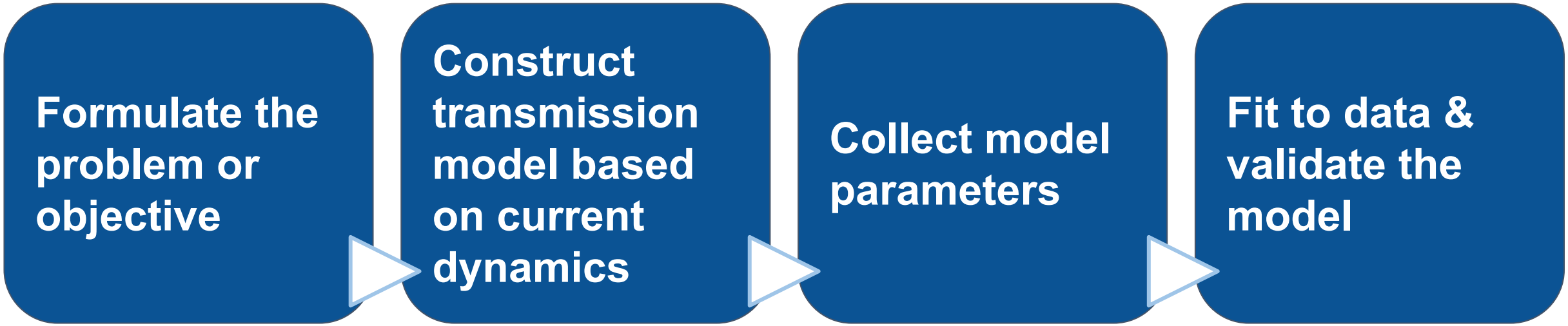
Heterogeneity and Age Patterns

Recap

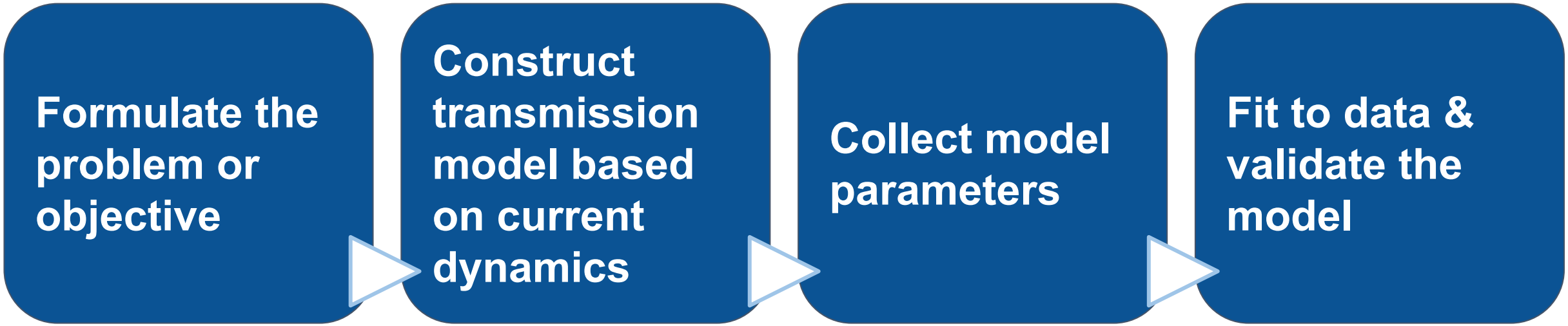
Day 1

RECAP
Steps of Developing a Model



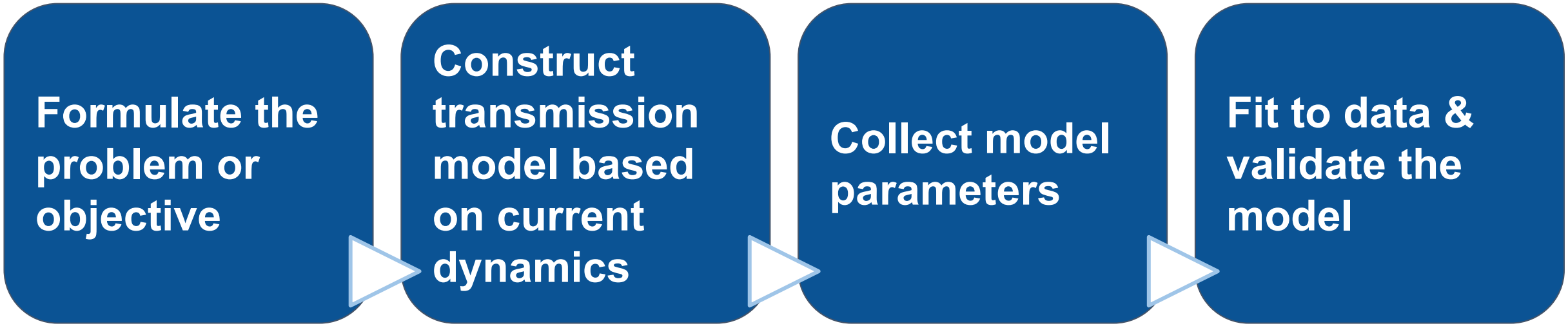
- Objective informs model utility (*theoretical, inference, strategic, forecast)* informs model type

RECAP
Steps of Developing a Model



- The basic SIR model
- Extension of the basic model: *vaccination activities*

RECAP
Steps of Developing a Model



- How data are related to models
  incidence, prevalence, seroprevalence
- Critical model parameters:
  R_0 *and its components,* β *and* γ

Review of basic compartmental models

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

- **S**, **I**, and **R** represent the number of individuals currently **susceptible**, **infected**, and **recovered**
- Contact process quantifies the rate at which **susceptibles** and **infecteds** interact
- Transmission parameter: ***β*** is rate of infectious contact * probability of infection given contact. High ***β*** = more transmission
- Higher recovery rate ***γ*** = shorter duration of infection

Heterogeneity and Age Patterns

Learning Objectives

By the end of this session you should learn:

- How to define and estimate force of infection
- The utility of heterogeneity in models
- The specific utility of age heterogeneity in models
- The relationship between mean age of infection to FOI and R_0
- The difference between age contact patterns, WAIFW, and FOI

Force of infection (λ)

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

$\lambda = \beta I$

per capita rate at which susceptible individuals contract the infection OR transmission rate per susceptible individual

---

$\therefore \beta SI$ or $S\lambda$ is the total transmission rate of the entire susceptible population

βSI assumes **homogeneous mixing** in the population which means everyone interacts with equal probability with everyone else

Modeling Heterogeneity

using structured models

Host Heterogeneities

- The **basic SIR** model only compartmentalizes the populations by infection status and history (**one degree of subdivision**).

- In this lecture we introduce **second degree of subdivision** in which all individuals in each second degree subdivision will have the same parameters (e.g., β).

- By taking into account heterogeneities of the second degree of subdivision, we create a **structured model**.

Foot and Mouth Disease Example

Foot-and-mouth disease (FMD)

- Caused by the FMD virus (FMDV)
- Affects multiple species of mammals (including cows, sheep, goats, pigs)
- Can cause blisters around the hooves and mouth and spontaneous abortions
- Reduces milk yield and negative economic impact

Example – Foot-and-mouth (FMD)

Where does heterogeneity appear in the case of FMD?

- Pathogen: FMDV affects species differently
- Host: animals have different lifespans and behaviours
- Policy: some countries vaccinate cows, others also vaccinate pigs
- Environment: contact rates within and between species can differ based on how animals are kept

FMDV is different in 🐷 and 🐮!

second degree subdivision = species

- FMDV is highly transmissible in pigs compared to other species
- Pigs tend to have a shorter lifespan in animal husbandry contexts (1 year or less)
- Pigs are not always vaccinated in FMD control programs

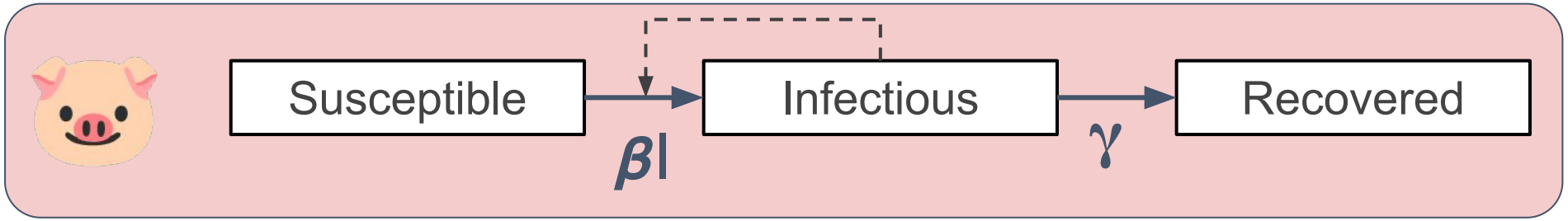
- Cattle are more susceptible to FMD compared to other species
- Cattle can live up to 14 years in some animal husbandry contexts (e.g., in India)
- Cattle are almost always vaccinated in FMD control programs

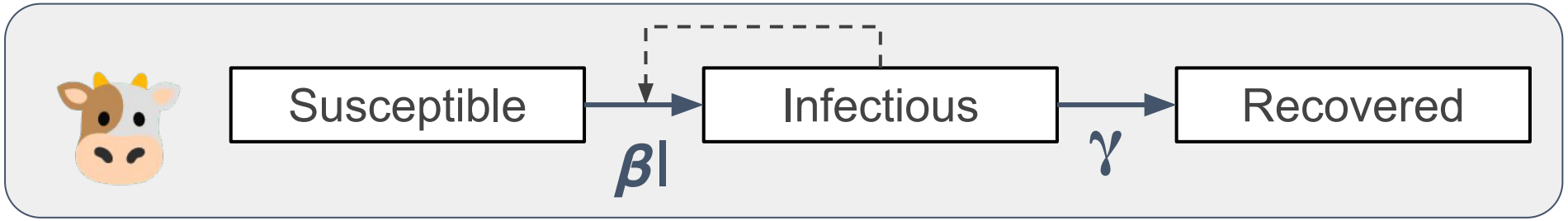
FMDV is different in 🐷 and 🐮!

How do we model those differences?

1. Make 2 separate models

Why is this a bad idea?





FMDV is different in 🐷 and 🐮!

How do we model those differences?

1. Make 2 separate models
2. Make one model with both species ✅

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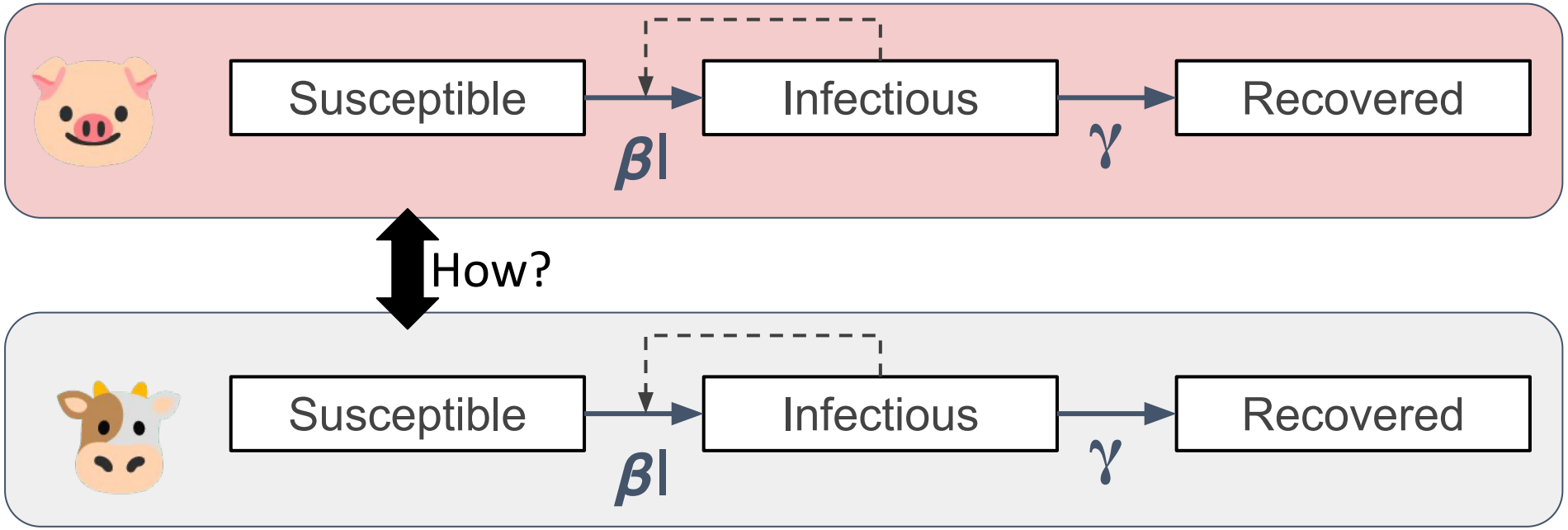
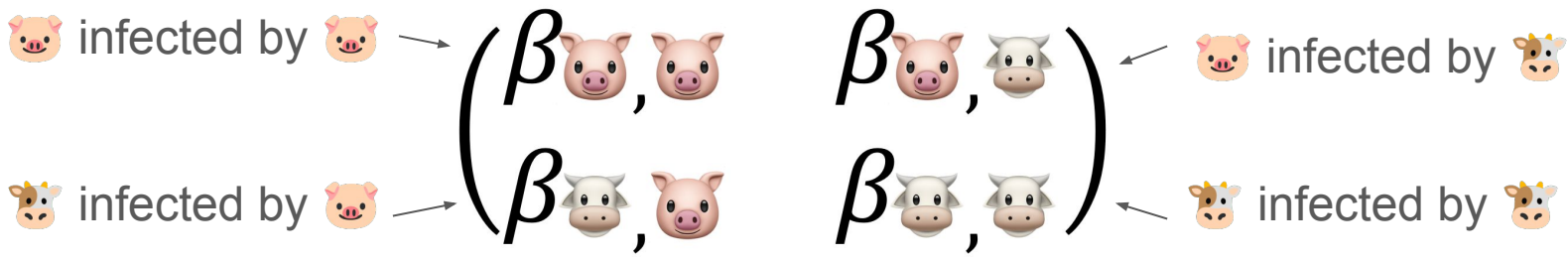


One model - Two species

"Talking" to each other via transmission parameter

Instead of having a single β term for transmission (reminder: β is rate of infectious contact * probability of infection given contact), we use a *m*x*m* matrix of β values for *m* different species in our model.



This **transmission matrix**, **WAIFW** (Who Acquires Infection from Whom), captures the transmission between the two groups.

