Age Structure

- Connection to previous lecture
  - Balance of birth and death rates creates population structure
  - Longer life means a greater fraction of population is likely to be immune and can contribute to herd immunity
  - Many births and high death rate means that most of the population is in the susceptible class and can contribute to transmission

R0 and Age

- Remember relationship between rate of recovery and duration of infection (or time to recovery)
  - Average time to an event is the inverse of its rate
- Relation between mean age of infection and R_0
  - R_0 reflects the rate of infection, mean age is the average time from birth to infection
  - Basic calculation requires strong assumption that age-specific force of infection is constant
- What does this mean for control?

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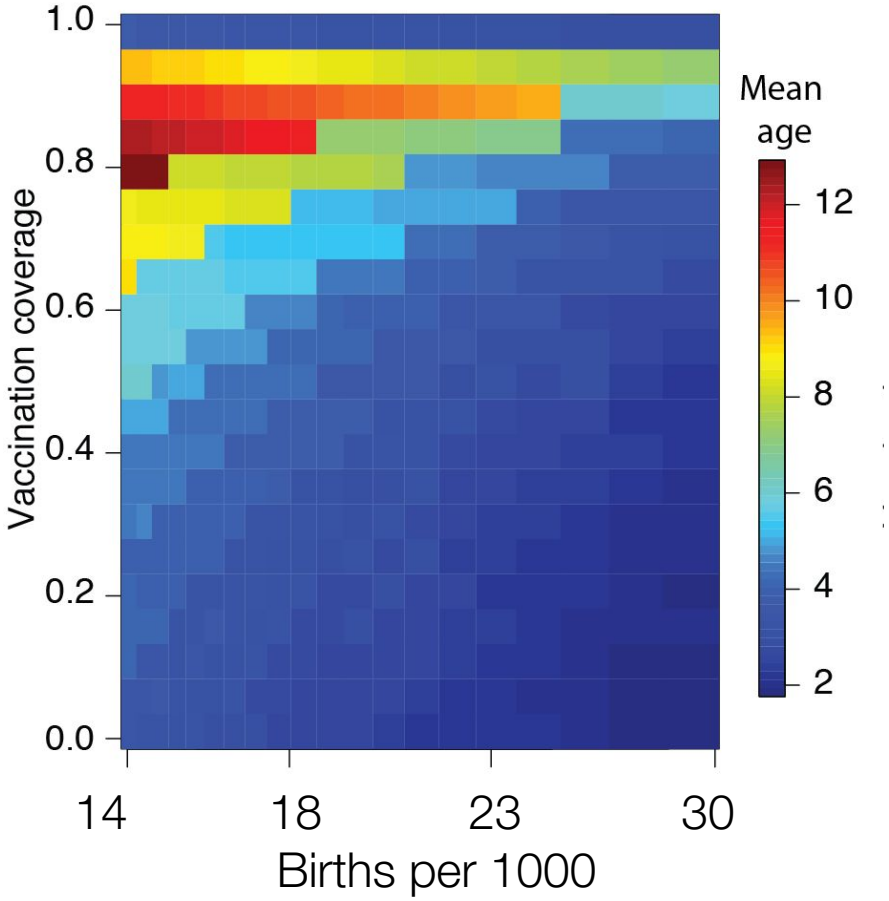
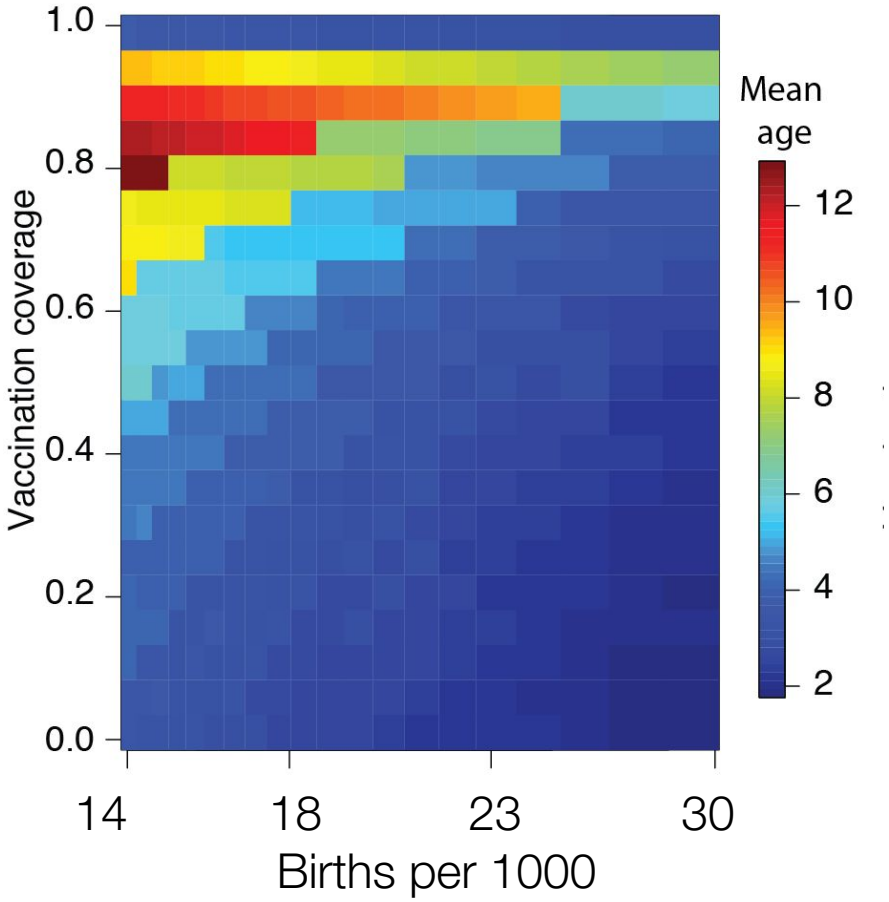
Intuition About Mean Age of Infection



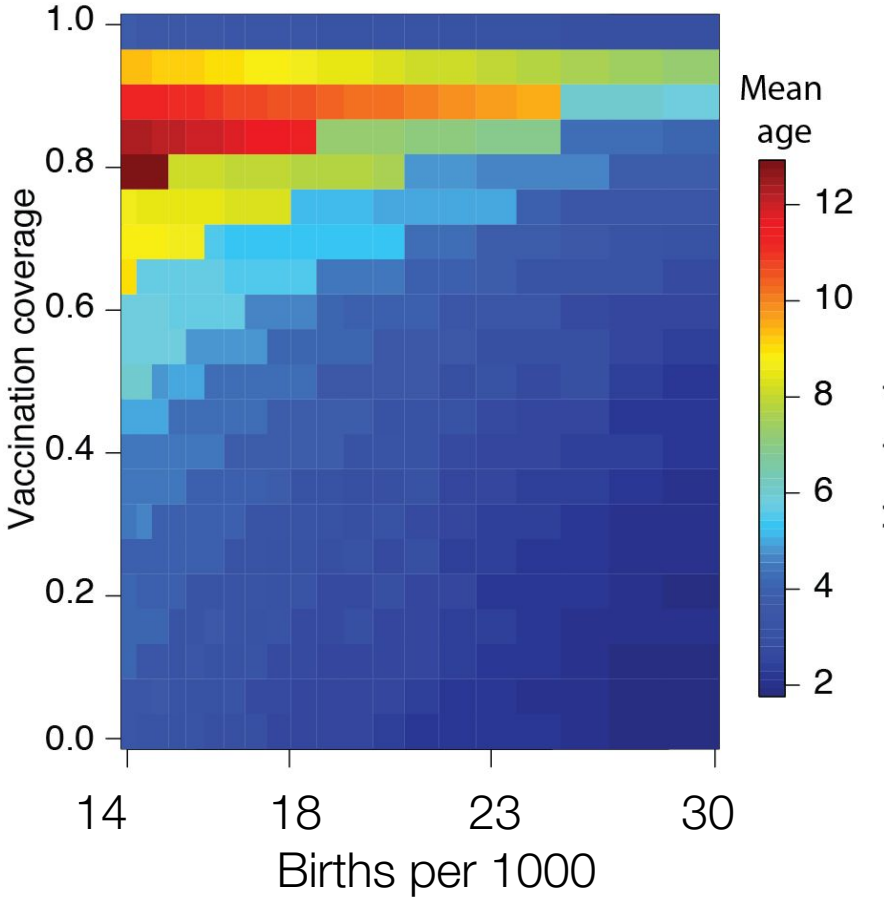
- Reduced prevalence of infection results in lower force of infection on each susceptible individual

Intuition About Mean Age of Infection



- Reduced prevalence of infection results in lower force of infection on each susceptible individual
- Longer wait until contact between susceptible and infectious individuals

Intuition About Mean Age of Infection



- Reduced prevalence of infection results in lower force of infection on each susceptible individual
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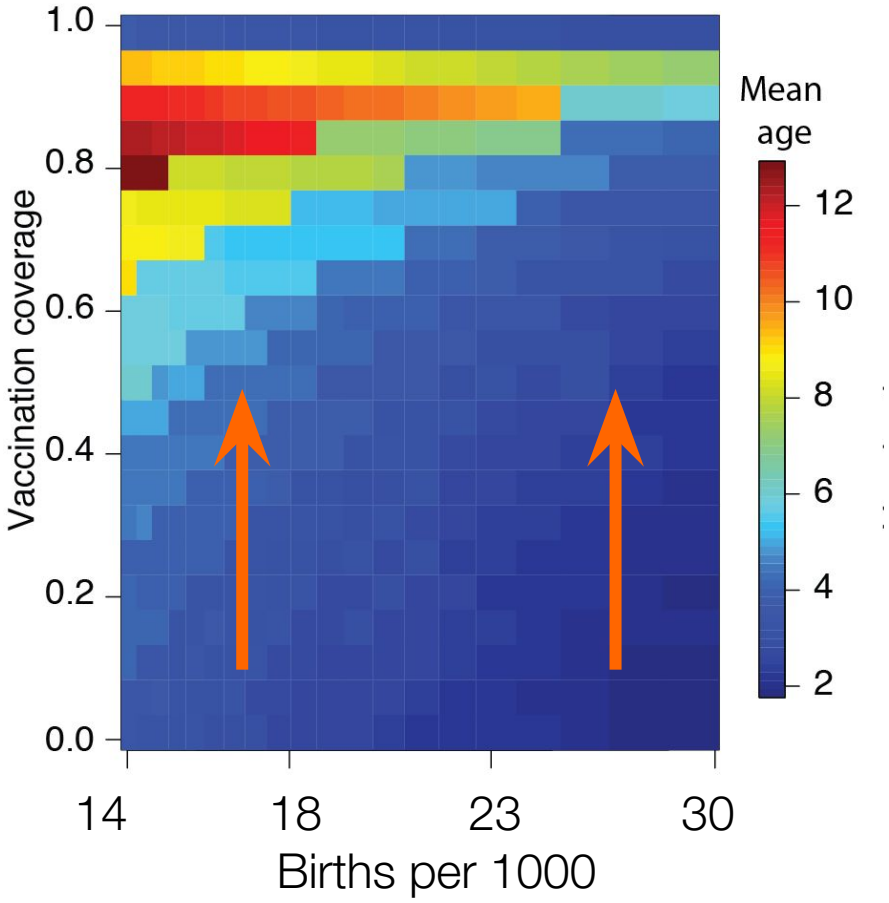
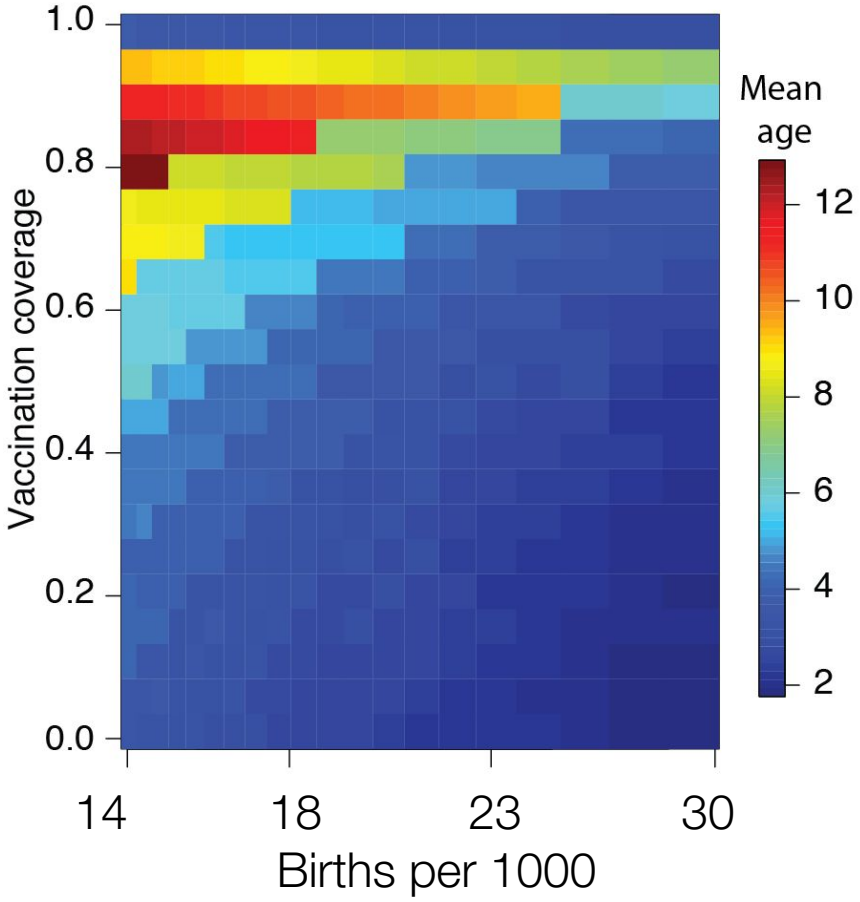
- Lower force of infection implies higher mean age at infection