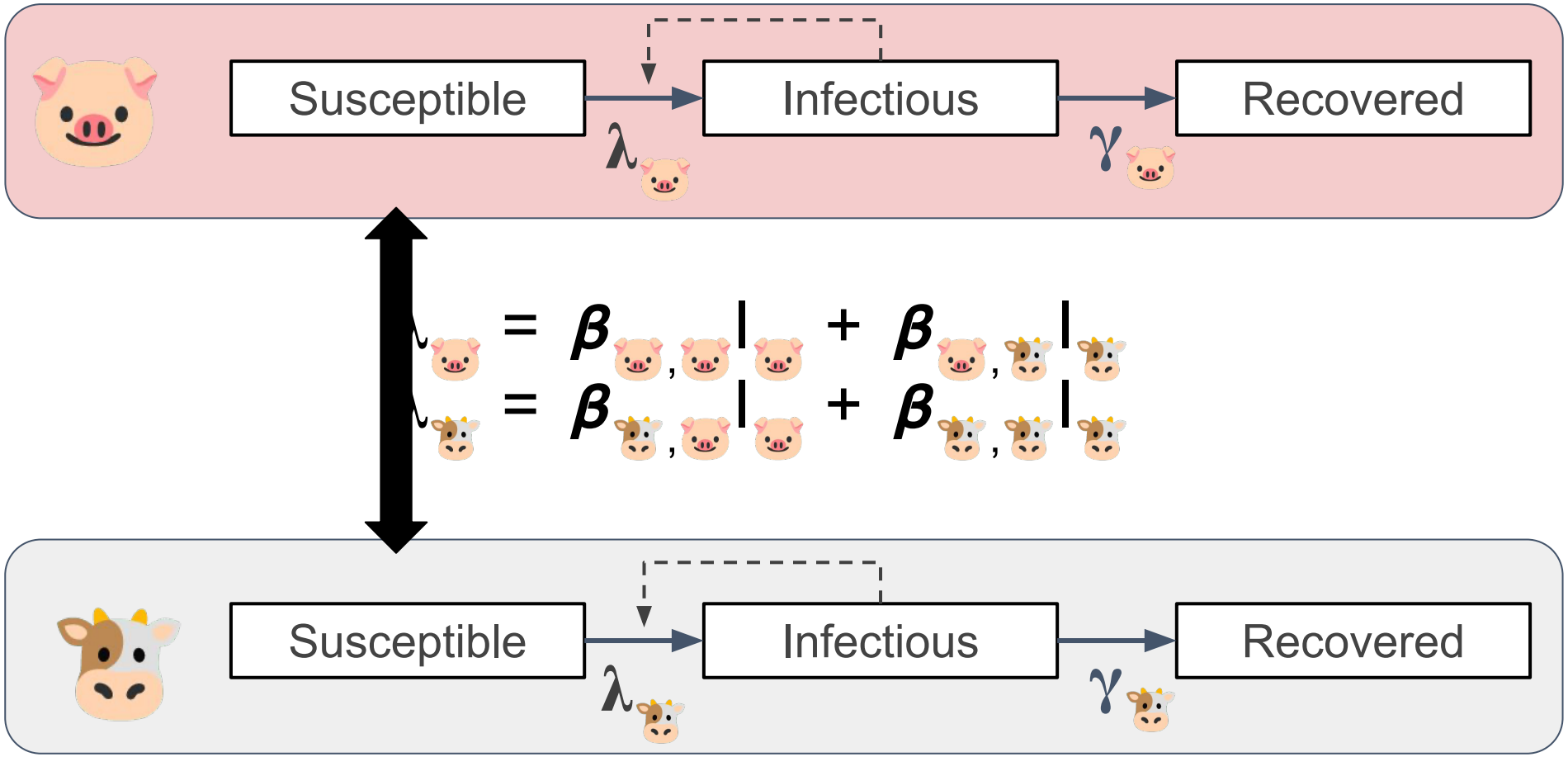
One model - Two species

"Talking" to each other via transmission parameter

As a result, the force of infection (reminder: $\lambda = \beta I$ is per capita rate at which susceptible individuals contract the infection) is based on the transmission matrix *mxm* of β values, as well as an I term for each *m* species.

$$\lambda_{🐷} = \beta_{🐷,🐷} I_{🐷} + \beta_{🐷,🐮} I_{🐮}$$
$$\lambda_{🐮} = \beta_{🐮,🐷} I_{🐷} + \beta_{🐮,🐮} I_{🐮}$$

Species structured HFMD model



Host Heterogeneities

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- In this lecture we introduce **second degree of subdivision** in which all individuals in each second degree subdivision will have the same parameters (e.g., β).

- By taking into account heterogeneities of the second degree of subdivision, we create a **structured model**.

Host Heterogeneities

- **Advantages of modeling heterogeneities**: more accurate models; we can determine prevalence of infection in each second degree subdivision; we can assess more targeted and effective control measures

- **Disadvantages of modeling heterogeneities:** Incorporating heterogeneities increases the number of equations and its sequel (i.e, the number of parameters we need to collect/estimate)

What other heterogeneities might be important to model?

Non-directional vs Directional Transitions

Heterogeneity with non-directional transitions:

- Risk groups in STI settings (e.g., using a condom vs. not using a condom)
- Vaccine status (e.g., COVID-19 vaccine impacts beta and gamma)
- Sex
- Number of contacts (e.g., superspreaders vs not superspreaders)
- Co-morbidities or immune suppression

Heterogeneity with directional transitions:

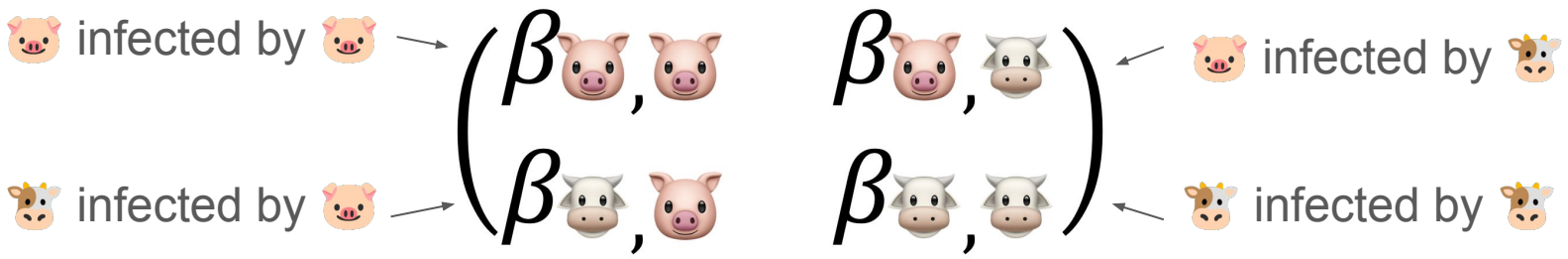
- Aging
- Life stages in animals
- Time since infection

Heterogeneity by Age

Directional Transitions

Modeling age heterogeneity

It is the **same as modeling heterogeneity with non-directional transitions** (i.e., age-specific parameters and a matrix of β or WAIFW to "talk" to each other), but



2 populations, therefore WAIFW 2x2 matrix (4 βs)
diagonal (top left to bottom right) - assortative transmission

Modeling age heterogeneity

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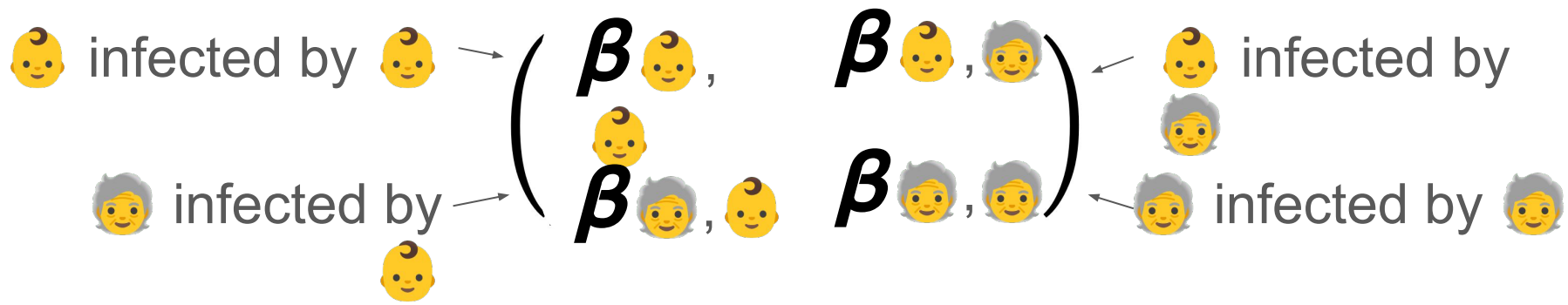

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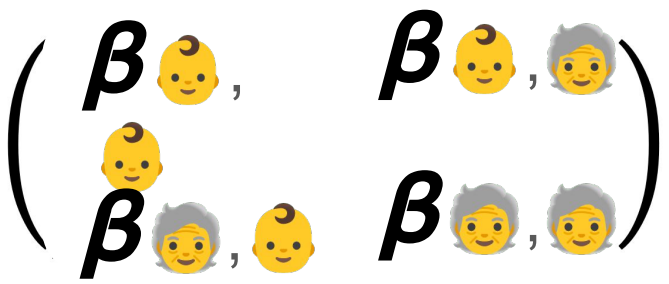
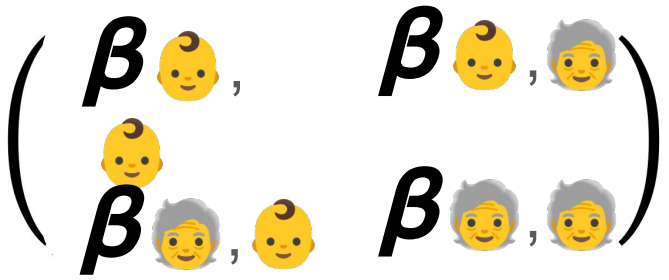


WAIFW matrix

diagonal is assortative transmission

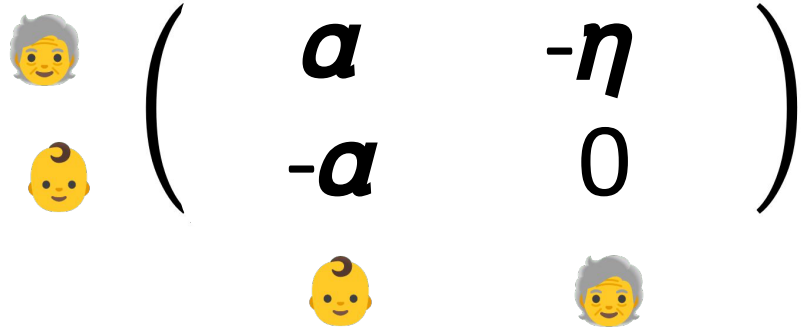
Modeling age heterogeneity

It is the **same as modeling heterogeneity with non-directional transitions** (i.e., age-specific parameters and a matrix of β or WAIFW to "talk" to each other), but **with the addition of individuals ageing**



WAIFW matrix

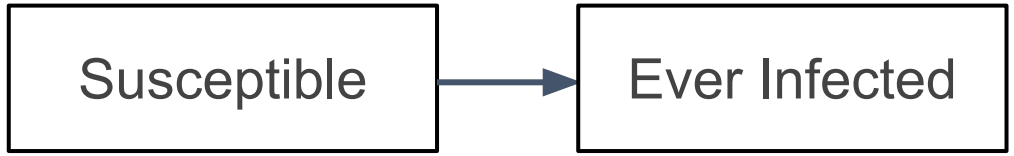
diagonal is assortative transmission



ageing matrix

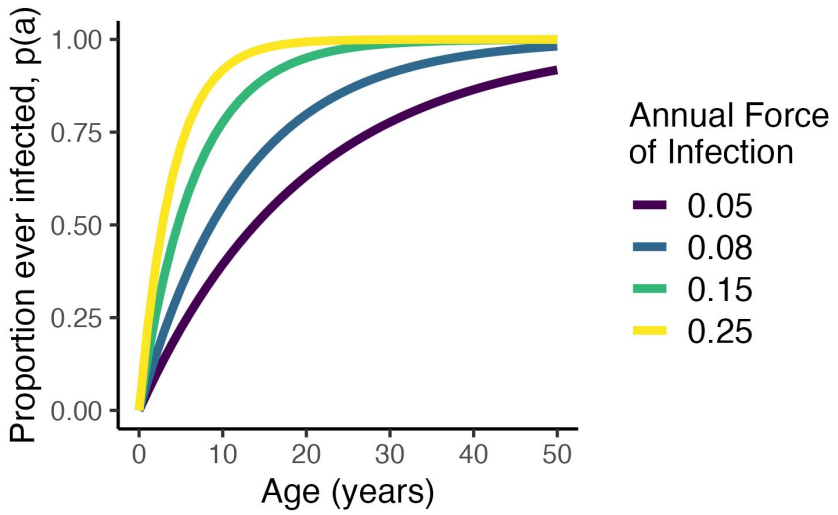
from column age group to row age group

Simple Catalytic Model

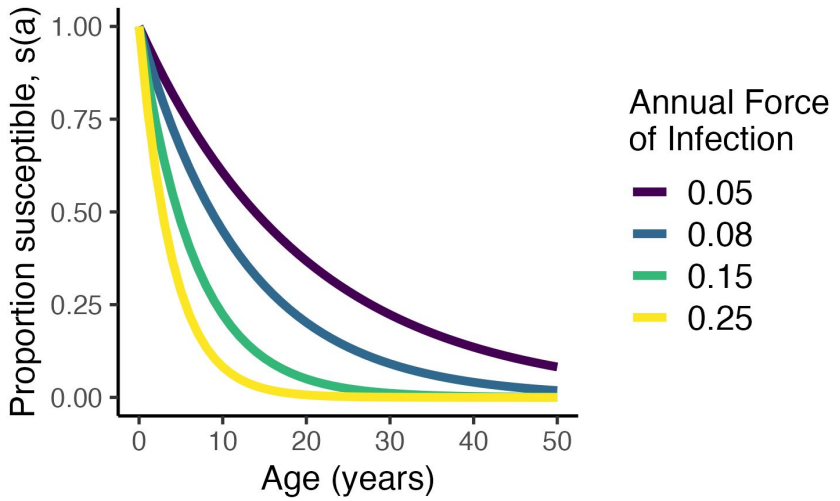


Assuming constant force of infection and homogeneously mixing population:

$p(a) = 1-e^{-\lambda a}$



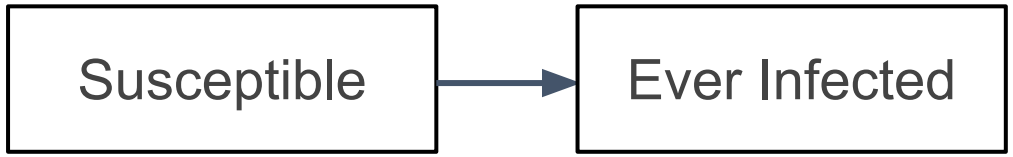
$s(a) = e^{-\lambda a}$



Reminder: The average time to event = 1/{rate at which event occurs}

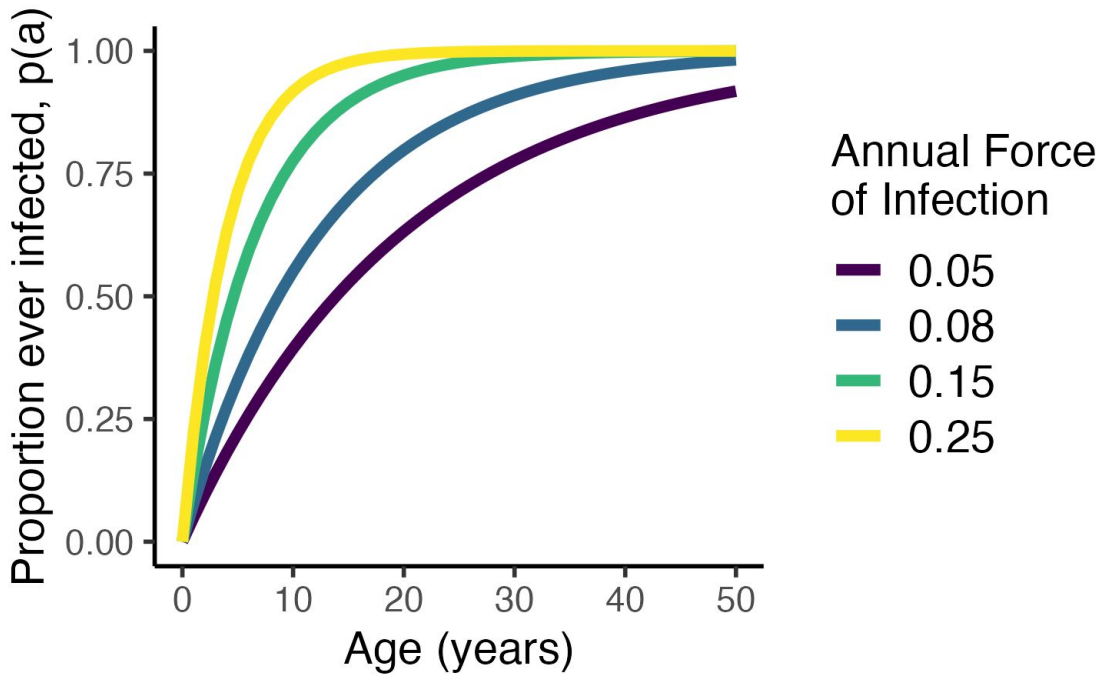
Average age of infection, $A \approx 1/\lambda$

In childhood infections, ageing alone is associated with disease transmission



$$p(a) = 1-e^{-\lambda a}$$

Simple Catalytic Model:
Assumes constant force of infection and homogeneously mixing population



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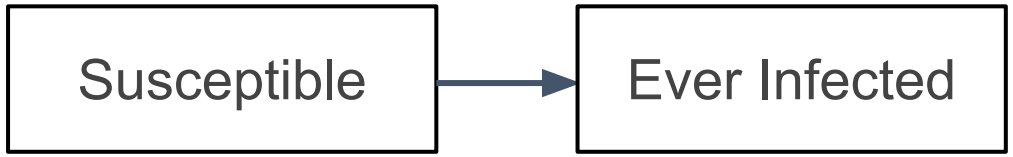

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Simple Catalytic Model:
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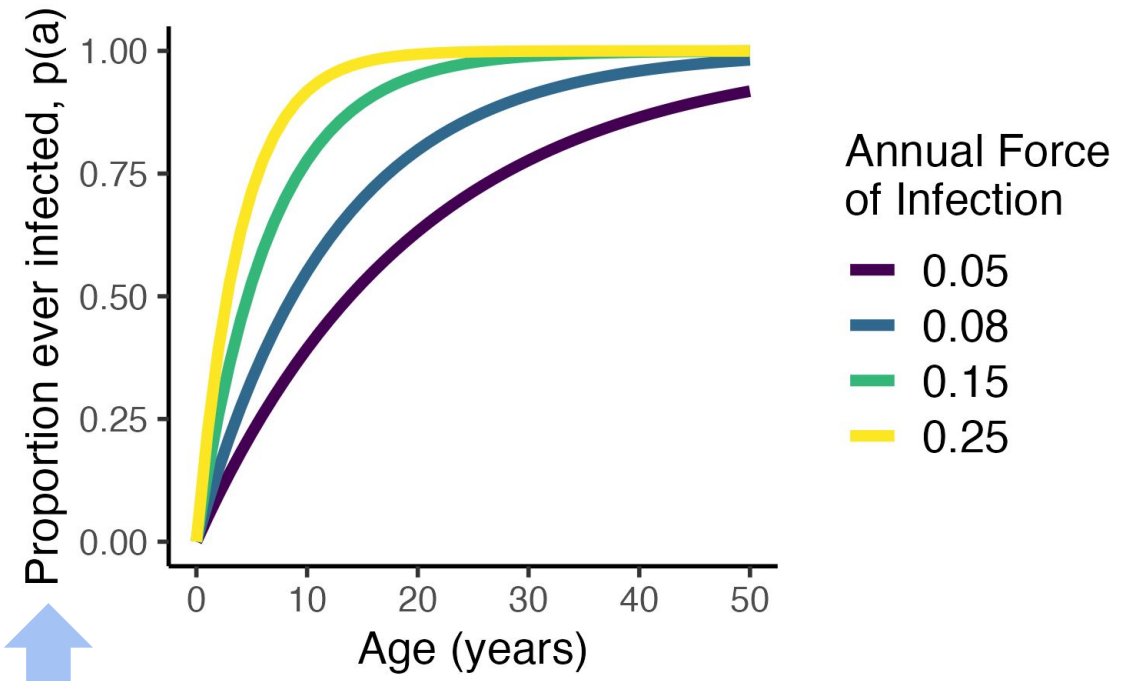
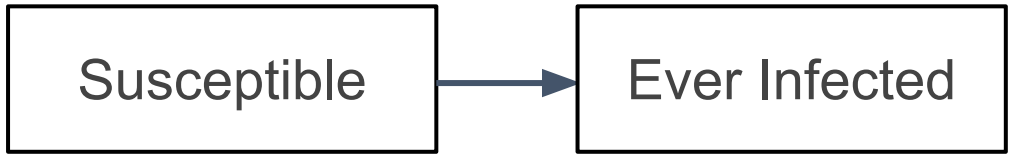


- R class in SIR model
- Proportion with IgG antibody > protective level
- Proportion seropositive
- Proportion immune
- Seroprevalence

In childhood infections, ageing alone is associated with disease transmission



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Simple Catalytic Model:
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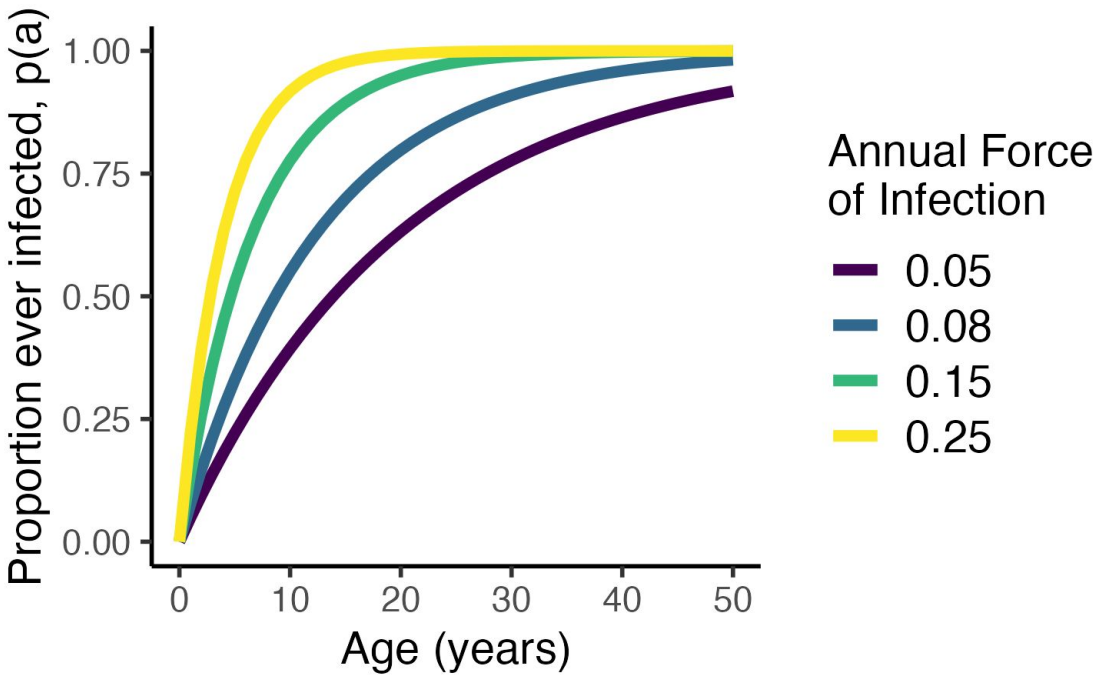


Reminder: The average time to event = 1/{rate at which event occurs}
Average age of infection, A $\approx 1/\lambda$

Mean age of infection and R_0

- The mean age is the average time from birth to infection
- Important indicator of prevalence

$A \approx 1/\boldsymbol{\lambda}$

some substitutions given SIR model with births/deaths ($\boldsymbol{\mu}$) $\rightarrow$

$A \approx 1 / \boldsymbol{\mu}(R_0 - 1)$

$A \approx L / (R_0 - 1)$ where L is life expectancy

Reminder:

$$\frac{dS}{dt} = \mu N - \beta SI - \mu S$$
$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$

- This basic calculation requires strong assumption that age-specific force of infection is constant

Intuition of mean age of infection and R_0

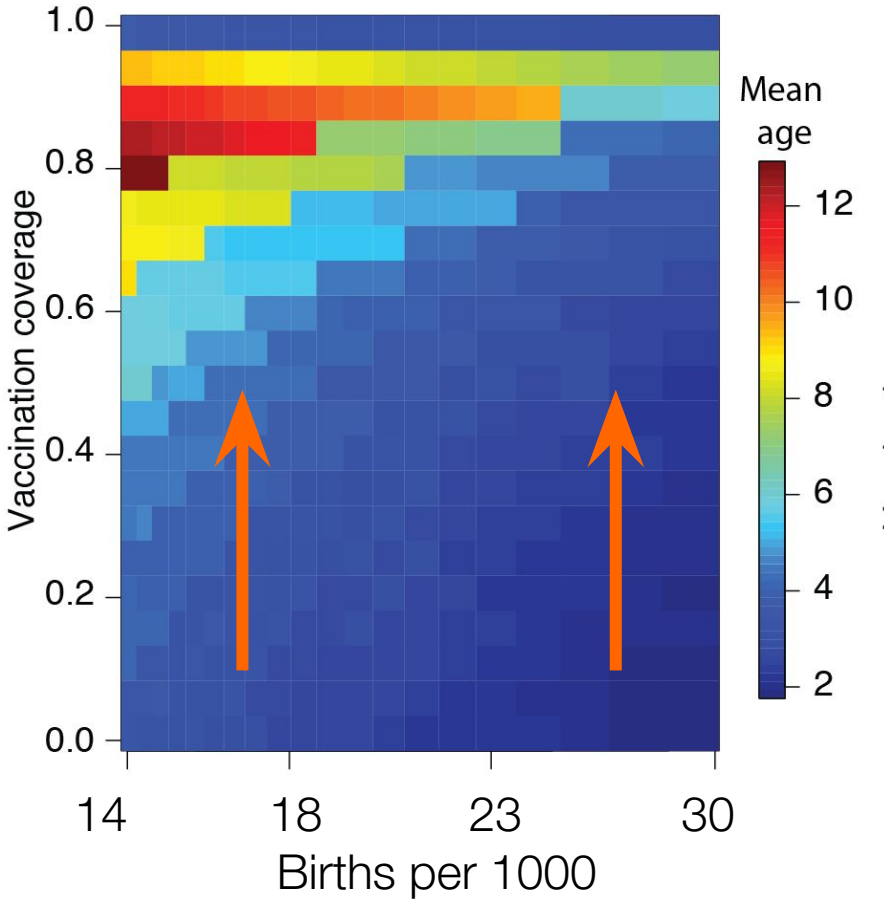
- Reduced prevalence of infection results in lower force of infection on each susceptible individual
- Longer wait until contact between susceptible and infectious individuals
- Lower force of infection implies higher mean age at infection

$$A \approx 1 / \boldsymbol{\mu}(R_0 - 1)$$

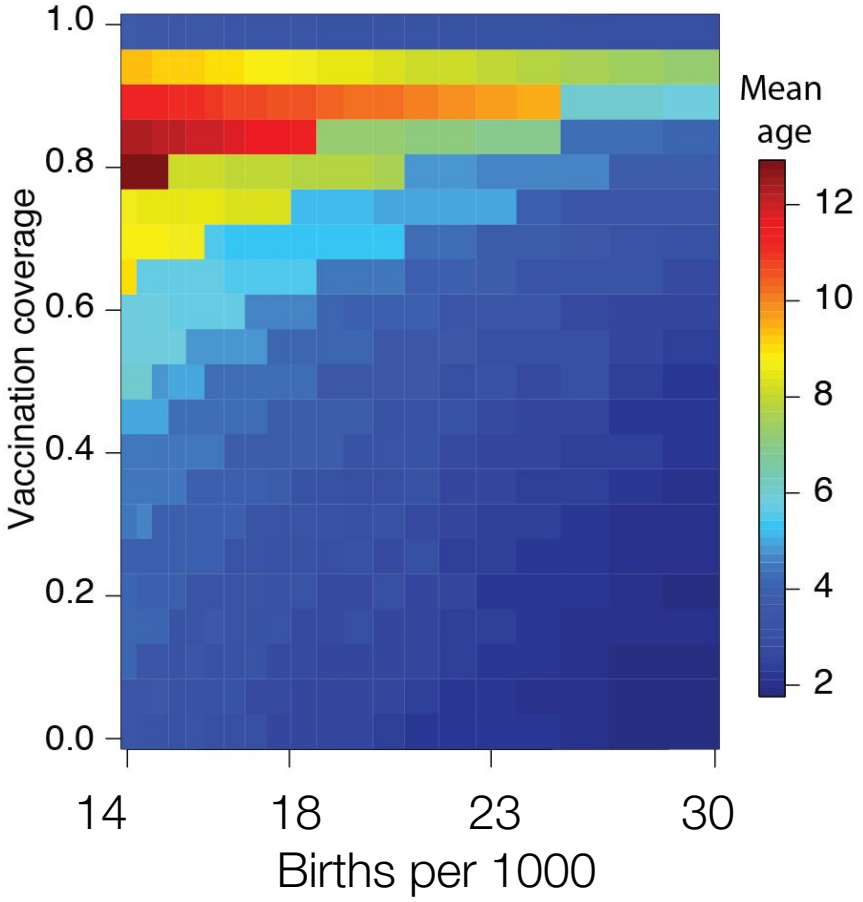
Intuition of mean age of infection and R_0

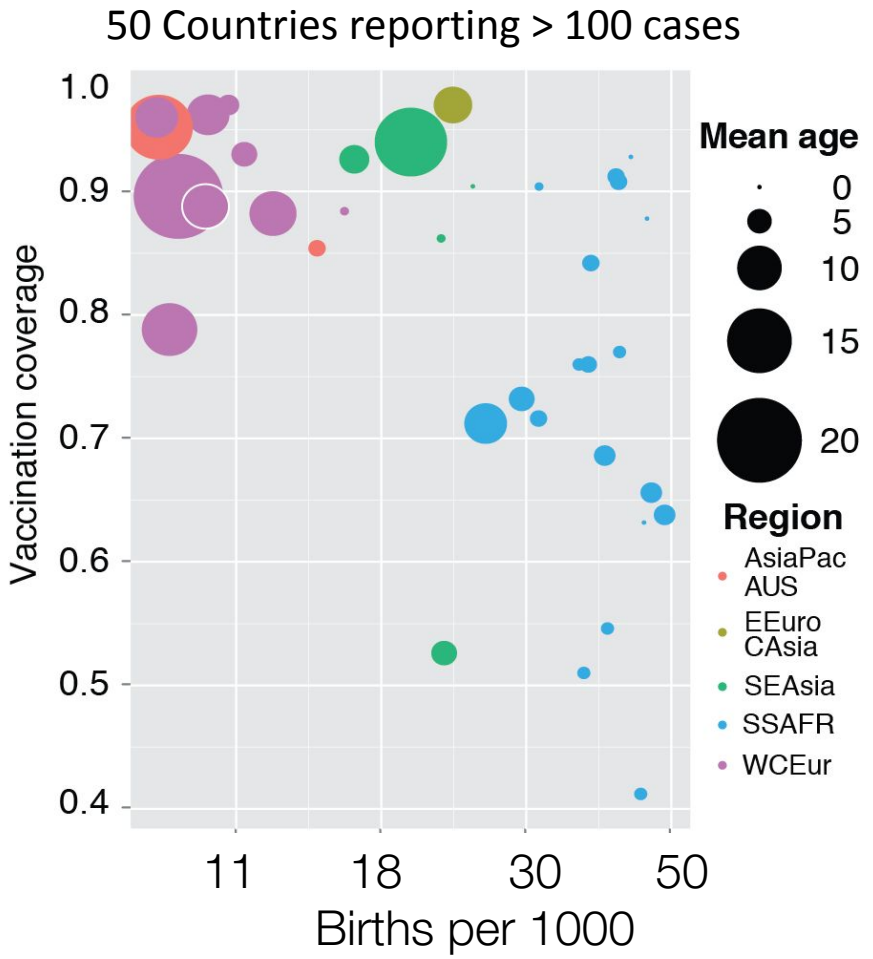
- Reduced prevalence of infection results in lower force of infection on each susceptible individual
- Longer wait until contact between susceptible and infectious individuals
- Lower force of infection implies higher mean age at infection
- But the absolute value of mean age is mediated by underlying demographic rates

$$A \approx 1 / \mu(R_0 - 1)$$



Observation About Mean Age of Infection





Ferrari et al 2013

Estimating Force of Infection

Why age-specific FOI?