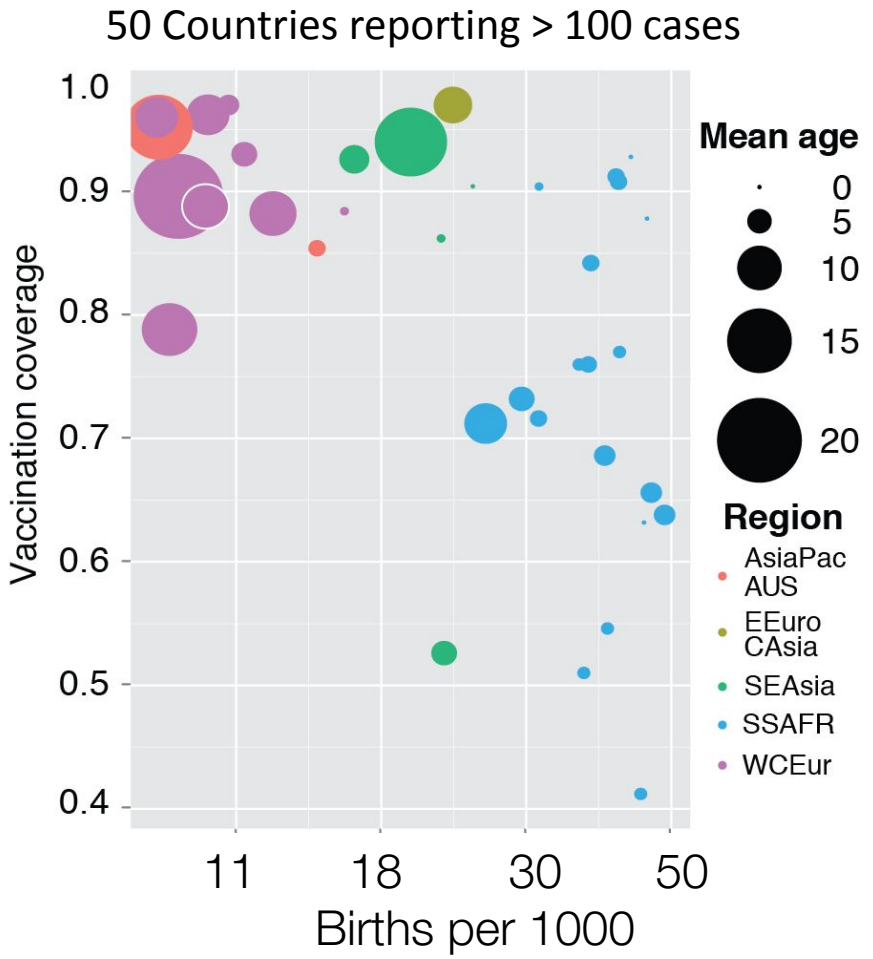
Intuition About Mean Age of Infection



- 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

Observation About Mean Age of Infection





Ferrari et al 2013

R0 and Age

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R0 and Age

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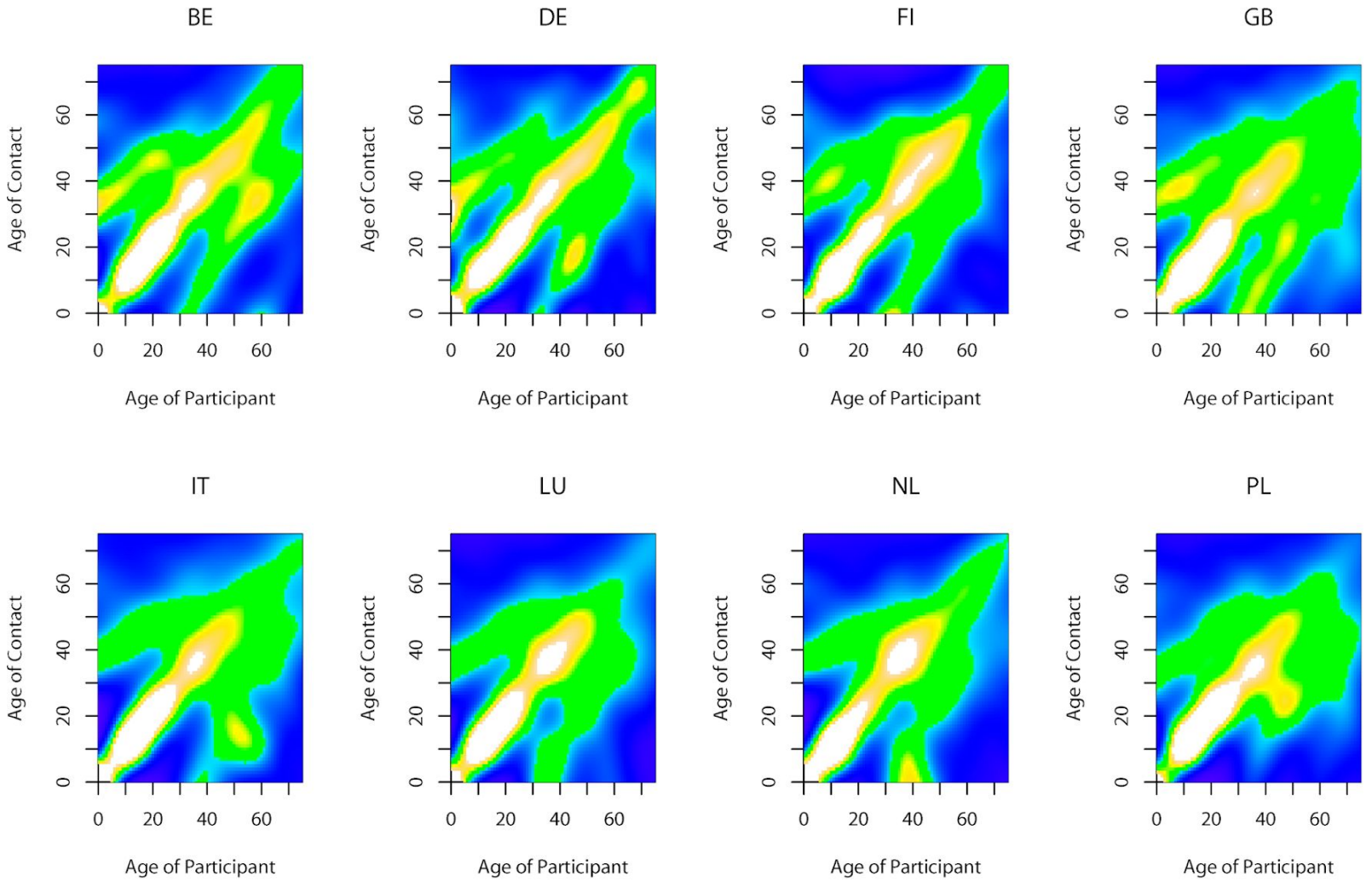
- Relation between mean age of infection and R_0
  - R_0 reflects the rate of infection, mean age is the average time from birth to infection
  - Basic calculation requires strong assumption that age-specific force of infection is constant
    - What evidence do we have that this is or IS NOT the case?
- What does this mean for control?

Age-related contact patterns



Mossong et al. *PLoS Med* 2007

Age-related contact patterns

PLOS COMPUTATIONAL BIOLOGY

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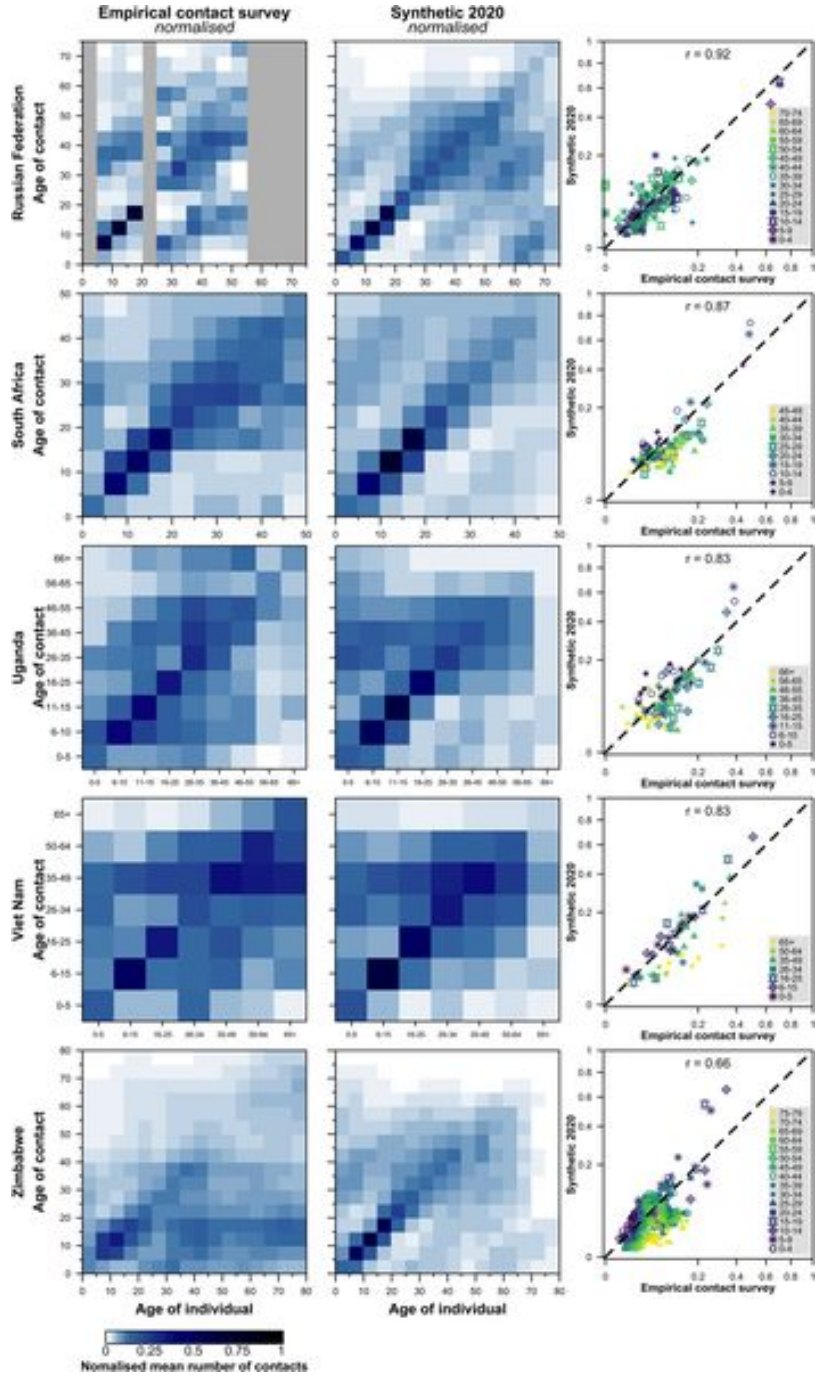
RESEARCH ARTICLE

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



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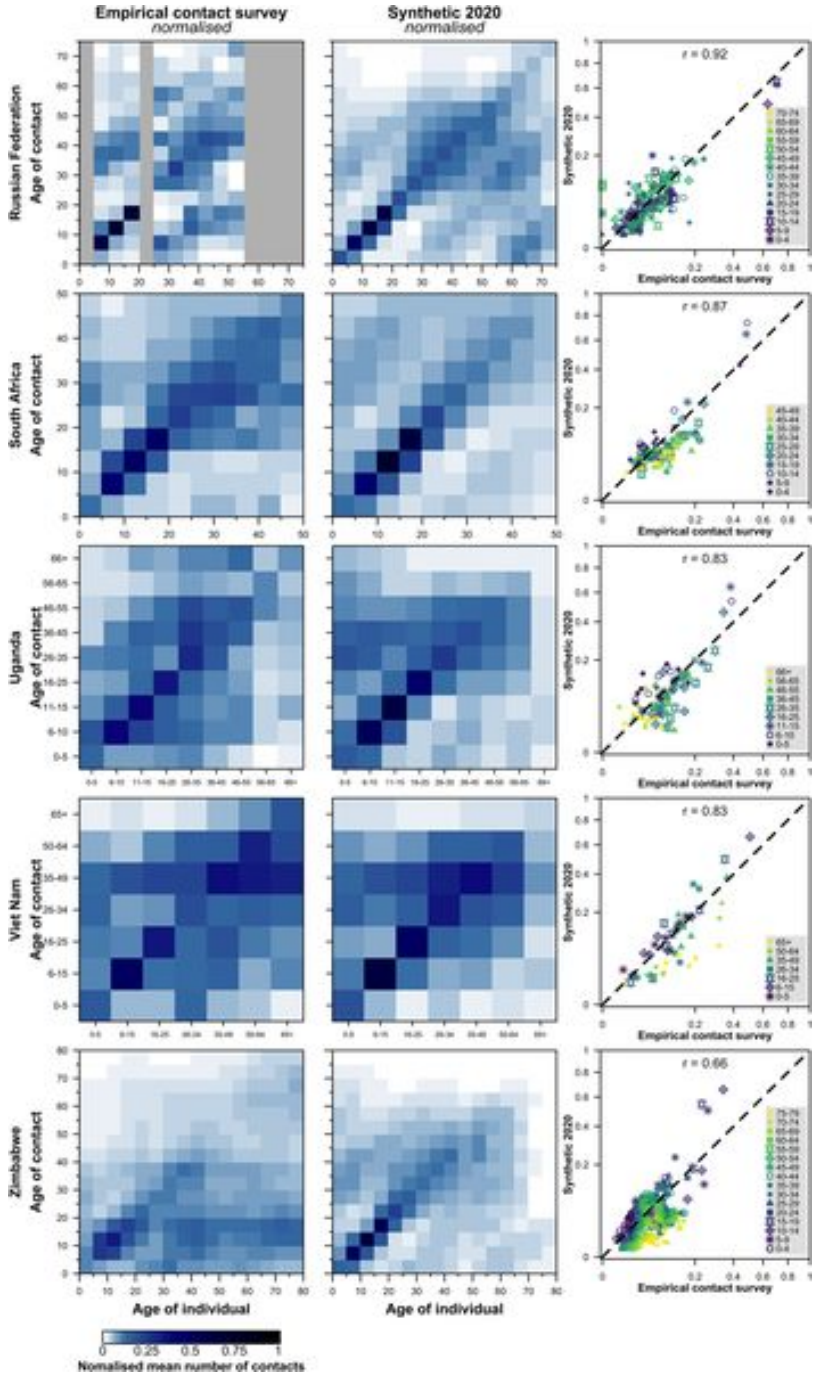
How diary studies relate to transmissible contacts is unclear

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



Estimated FOI – Catalytic model

- Empirical evidence based on distribution of infection or seroprevalence

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

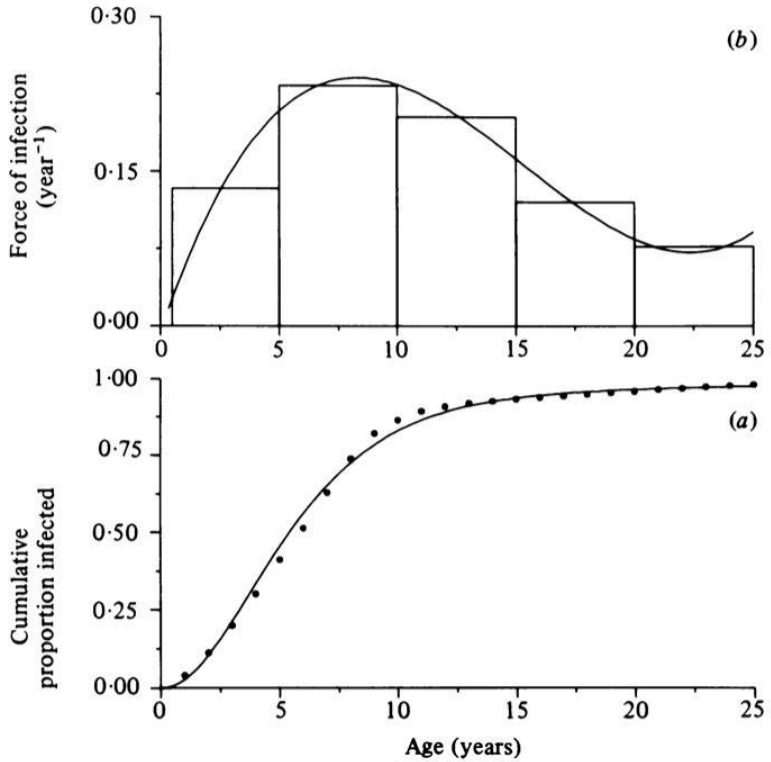
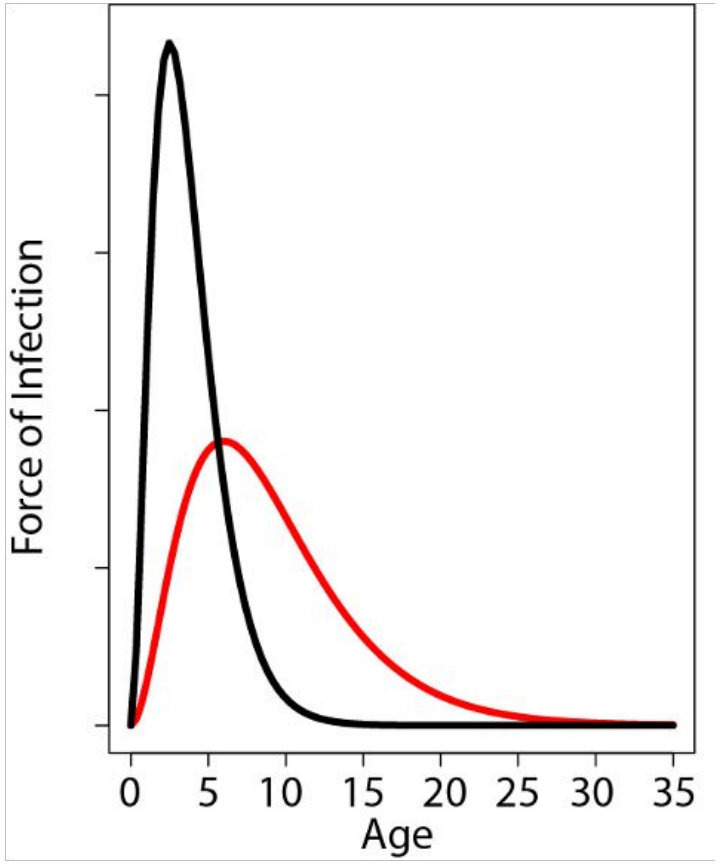


Fig. 1. Analysis of measles notifications for Baltimore, USA, 1906–15. (*a*) Observed and expected cumulative proportions infected by age ($F(a)$) in equation (5). (*b*) The fitted force of infection polynomial ($\lambda(a)$ in equation (4)). Here and in Figs. 2–7 the histogram represents average force 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.