J. Hyg., Camb. (1985), **95**, 419–436
Printed in Great Britain

The estimation of age-related rates of infection from case notifications and serological data

BY B. T. GRENFELL AND R. M. ANDERSON

Department of Pure and Applied Biology, Imperial College, London University, London SW7 2BB

Empirical evidence based on:

- age-specific serological data OR
- age distribution of infected individuals

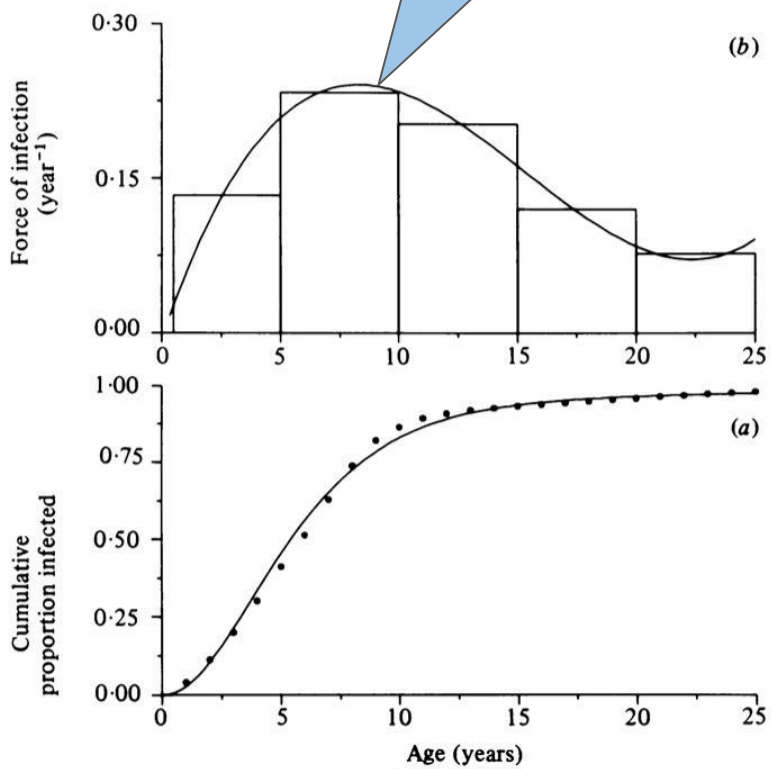
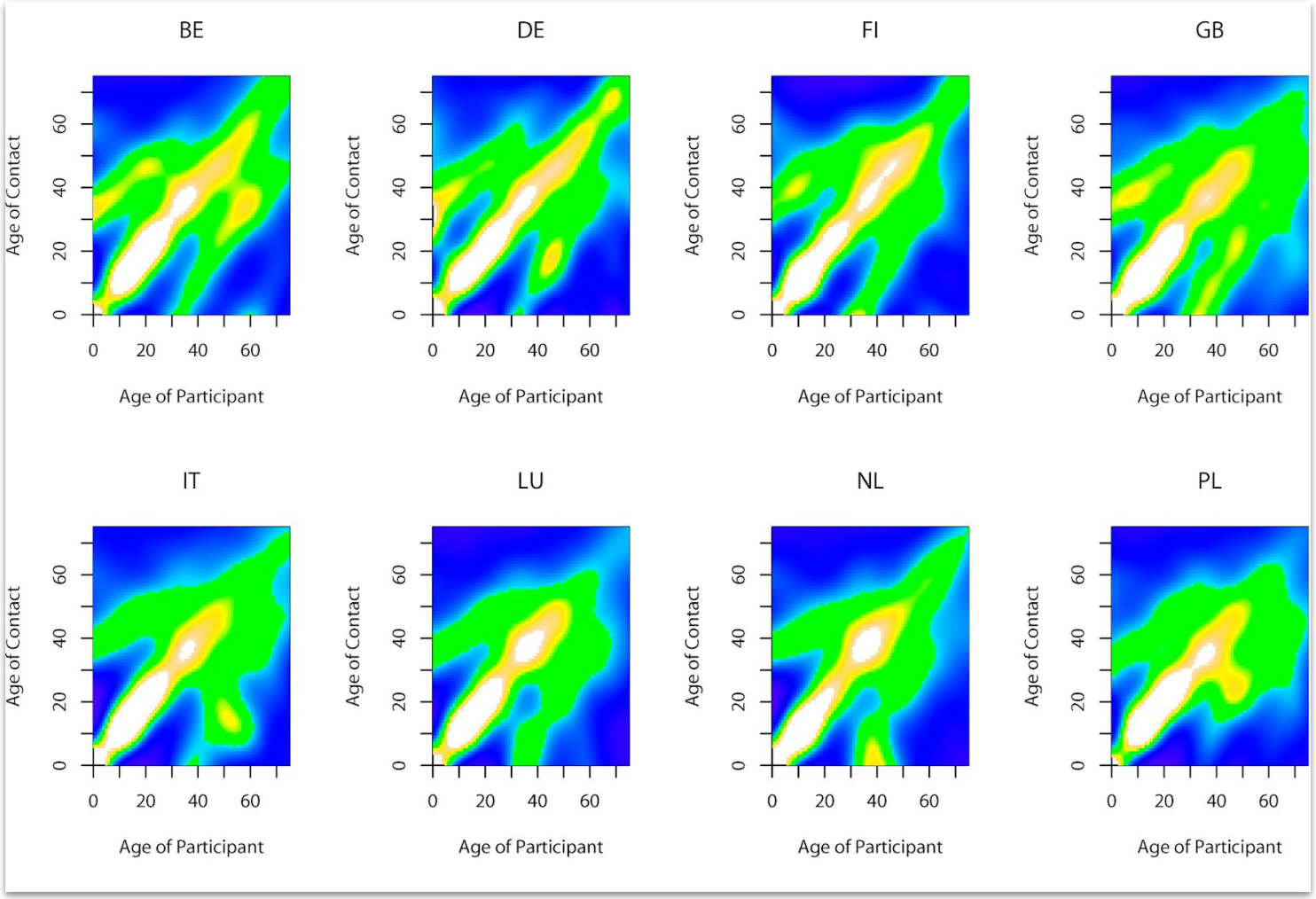


Fig. 1. Analysis of measles notifications for Baltimore, USA, 1906–15. (*a*) Observed and expected cumulative proportions infected by age ($F(a)$) in equation (5). (*b*) The fitted force of infection polynomial ($\lambda(a)$ in equation (4)). Here and in Figs. 2–7 the histogram represents average force of infection estimates (in the age ranges 0·5–5 years, 5–10 years, etc.) derived from the fitted polynomial, which is documented in Table 1.

Age-specific contact patterns



Mossong et al. PLoS Med 2007

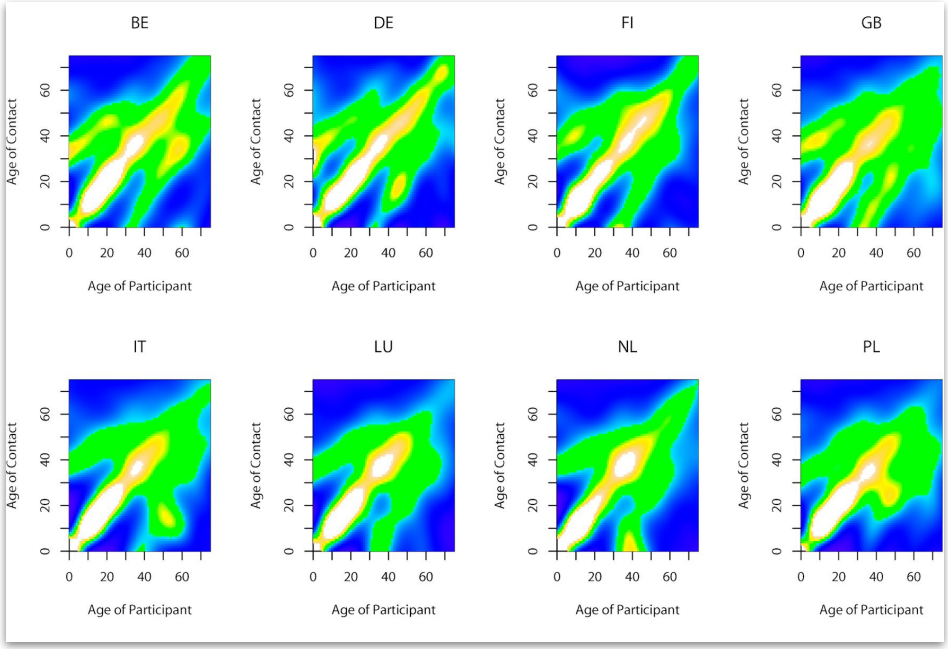
"age assortative contacts" = lots contacts along diagonal

How does this differ from WAIFW?

How does this differ from age-specific FOI?

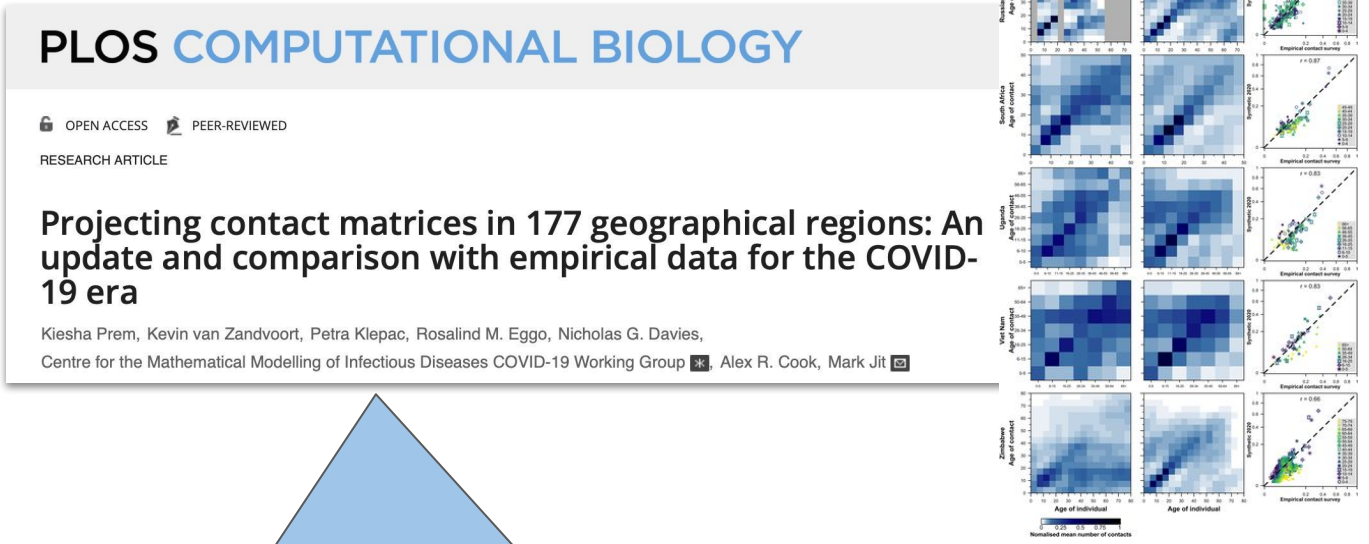
Age-specific contact patterns

"assortative" = lots contacts along diagonal



Mossong et al. PLoS Med 2007

How does this differ from the WAIFW matrix?
How does this differ from age-specific FOI?



PLOS COMPUTATIONAL BIOLOGY

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Projecting contact matrices in 177 geographical regions: An update and comparison with empirical data for the COVID-19 era

Kiesha Prem, Kevin van Zandvoort, Petra Klepac, Rosalind M. Eggo, Nicholas G. Davies,
Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, Alex R. Cook, Mark Jit

How diary studies relate to transmissible contacts is unclear

The applicability of these matrices to different pathogens and modes of transmission is still uncertain

Reminder: Transmission parameter: β is rate of contact * probability of infection given contact

Fitting (slightly less simple) Catalytic Model

Serological Data

- Griffiths (1974)
- Grenfell and Anderson (1985)

$\phi(a) = \text{force of infection at age a}$

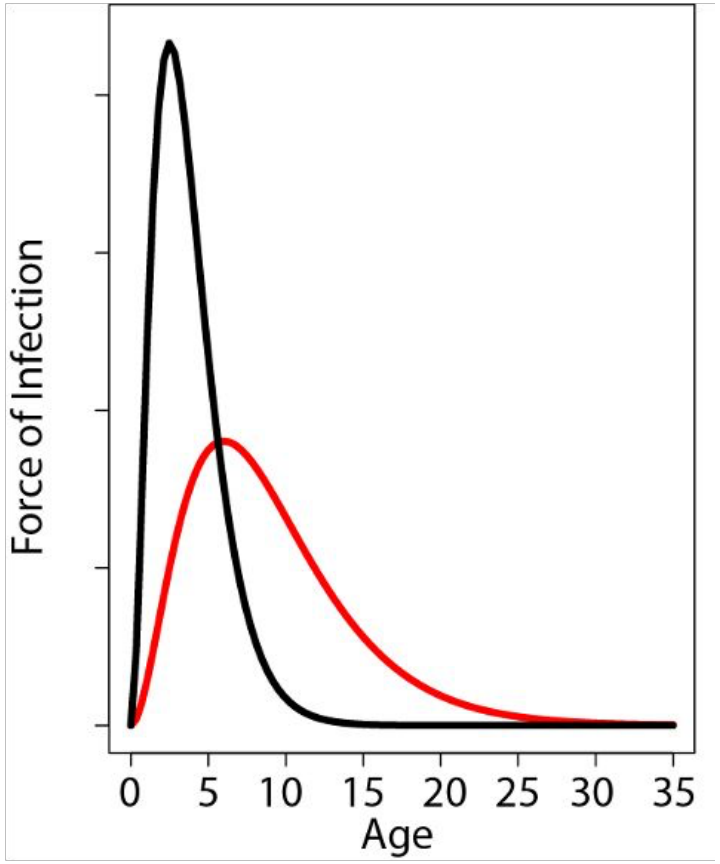
$$P(sero(+) \mid age) = 1 - \exp\left(- \int_0^{age} \phi(x)\,dx \right)$$

$$\#\, sero(+)_{age} \sim \text{binomial}\left(N_{\text{tested, age}}, P(sero(+) \mid age) \right)$$

Case Data

- Expected age distribution of cases is a function of:
    - Remaining susceptible by age a
    - Force of infection at age a, conditional on remaining susceptible
- Grenfell and Anderson (1985)
    - Multinomial likelihood