Inference from Age Distribution of Cases

- Differences in behavior and exposure result in age-specific risk, or force of infection
- The likelihood of observing a case at age A is related to the integral of all risk prior to A
- Basis of the catalytic model
  - Griffiths (1974)
  - Grenfell and Anderson (1985)

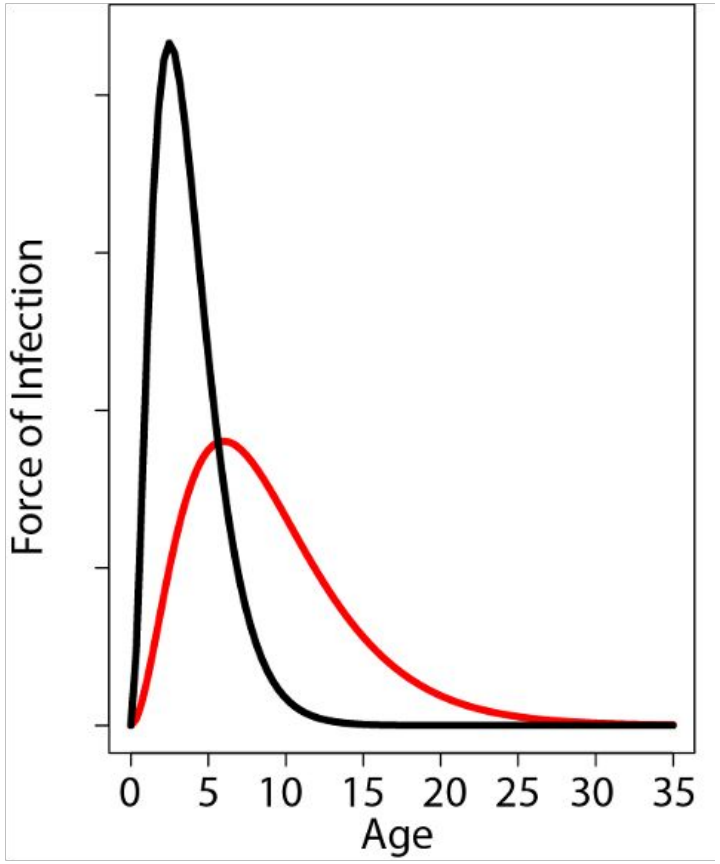
Catalytic Model



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)

Catalytic Model



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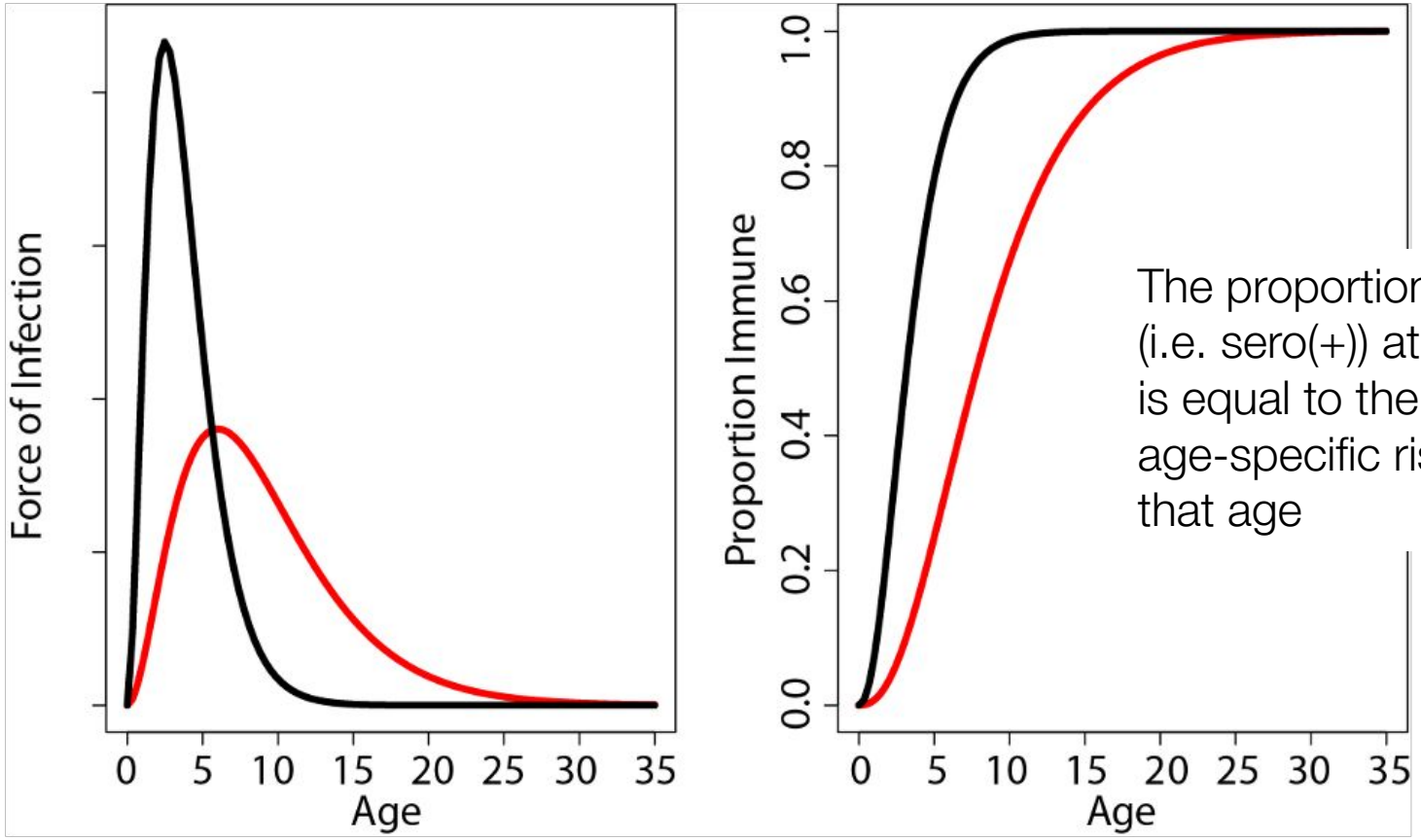
The shape of this function reflects the absolute risk (height) and the age ranges over which infection is most likely (breadth of the curve)

How does this differ from the WAIFW matrix?

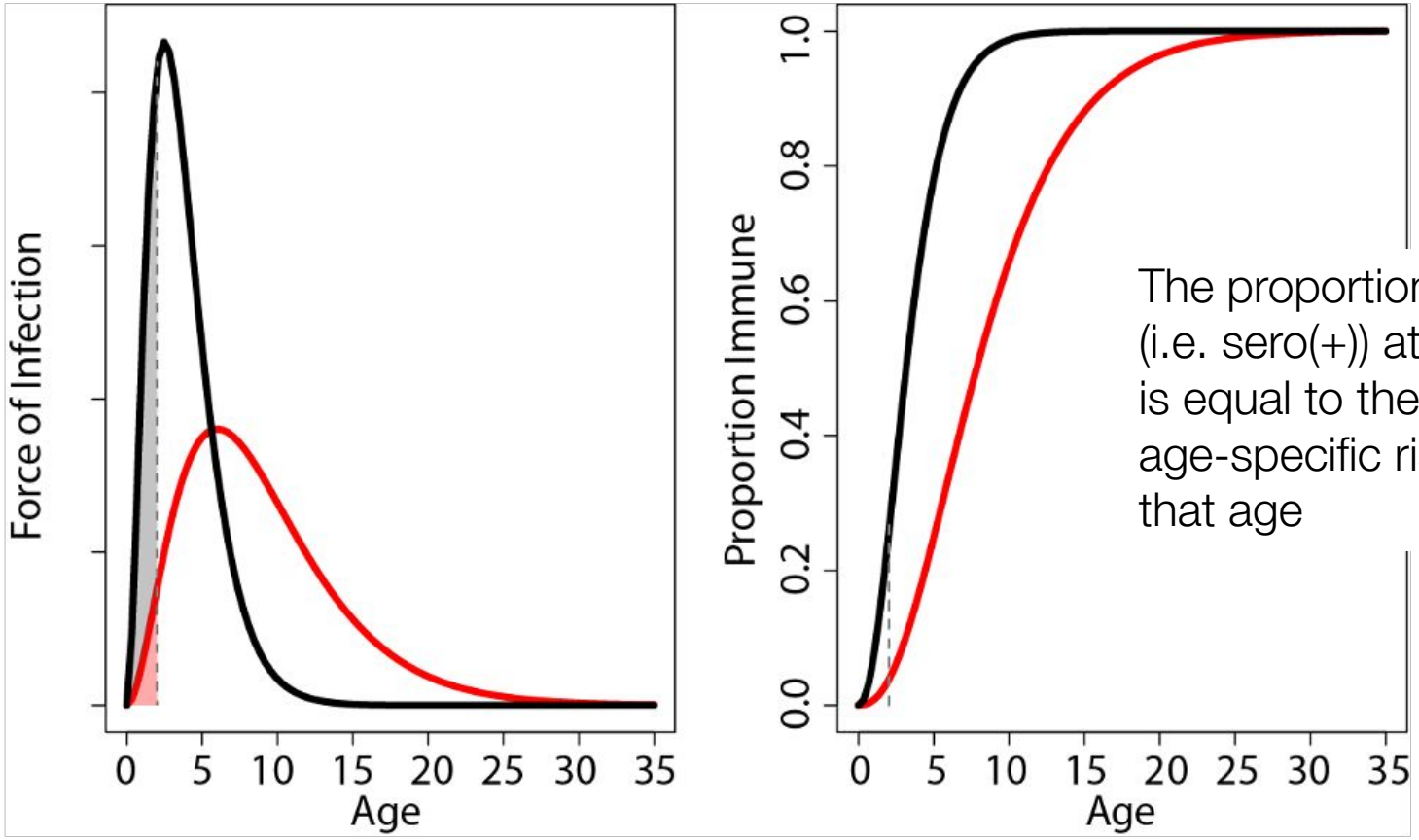
How does this differ from diary studies?

Catalytic Model



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

Catalytic Model



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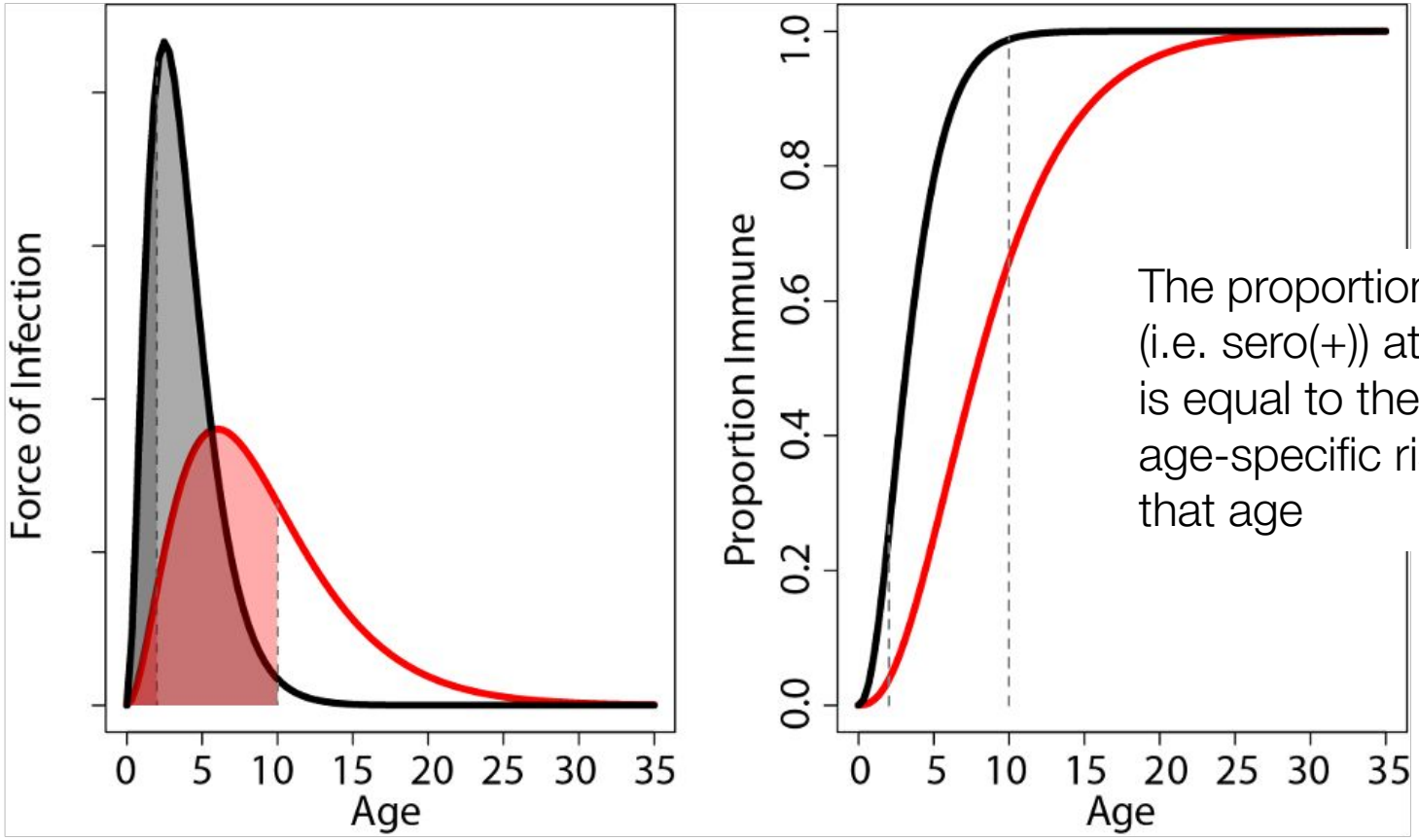

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Fitting the Catalytic Model

- Serological Data

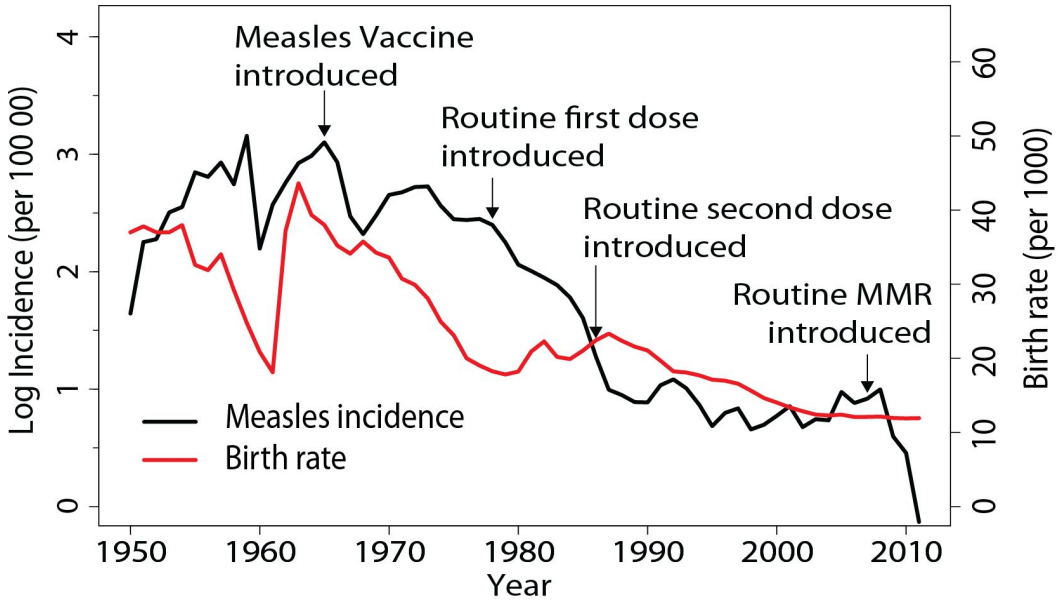
$$\phi(a) = \text{force of infection at age a}$$

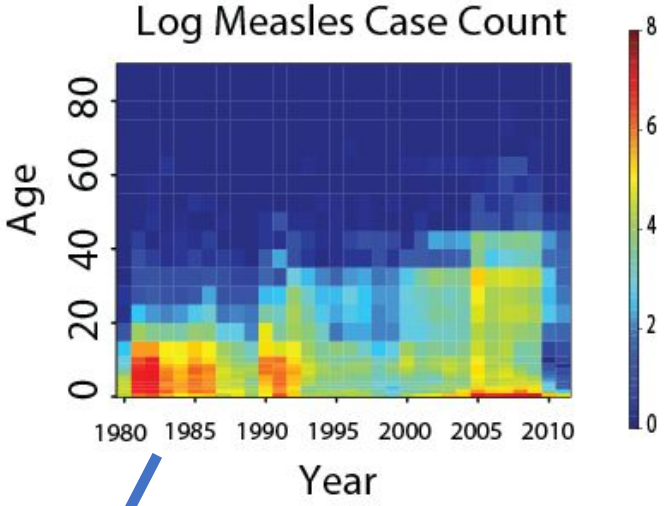
$$P(sero(+) \mid age) = 1 - \exp\left(-\int_0^{age} \phi(x)\,dx \right)$$

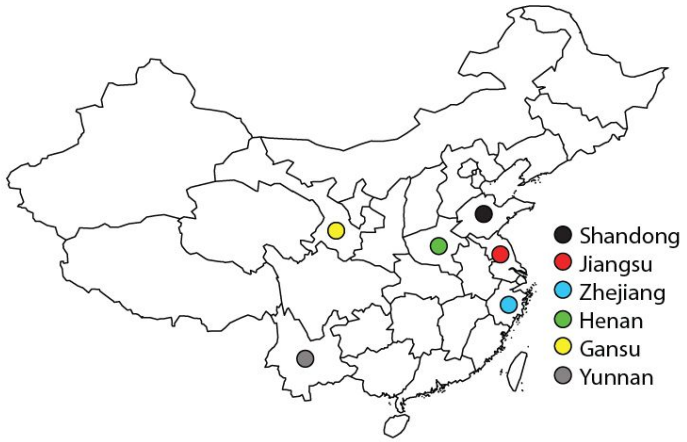
$$\#\,sero(+)_{age} \sim \text{binomial}\left(N_{\text{tested, age}}, P(sero(+) \mid age) \right)$$

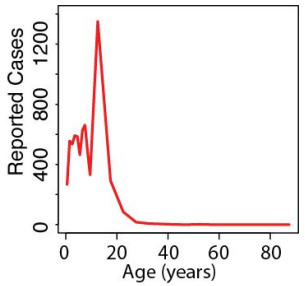
- Case Data
  - Expected age distribution of cases is a function of:
    - Remaining susceptible by age a
    - Force of infection at age a, conditional on remaining susceptible
  - Grenfell and Anderson (1985)
    - Multinomial likelihood