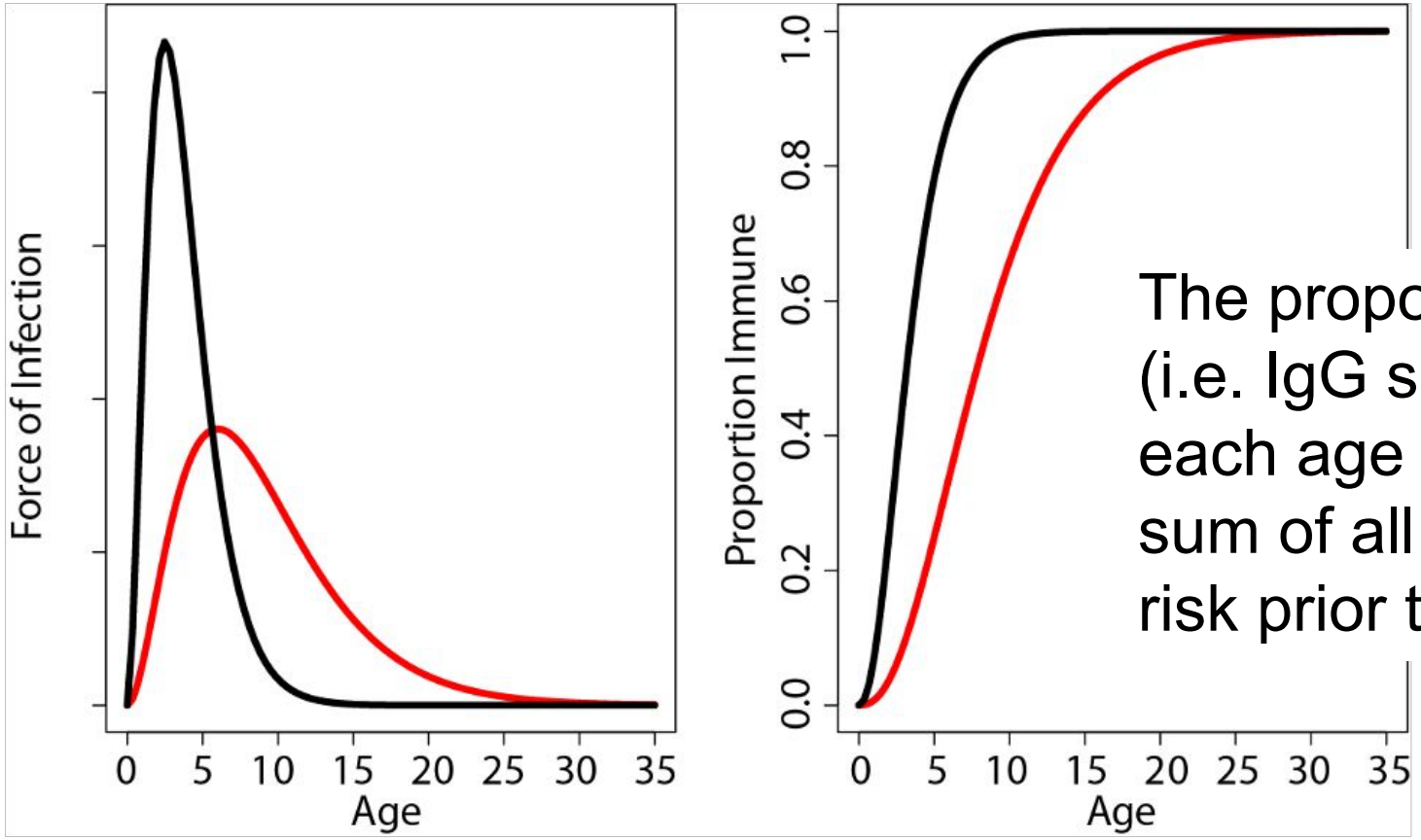
Age-Specific FOI



The age specific Force of Infection is the rate at which individuals of each age are exposed to infection

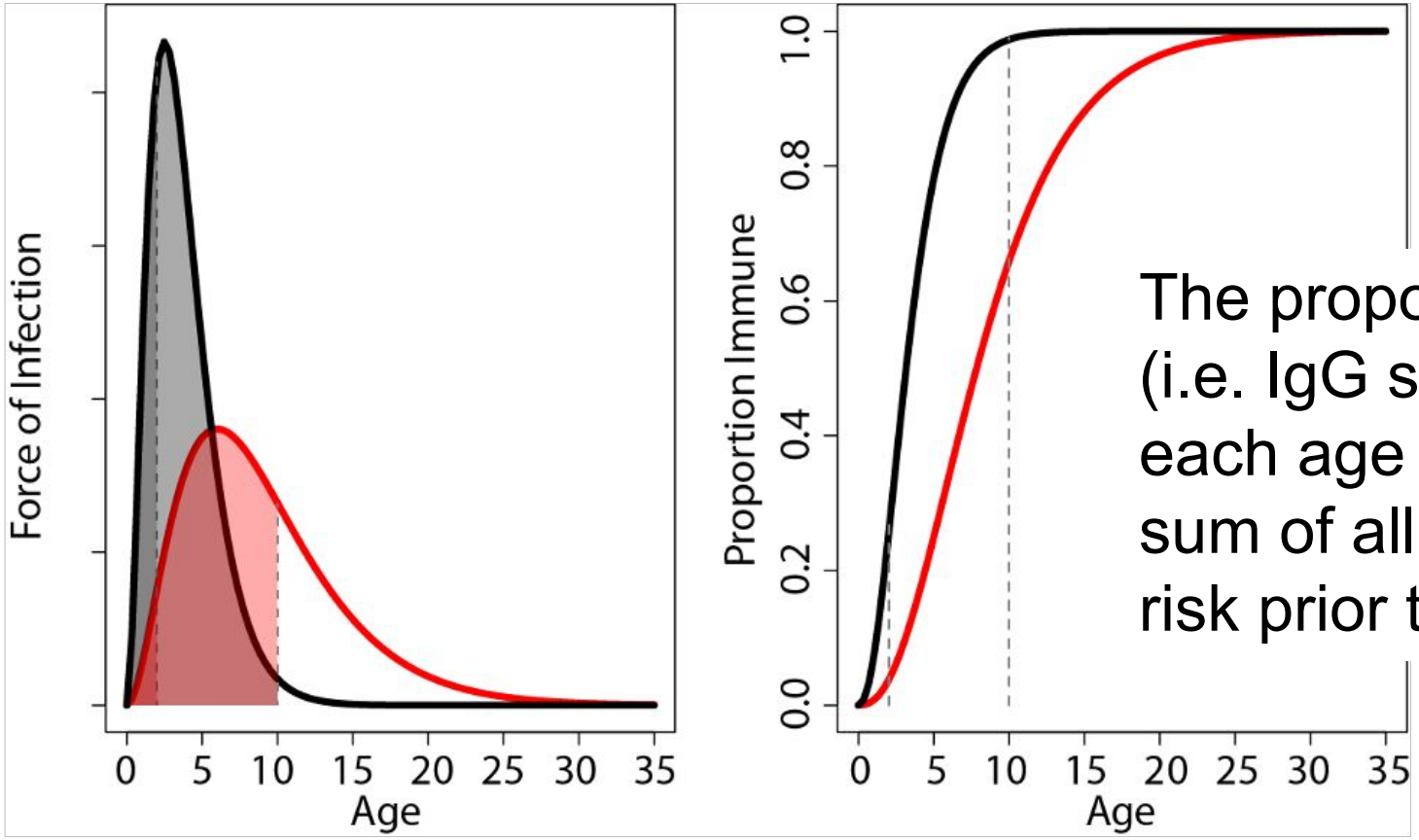
The shape of this function reflects the absolute risk (height) and the age ranges over which infection is most likely (breadth of the curve)

Age-Specific FOI



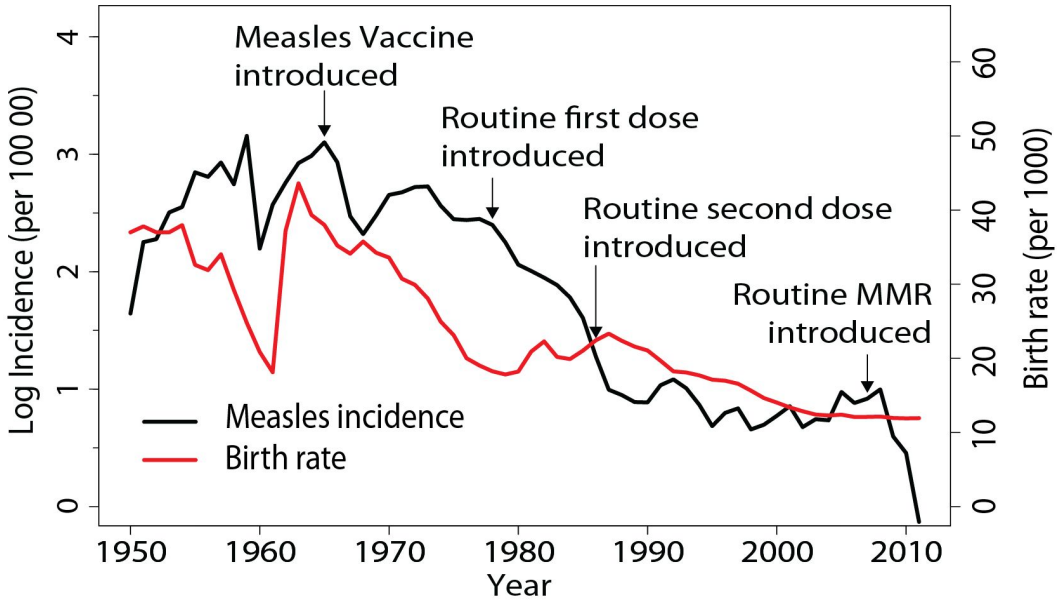
The proportion immune (i.e. IgG seropositive) at each age is equal to the sum of all age-specific risk prior to that age

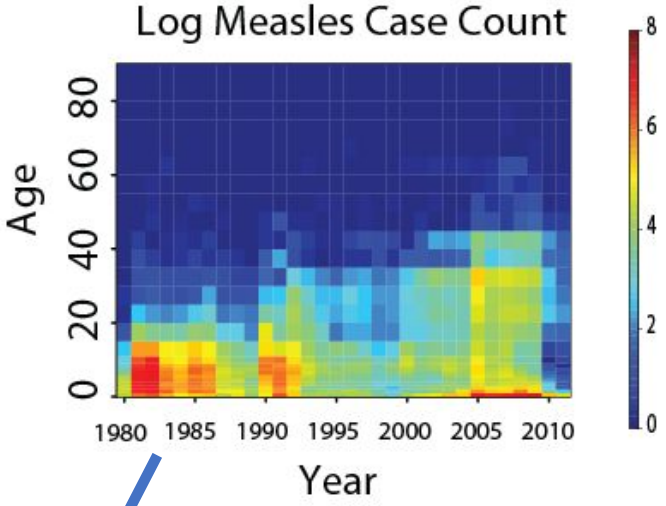
Age-Specific FOI

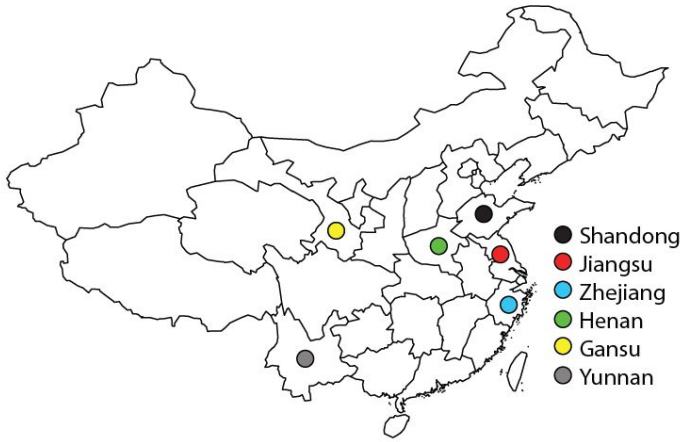


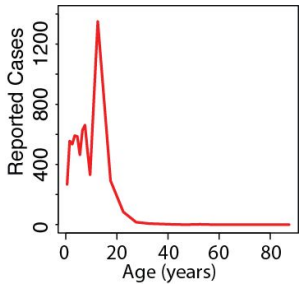
The proportion immune (i.e. IgG seropositive) at each age is equal to the sum of all age-specific risk prior to that age