Age Distribution in Jiangsu

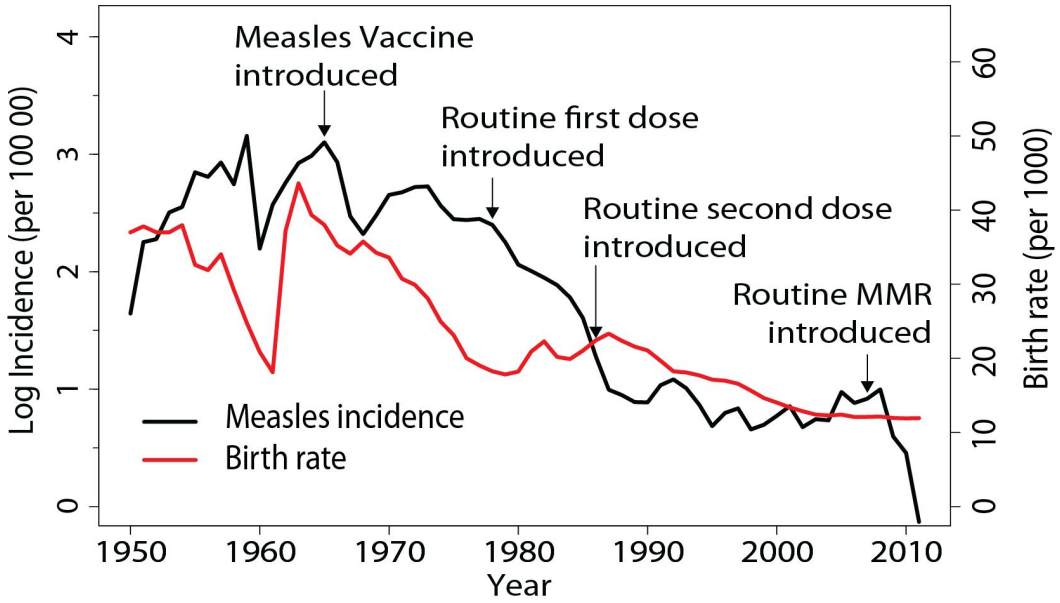


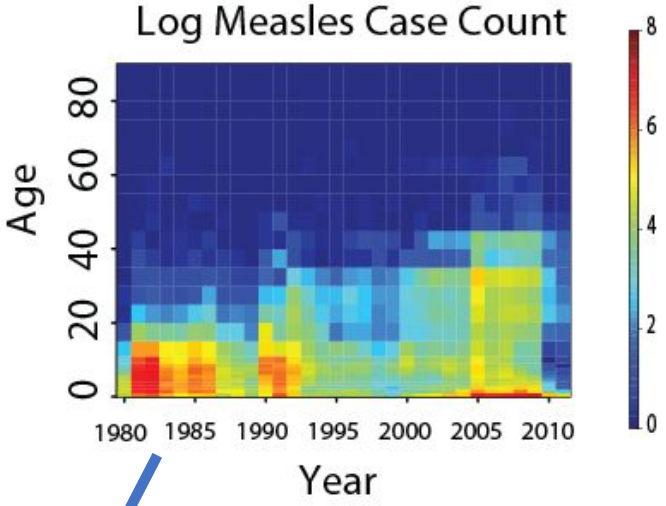


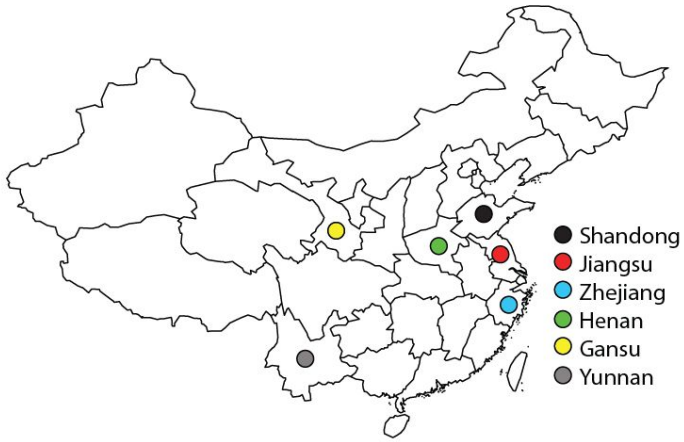


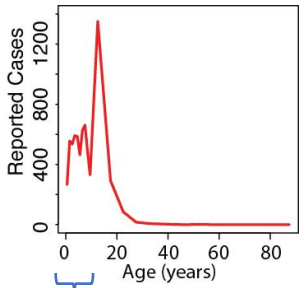


Age Distribution in Jiangsu



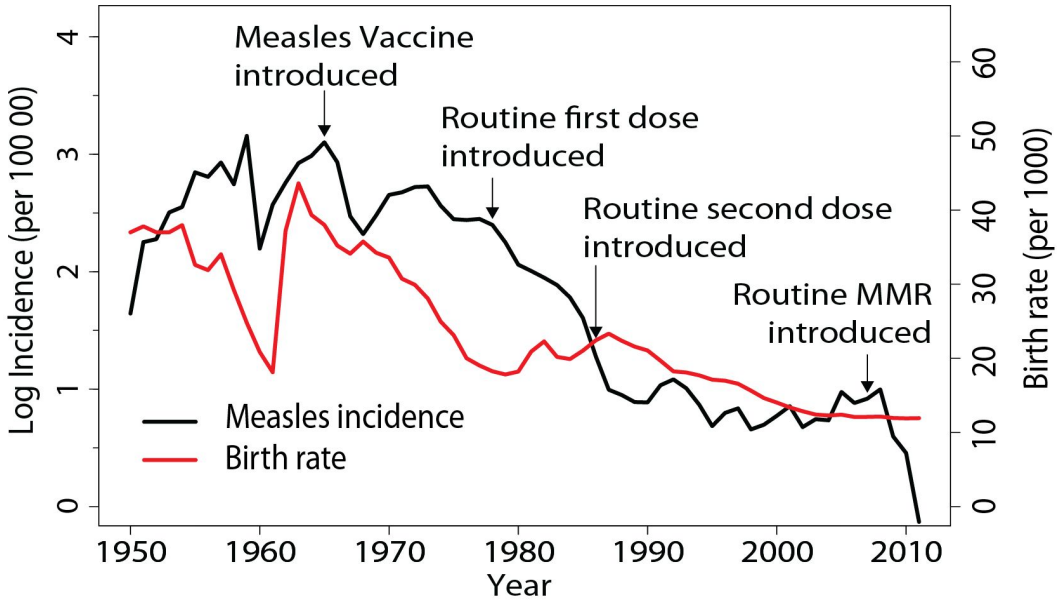


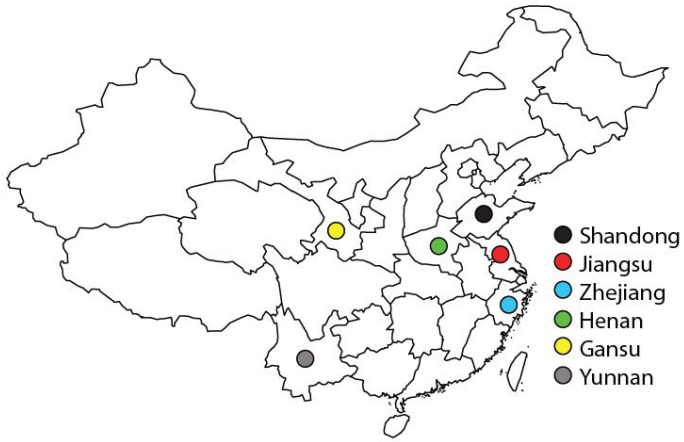


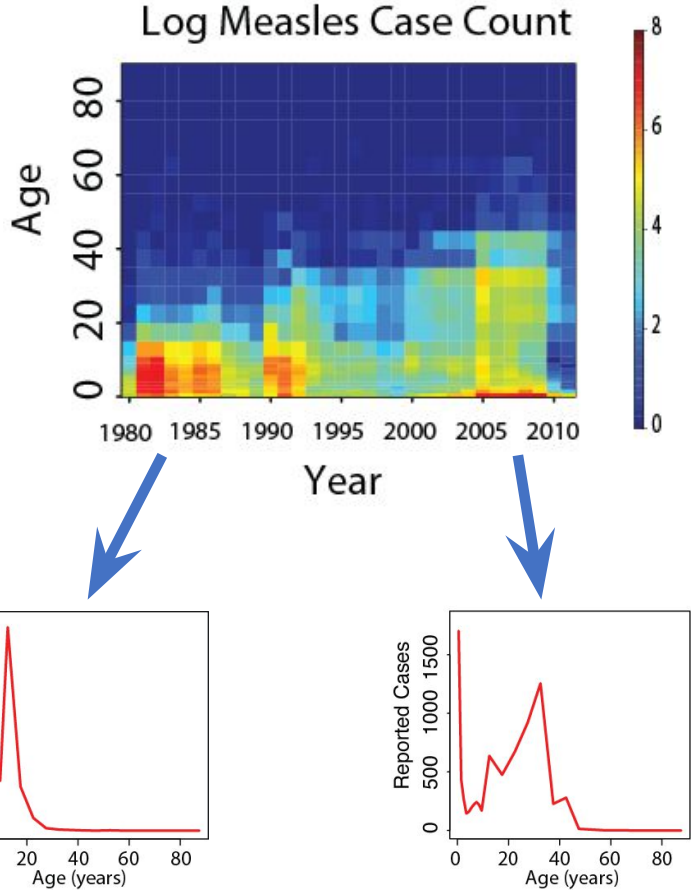


1y up to age 10y
5y afterwards

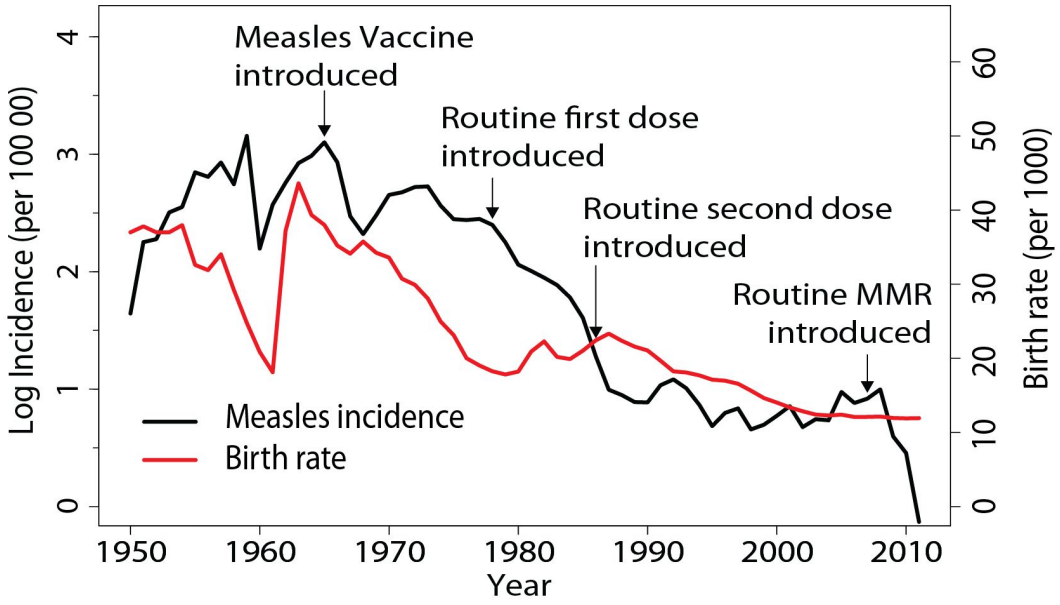
Age Distribution in Jiangsu

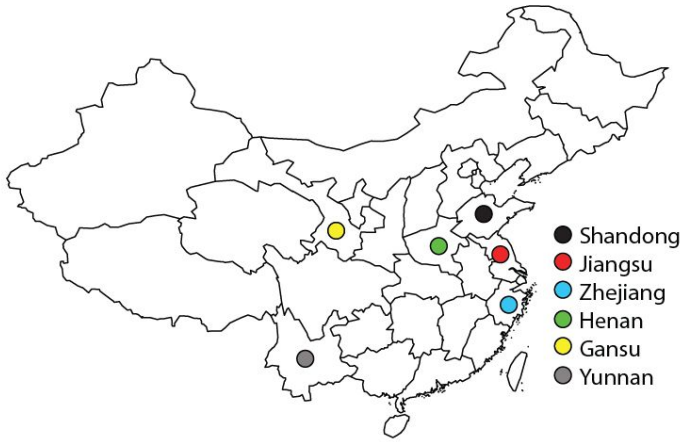


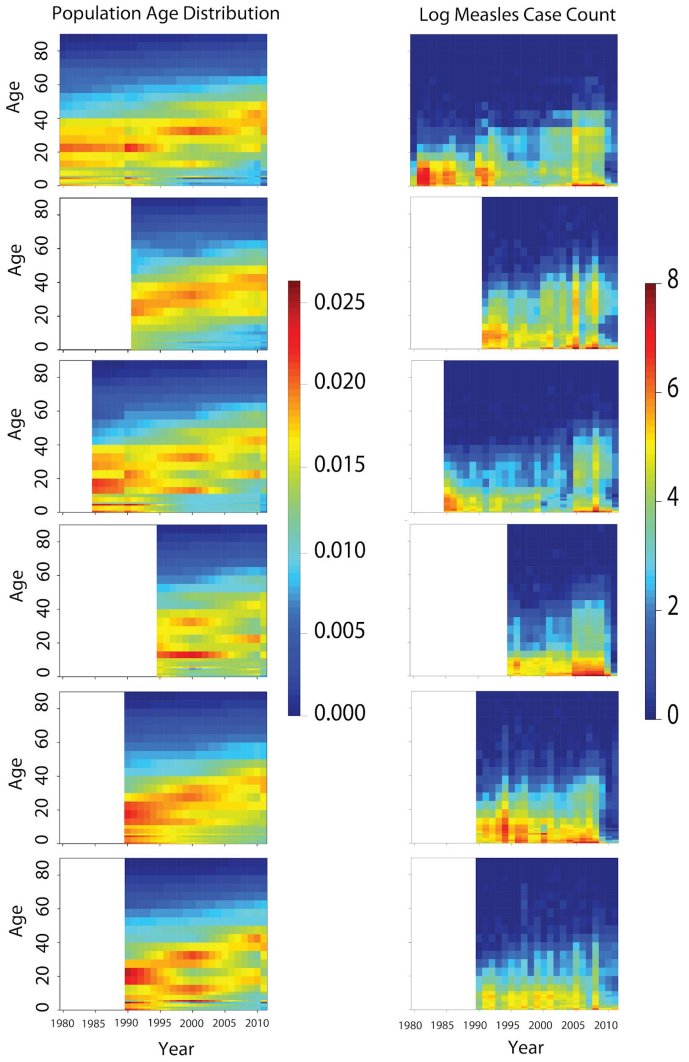




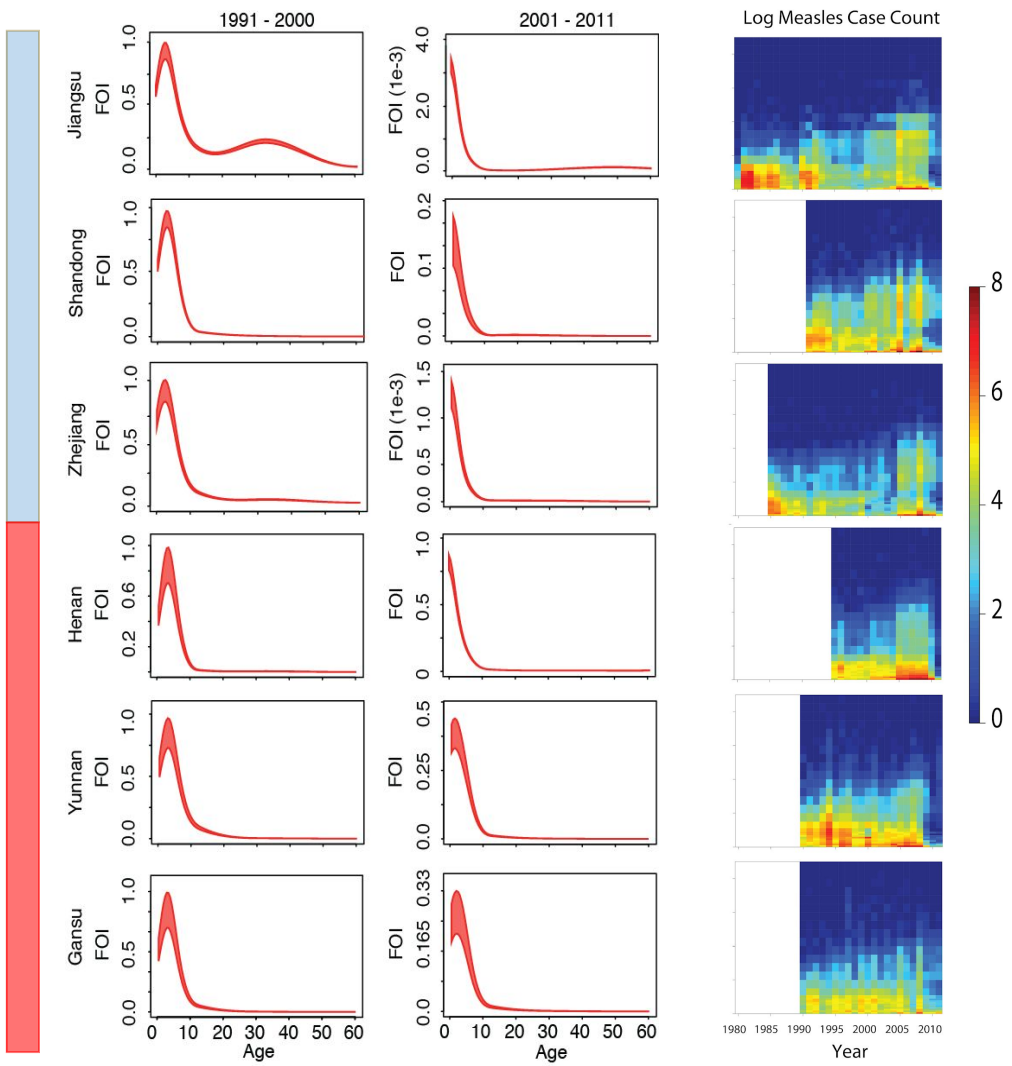
Pattern Consistent Across China







Provincial Variation



Reduction in R_E from 90's to 00's

97%

90%

95%

24%

68%

73%

Farrington, Kanaan, Gay 2001

Transmission, Severity, and Control

- 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

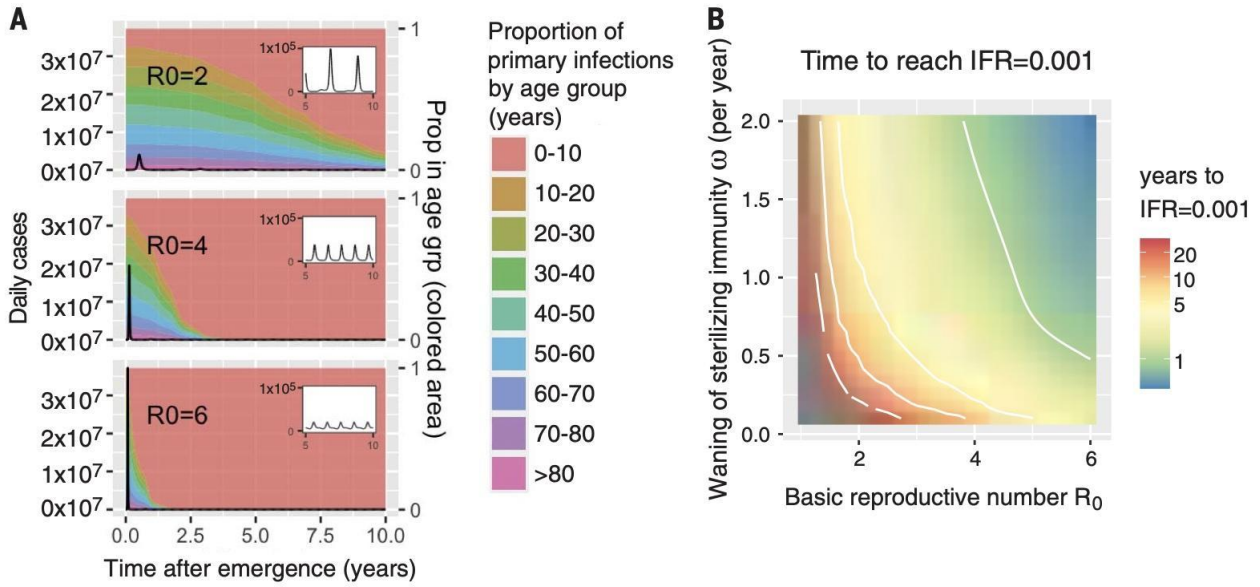


Fig. 2. The time scale of the transition from epidemic to endemic dynamics for emerging coronaviruses depends on R_0 and the rate of immune waning. Transition from epidemic to endemic dynamics for emerging HCoVs, simulated from an extension of the model presented in fig. S1 that includes age structure. 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 4-8 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

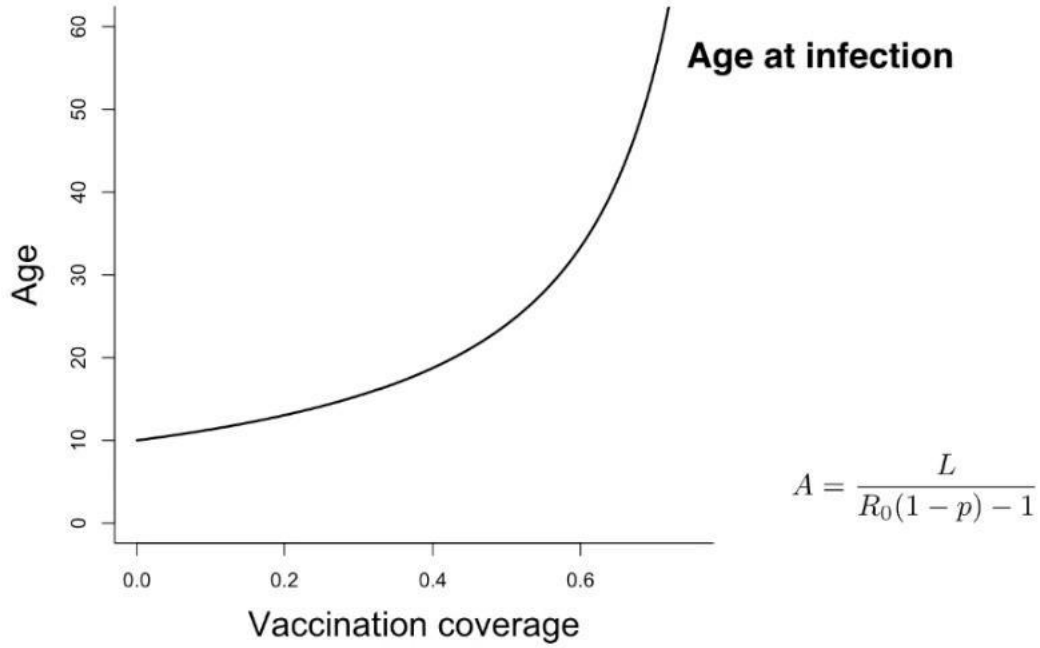
Introduction of Rubella Containing Vaccine

Strategies for implementation

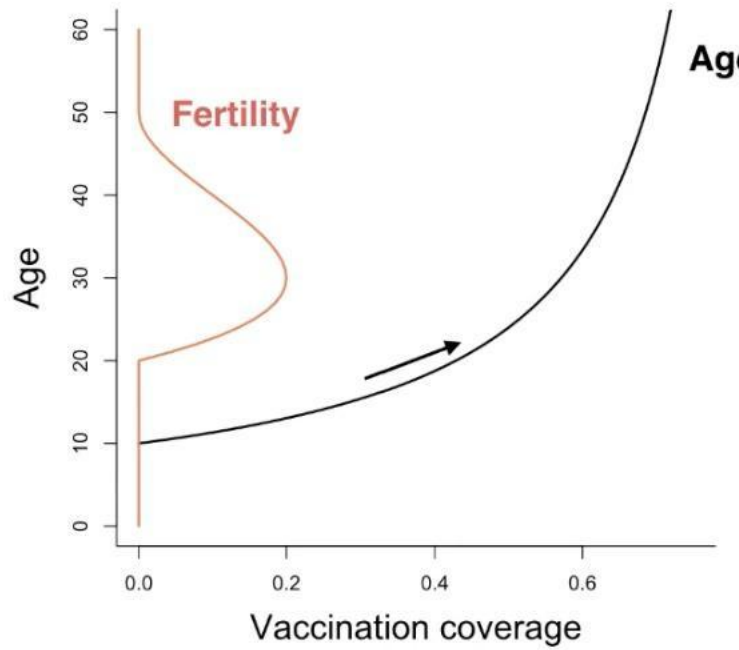
Introduction of RCV into childhood immunization programmes implies a long-term commitment to achieving and maintaining sufficient immunization coverage to ensure sustained population immunity and thereby avoid a paradoxical epidemiological effect. Low coverage of rubella vaccination of infants and young children can reduce but not interrupt the circulation of rubella virus, ultimately resulting in increased susceptibility of women of reproductive age (WRA). This may increase the risk of CRS above that which existed before introduction of the vaccine (a paradoxical effect; see section on Epidemiological impact of rubella vaccination). If vaccination coverage is sufficiently high (generally estimated to be ≥80% in each birth cohort), rubella transmission will be markedly reduced or interrupted, thereby reducing the risk of exposure of pregnant women. However, as it is recommended that RCV be provided in combination with measles vaccine, and measles elimination requires ≥95% coverage, the goal for rubella vaccination coverage should also be ≥95%.

Countries that are planning to introduce RCVs should have ≥80% coverage with the first dose of measles vaccine during routine immunization and/or campaigns to demonstrate their ability to achieve these levels of RCV coverage and thereby avoid the previously mentioned paradoxical effect. RCV coverage that remains <80% over the long term is expected to shift infection to older ages, when the risk of CRS is highest. The recommended vaccination strategy is to begin with an MR vaccination campaign targeting both sexes and a wide age range (e.g. 9 months–15 years), based on the

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

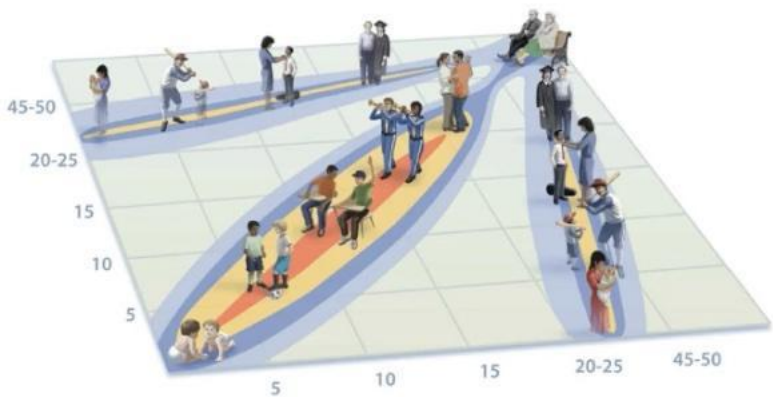
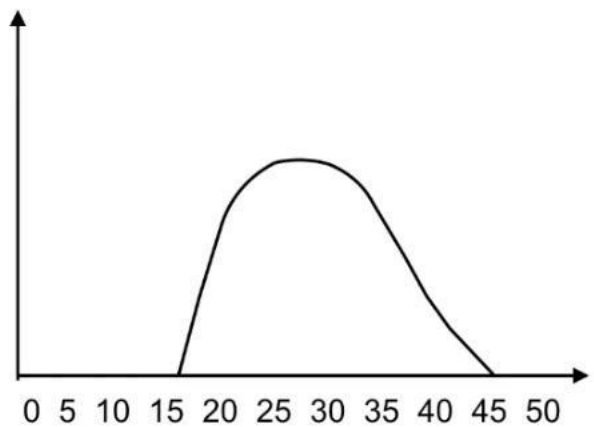
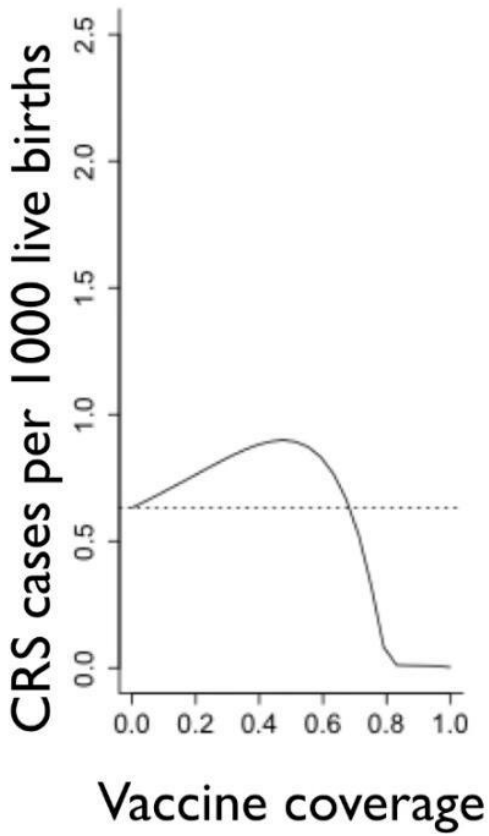