Age Distribution in Jiangsu

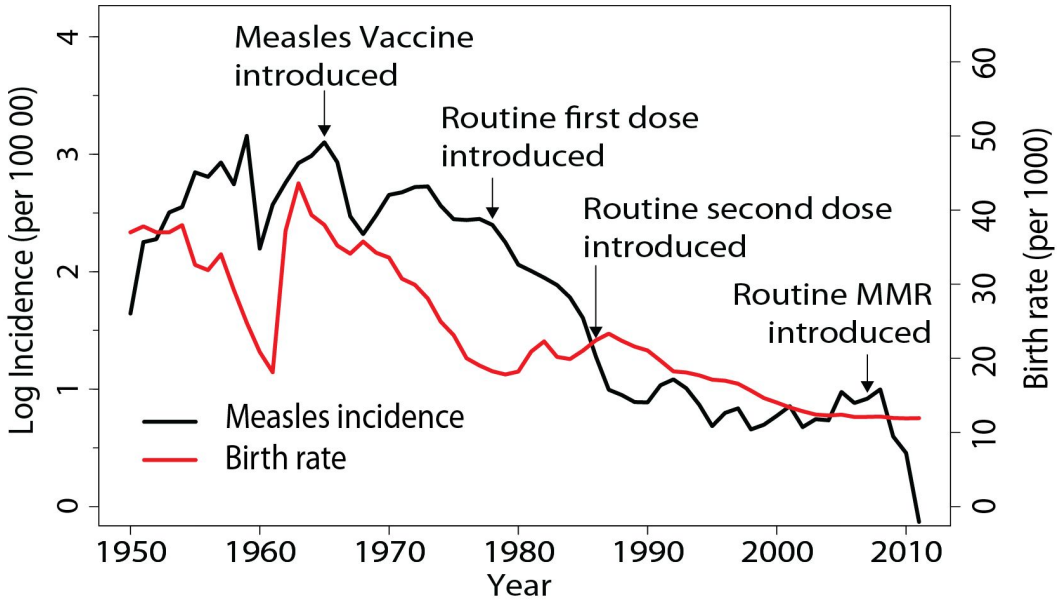


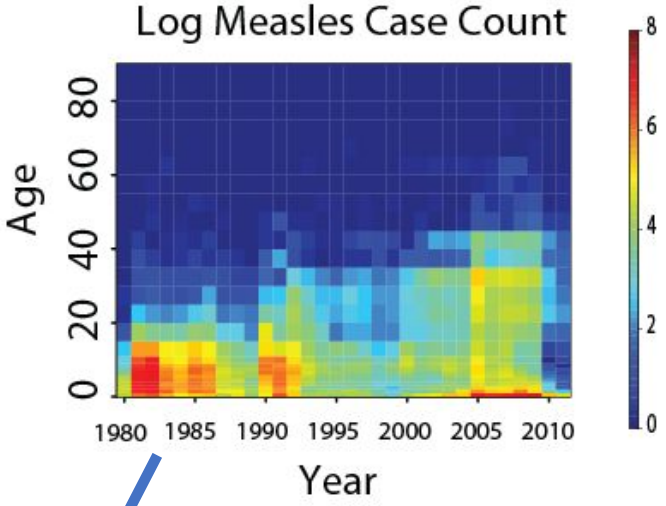


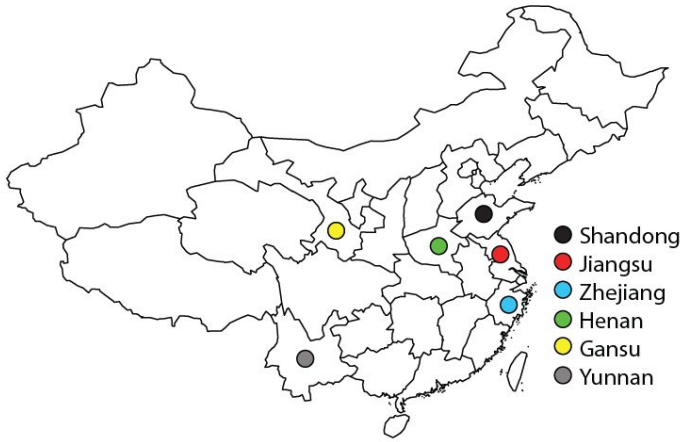


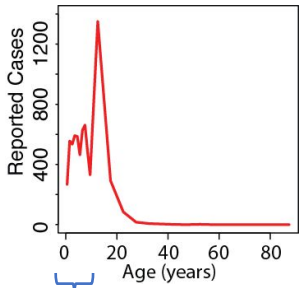


Age Distribution in Jiangsu



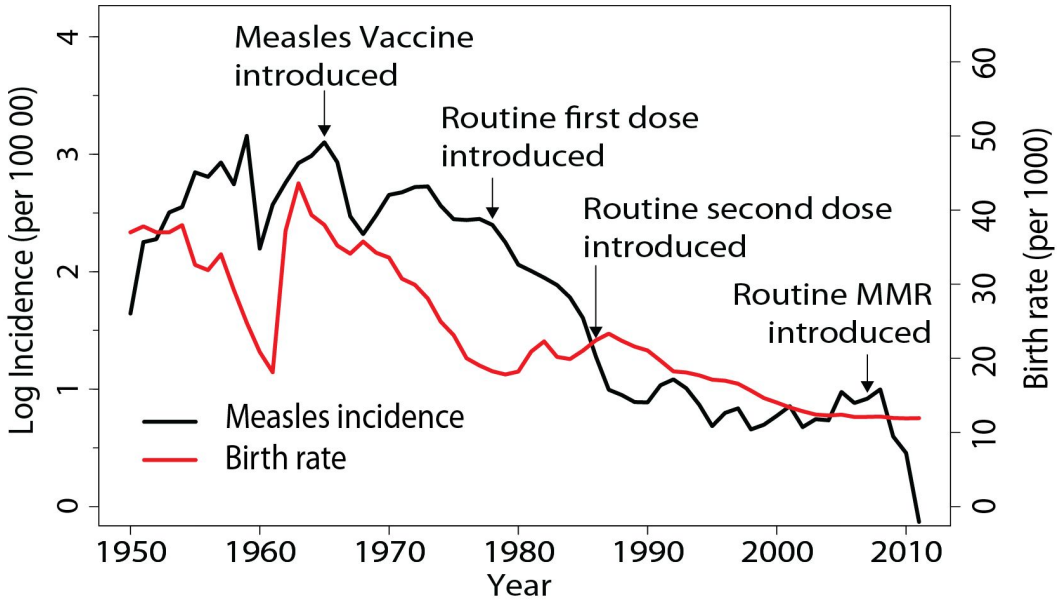


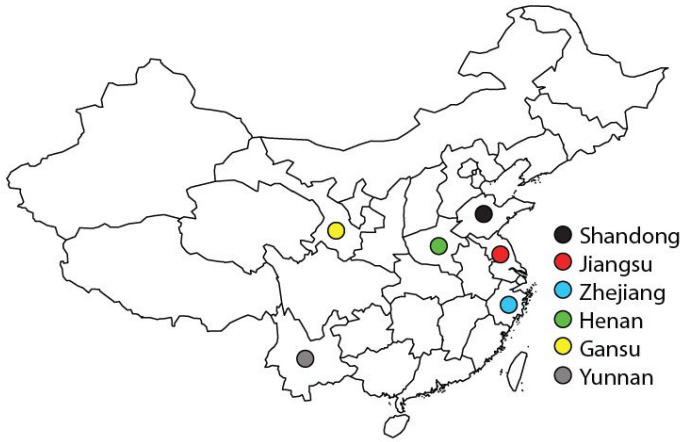


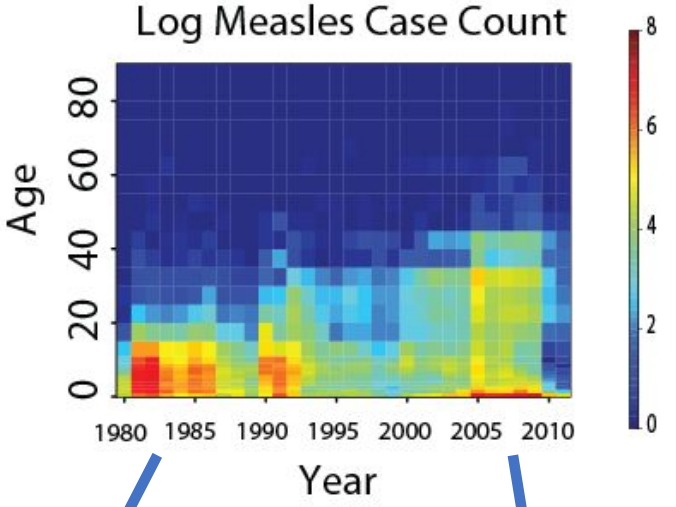


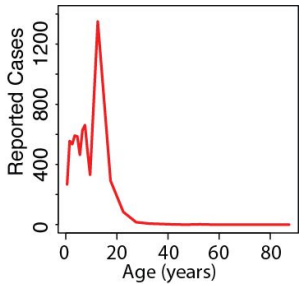
1y up to age 10y
5y afterwards

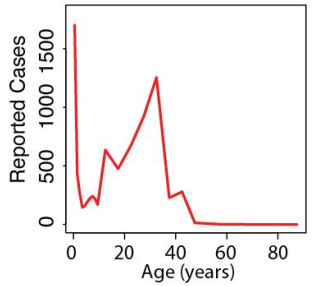
Age Distribution in Jiangsu



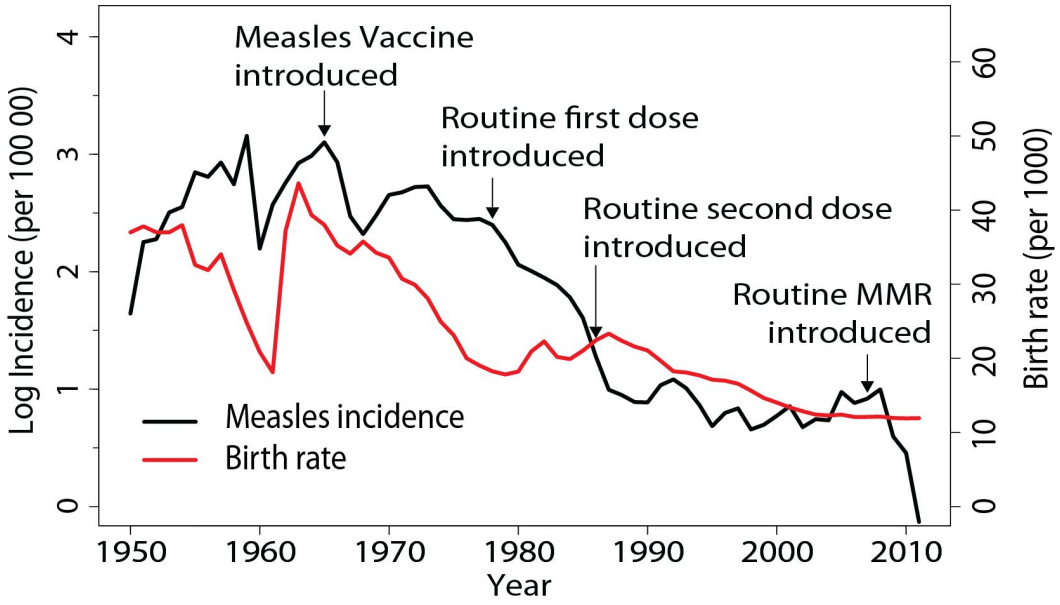


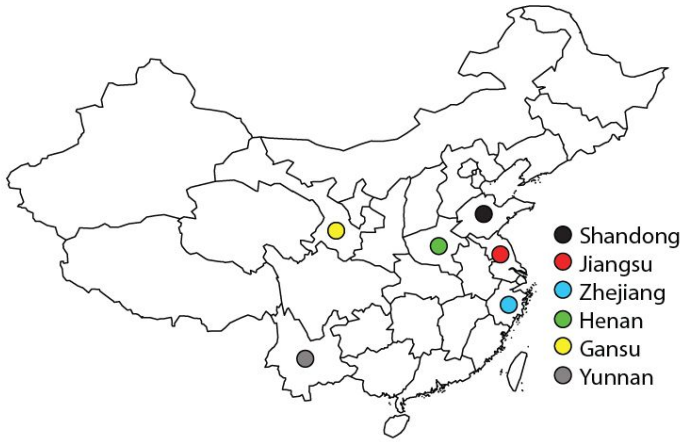


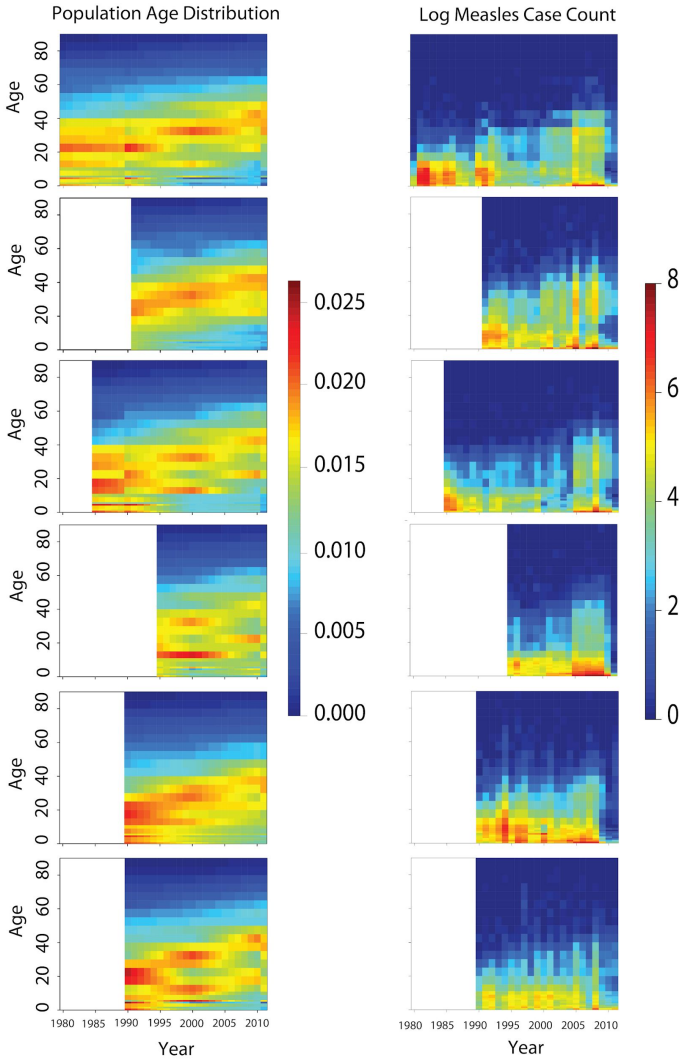




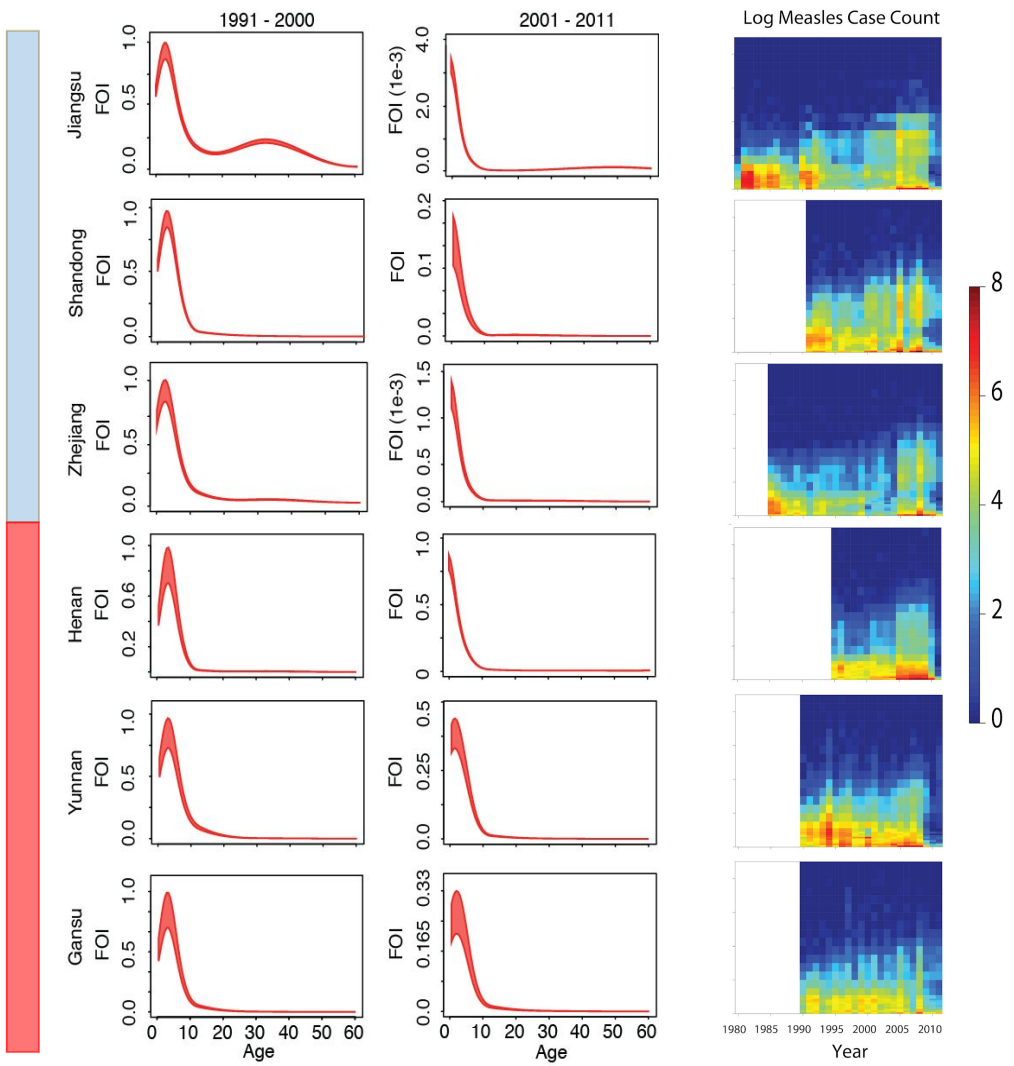
Pattern Consistent Across China







Provincial Variation



Reduction in R_E from 90's to 00's

97%

90%

95%

24%

68%

73%

Farrington, Kanaan, Gay 2001

Age-specific severity

- Most severe in the young:
  - Measles, pertussis, diphtheria
- Most severe in the elderly
  - COVID-19
- Most severe in the young AND the elderly
  - Influenza
- Most severe in intermediate ages
  - Zika virus, rubella – severe complications in pregnancy