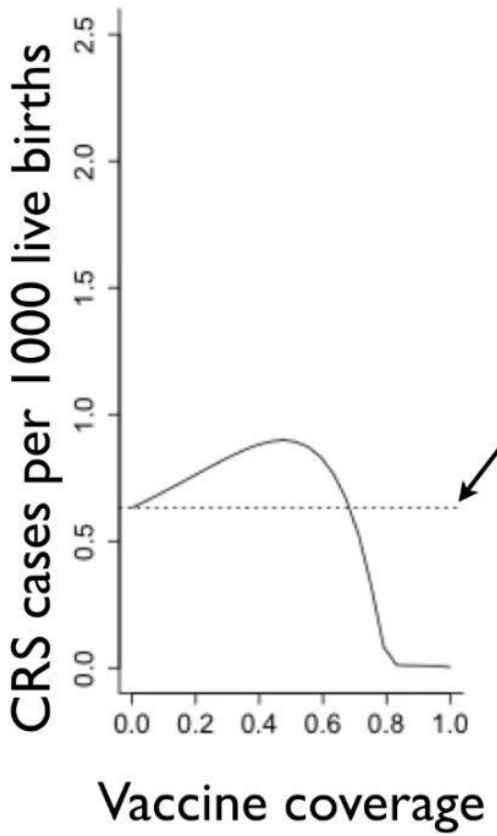
Image: Rohani & King

Age profile of fertility



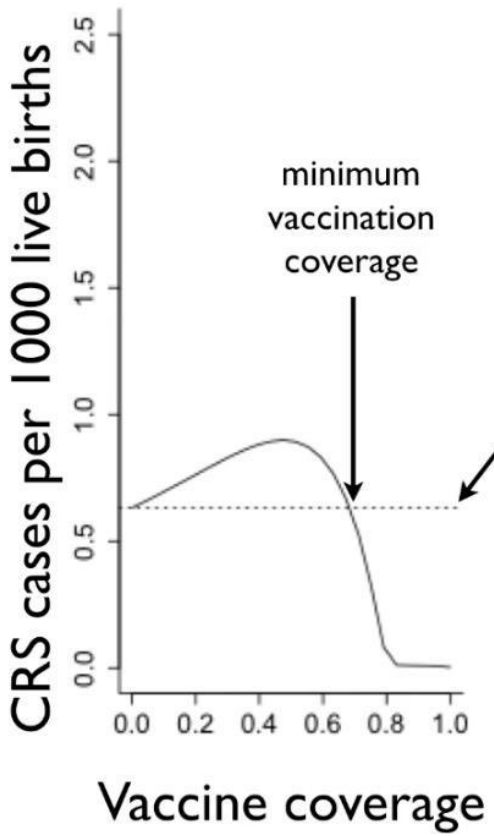


CRS: Congenital **R**ubella **S**yndrome (brain damage, deafness, blindness in children born to women who were infected during the first trimester)

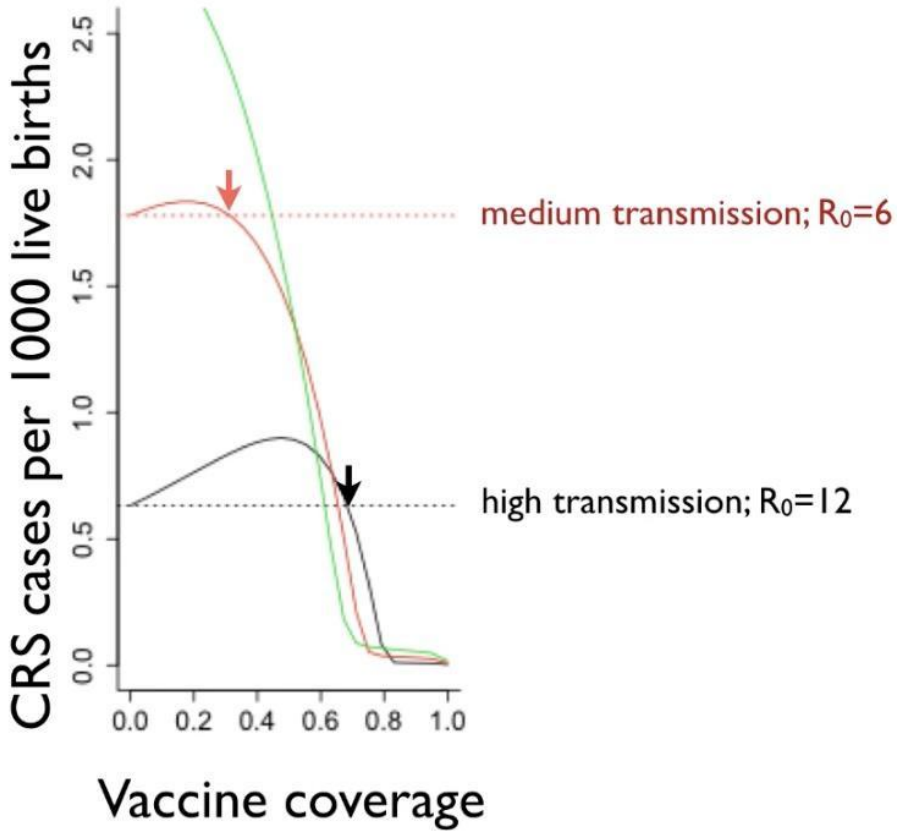


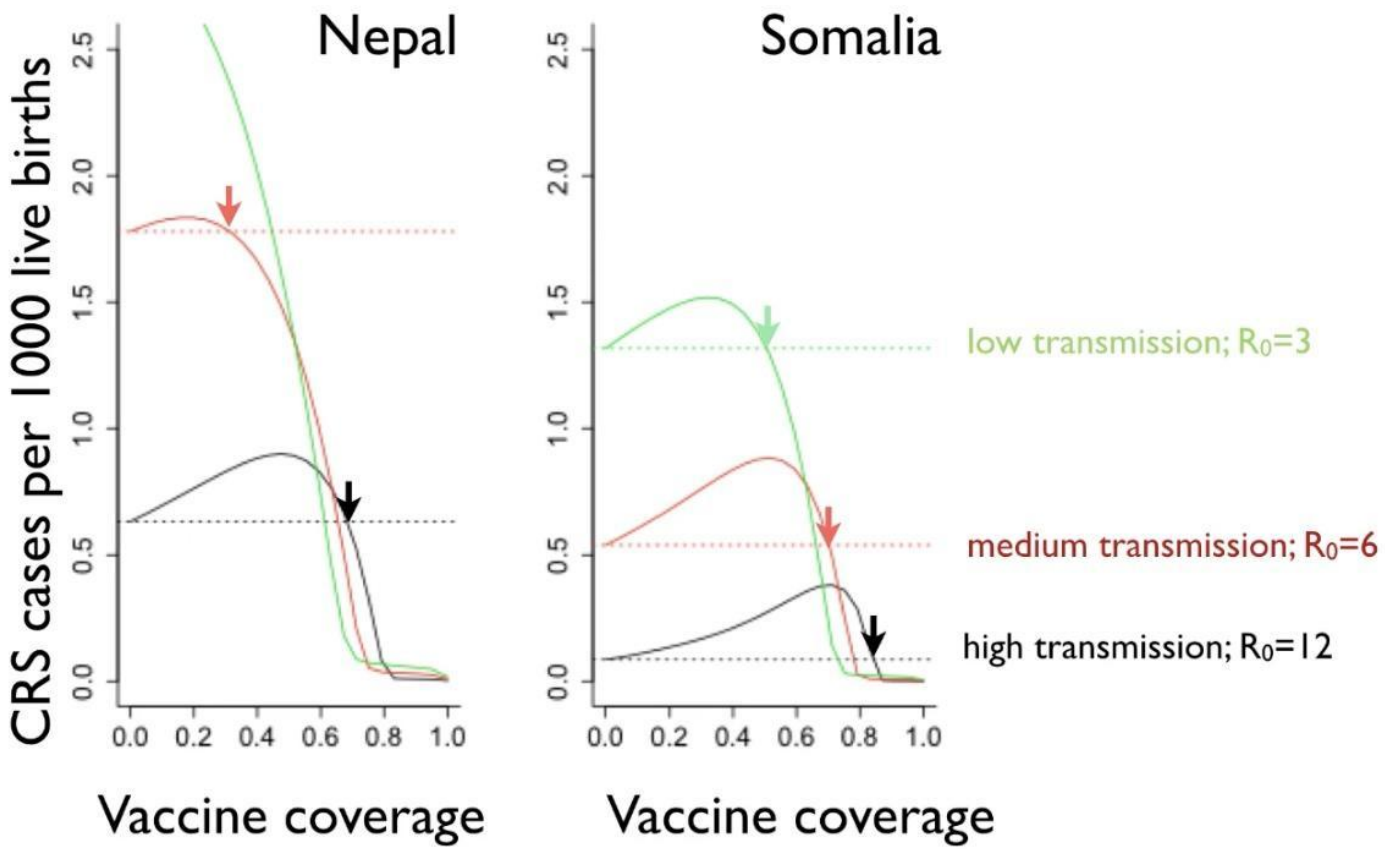
CRS: Congenital **R**ubella **S**yndrome (brain damage, deafness, blindness in children born to women who were infected during the first trimester)

CRS burden in the absence of vaccination



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


CRS cases per 1000 live births
0.0
0.5
1.0
1.5
2.0
2.5
0.0
0.2
0.4
0.6
0.8
1.0
Vaccine coverage
medium transmission; R0=6
high transmission; R0=12


Nepal
Somalia
CRS cases per 1000 live births
0.0
0.5
1.0
1.5
2.0
2.5
0.0
0.2
0.4
0.6
0.8
1.0
Vaccine coverage
Vaccine coverage
low transmission; R0=3
medium transmission; R0=6
high transmission; R0=12

80% Rule for Rubella Vaccine Introduction

- A single policy recommendation is convenient, but dynamics suggest that the optimal strategy for introduction is highly dependent on
  - Local vaccination coverage
  - Local transmission rate
  - Local age-specific maternity