COVID-19 and transition to endemicity

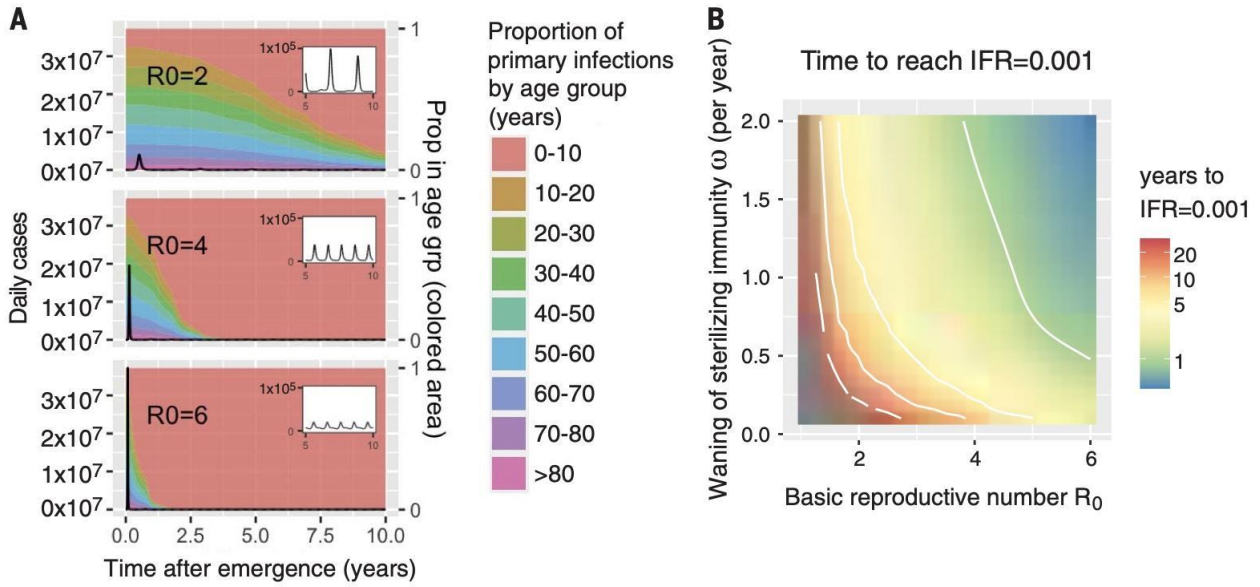


Fig. 2. The time scale of the transition from epidemic to endemic dynamics for emerging coronaviruses depends on R_0 and the rate of immune waning. Transition from epidemic to endemic dynamics for emerging HCoVs, simulated from an extension of the model presented in fig. S1 that includes age structure. Demographic characteristics (age distribution, birth, and age-specific death rates) are taken from the United States, and seasonality is incorporated via a sinusoidal forcing function (see SM section 2.2). Weak social distancing is approximated by $R_0 = 2$. (See figs. S9 to S11 for strong social distancing results, $R_0 < 1.5$.) (**A**) Daily number of new infections (black line; calculations in SM section 2.3). An initial peak is followed by a low-incidence endemic state (years 5 to 10 shown in the inset). A higher R_0 results in a larger and faster initial epidemic and a more rapid transition to endemic dynamics. The proportion of primary cases in different age groups changes over time (plotted in different colors), and the transition from epidemic to endemic dynamics results in primary cases being restricted to younger age groups. Parameters for simulations: $\omega = 1$ and $\rho = 0.7$. (**B**) Time for the average IFR (6-month moving average) to fall to 0.001, which is the IFR associated with seasonal influenza. Gray areas represent simulations where the IFR did not reach 0.001 within 30 years. The time to IFR = 0.001 decreases as the transmissibility (R_0) increases and the duration of sterilizing immunity becomes shorter. Results are shown for $\rho = 0.7$. See SM section 2.3 and figs. S4 to S7 for sensitivity analyses and model specifications.

Higher disease severity in older adults observed *when entire population is susceptible*

What will distribution of immunity look like ***after*** endemic equilibrium is reached?

What does this mean for the future of disease severity?

RESEARCH

CORONAVIRUS

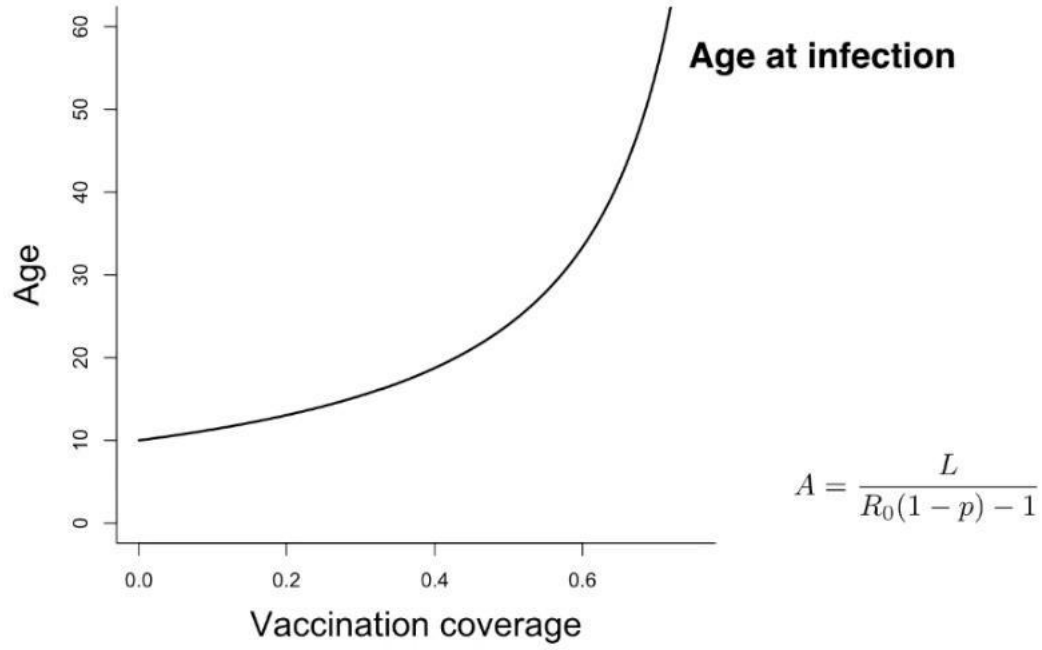
Immunological characteristics govern the transition of COVID-19 to endemicity

Jennie S. Lavine[1]*, Ottar N. Bjornstad[2], Rustom Antia[1]

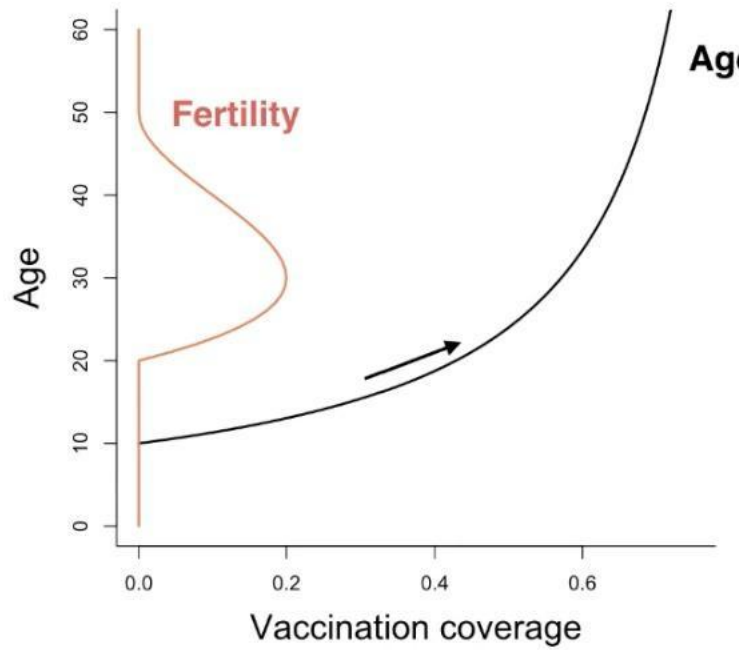
Rubella and CRS

- Rubella is a directly transmitted virus with R_0 of 2-6 in endemic regions
- Infections in children and adults are mild
- Infections during first trimester of pregnancy can lead to serious complications (Congenital Rubella Syndrome, CRS)
  - Deafness
  - Blindness
  - Congenital heart disease

Age Dynamics Following RCV Introduction



$$A = \frac{L}{R_0(1-p)-1}$$



$$A = \frac{L}{R_0(1-p)-1}$$

Heterogeneity in contacts over age

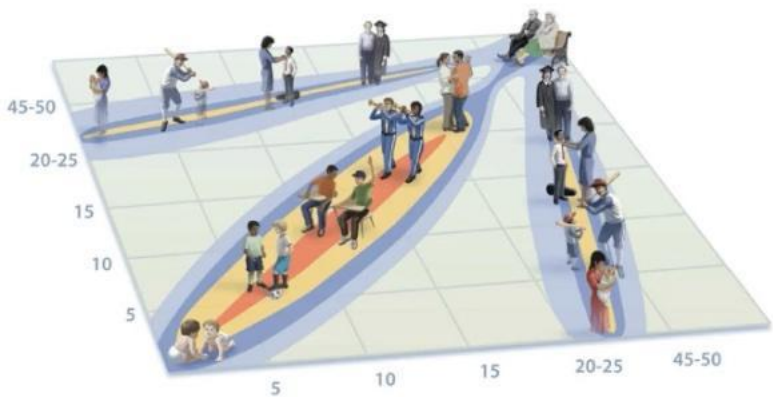
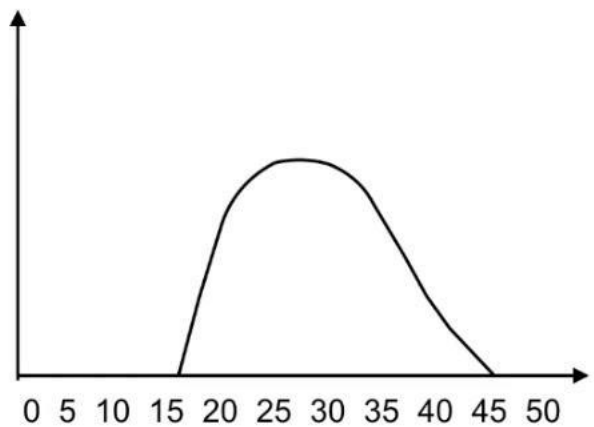


Image: Rohani & King

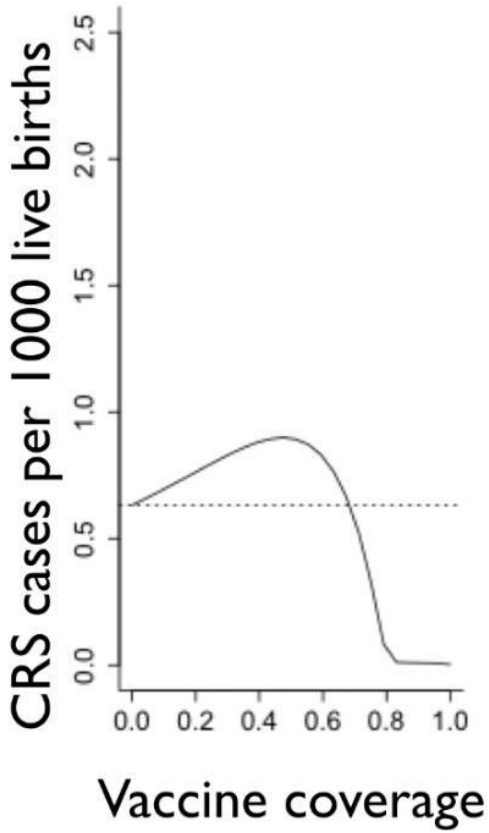
Age profile of fertility



Epidemiol. Infect. (2012), **140**, 2290–2301. © Cambridge University Press 2012
doi:10.1017/S0950268812000131

Impact of birth rate, seasonality and transmission rate on minimum levels of coverage needed for rubella vaccination

C. J. E. METCALF[1,2*], J. LESSLER[3], P. KLEPAC[2], F. CUTTS[4] AND B. T. GRENFELL[2,5]



CRS: Congenital **R**ubella **S**yndrome (brain damage, deafness, blindness in children born to women who were infected during the first trimester)

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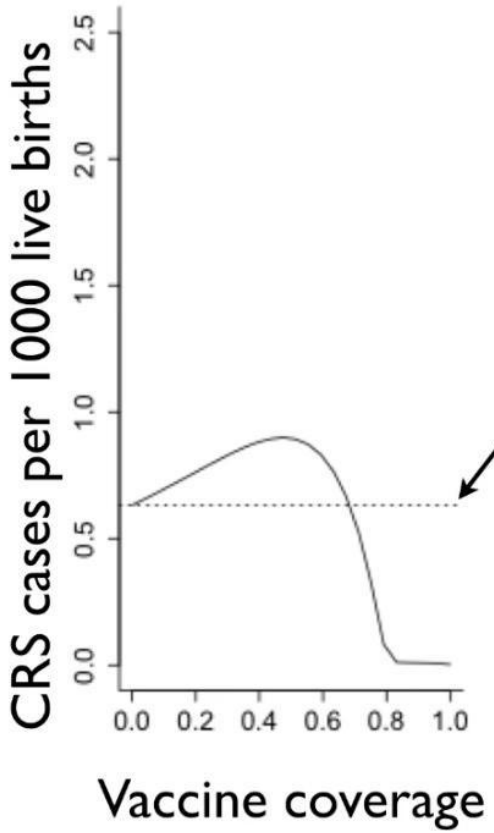

CRS: Congenital **R**ubella **S**yndrome (brain damage, deafness, blindness in children born to women who were infected during the first trimester)

CRS burden in the absence of vaccination

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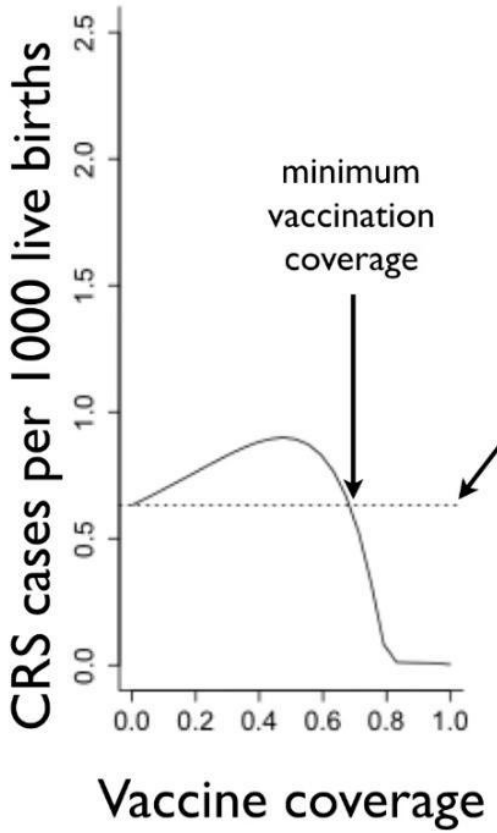

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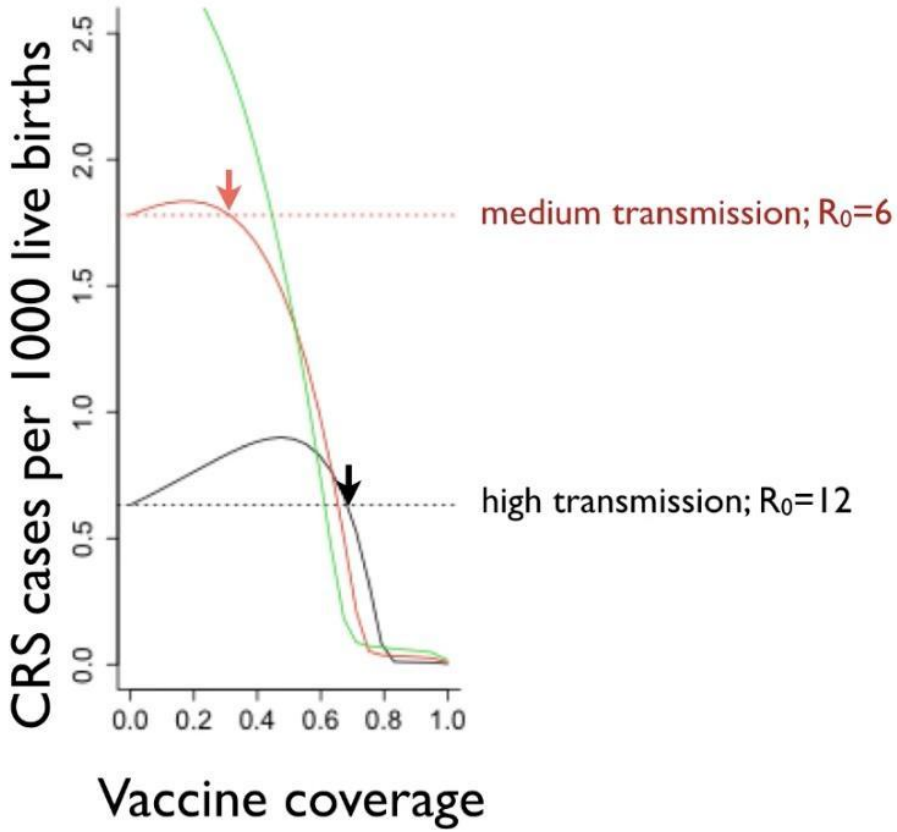

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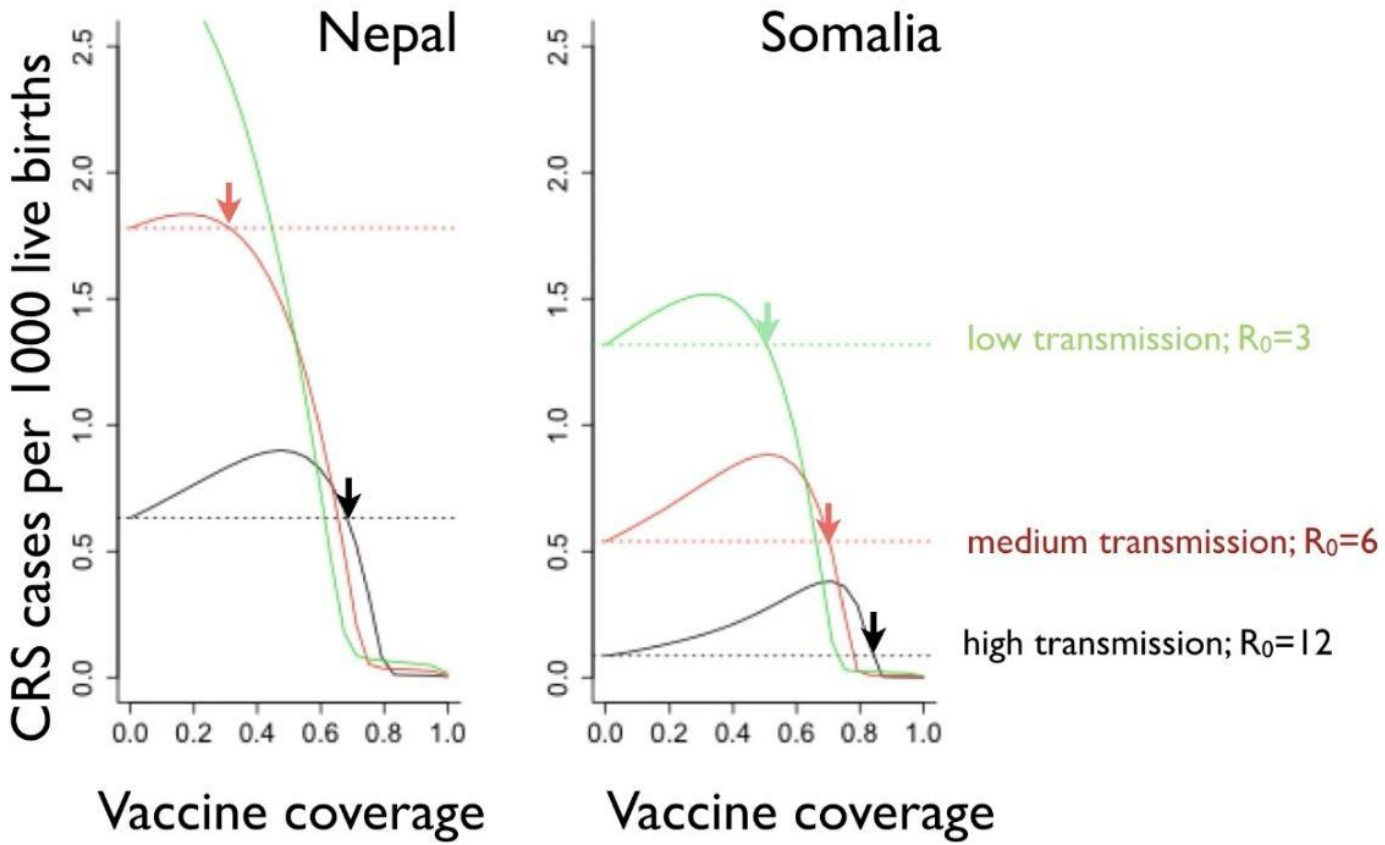


RCV Policy

- Since 2000, there was a single WHO policy recommendation that countries needed to reach 80% of birth cohorts with vaccination in order to introduce RCV

- As of September 2024, that has been changed (using modeling) to show that 80% was too conservative
  - The optimal strategy for introduction is highly dependent on local vaccination coverage (routine plus campaigns), local transmission rate (lower R_0 than modeled prior), and local demography (birth rates declining)

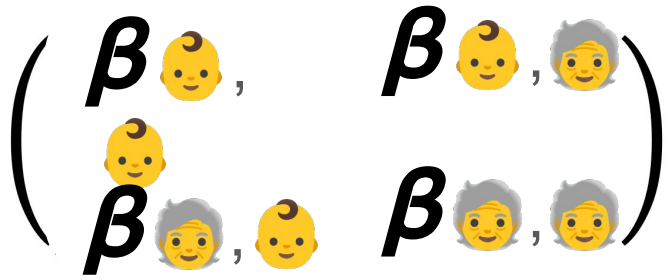
What age heterogeneities matter for IDs?

- Age-specific **contacts** → Age-specific **transmission**
- Age-specific **disease progression / outcomes**
- Age-specific **infectiousness** (e.g., viral shedding by age)
- Age-specific **susceptibility** (e.g., maternally derived immunity)
- Age-dependent **vaccination effectiveness**
- Age-specific **prevention** strategies
- Age-specific **treatments**
- Age-specific **surveillance** bias

Modeling Age Heterogeneity

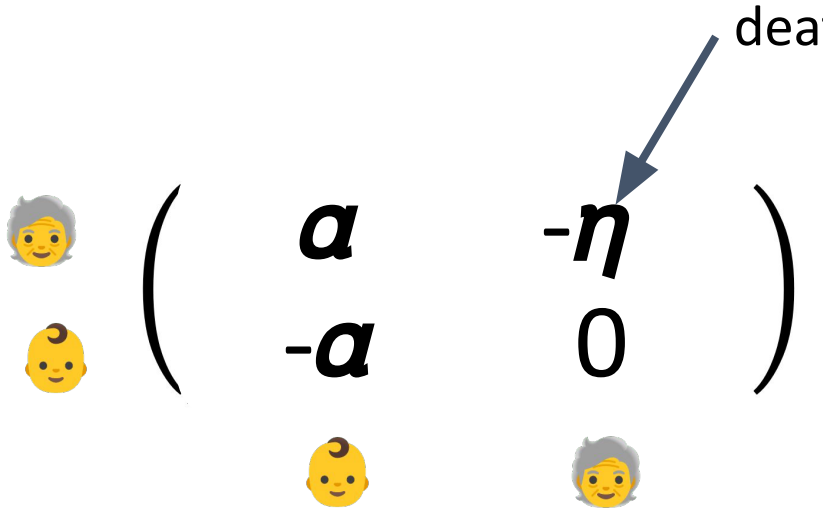
Modeling age heterogeneity

It is the **same as modeling heterogeneity with non-directional transitions** (i.e., age-specific parameters and a matrix of β or WAIFW to "talk" to each other), but **with the addition of individuals ageing**



WAIFW matrix

diagonal is assortative transmission



ageing matrix

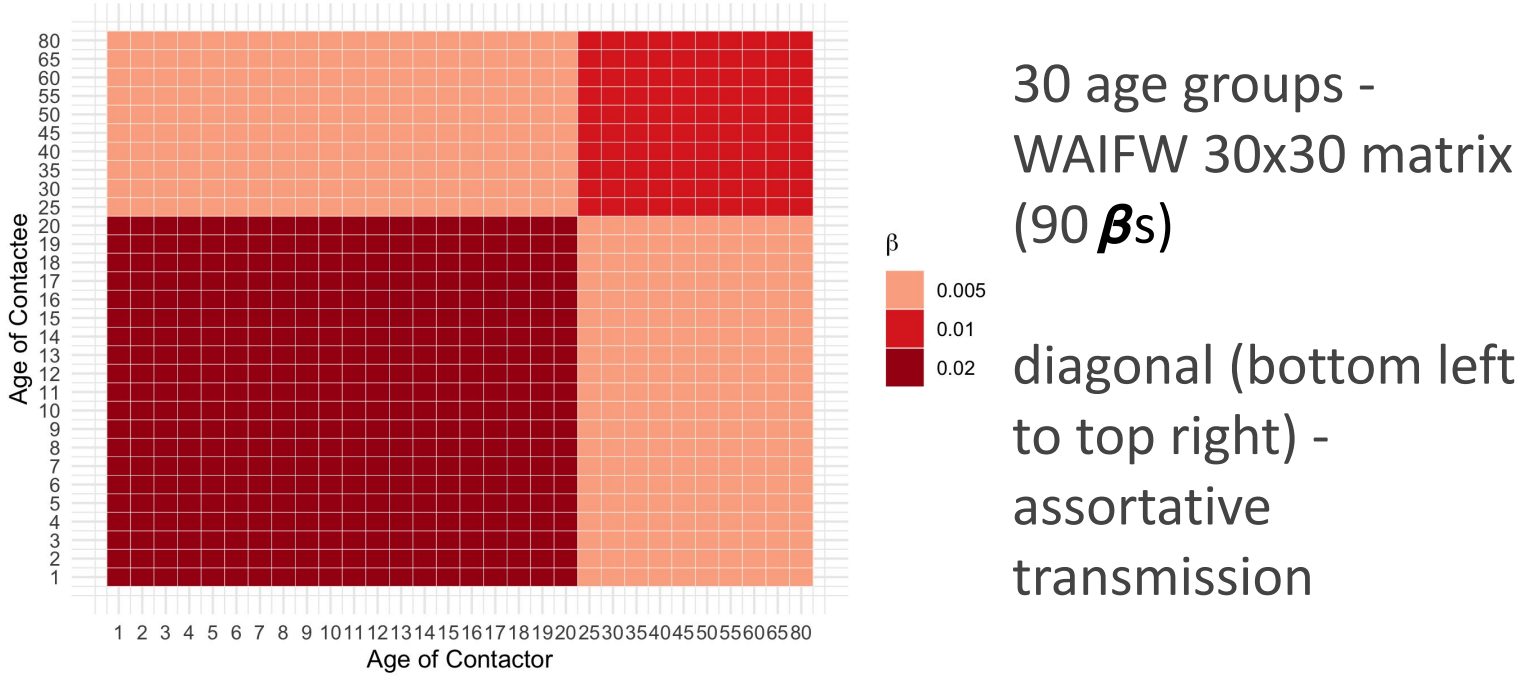
from column age group to row age group

Modeling age heterogeneity

It is the **same as modeling heterogeneity with non-directional transitions** (i.e., age-specific parameters and a matrix of β or WAIFW to "talk" to each other), but **with the addition of individuals ageing**

2 age groups - WAIFW 2x2 matrix (4 βs)

diagonal (top left to bottom right) - assortative transmission



30 age groups - WAIFW 30x30 matrix (90 βs)

diagonal (bottom left to top right) - assortative transmission

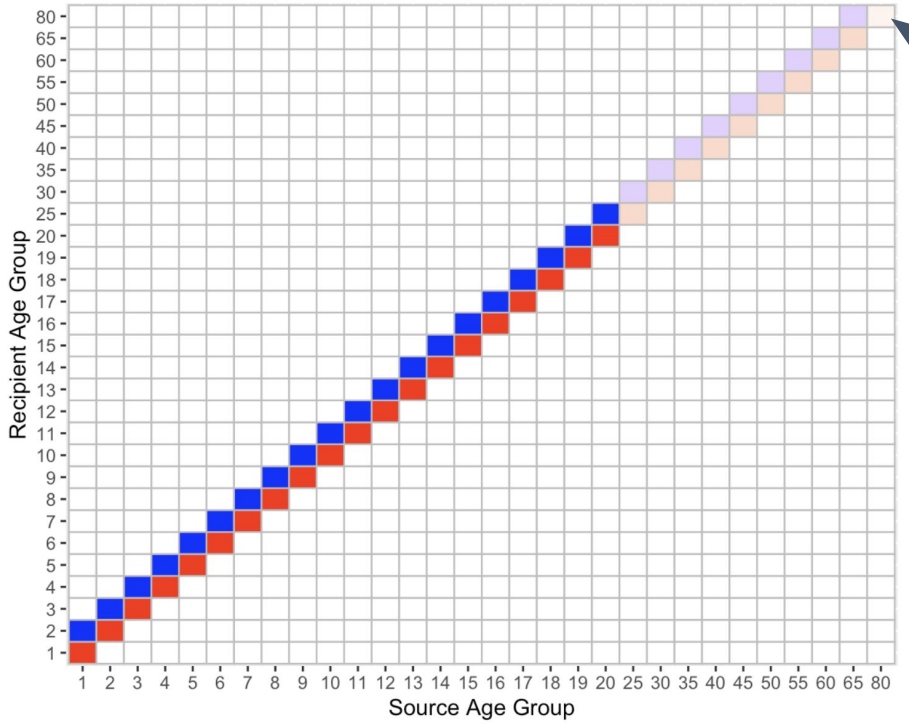
Modeling age heterogeneity

It is the **same as modeling heterogeneity with non-directional transitions** (i.e., age-specific parameters and a matrix of $\boldsymbol{\beta}$ or WAIFW to "talk" to each other), but **with the addition of individuals ageing**

deaths

$$\begin{pmatrix} \alpha & -\eta \\ -\alpha & 0 \end{pmatrix}$$

2 age groups ageing matrix



deaths

Freq
1
0.2
0
-0.2
-1

blue (>0) - ageing in
red (<0) - ageing out

30 age groups ageing matrix

A little demography

Characteristic	**Stable Population**	**Stationary Population**
Age Structure	Constant	Constant
Growth Rate	Constant (≠ 0)	Zero
Conditions	Constant births & deaths	births = deaths
Size Over Time	Changes (exponential)	Fixed