# The honeymoon is over: pertussis resurgence, natural boosting, & the legacy of imperfect vaccination

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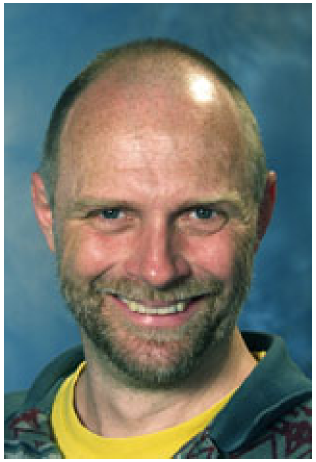

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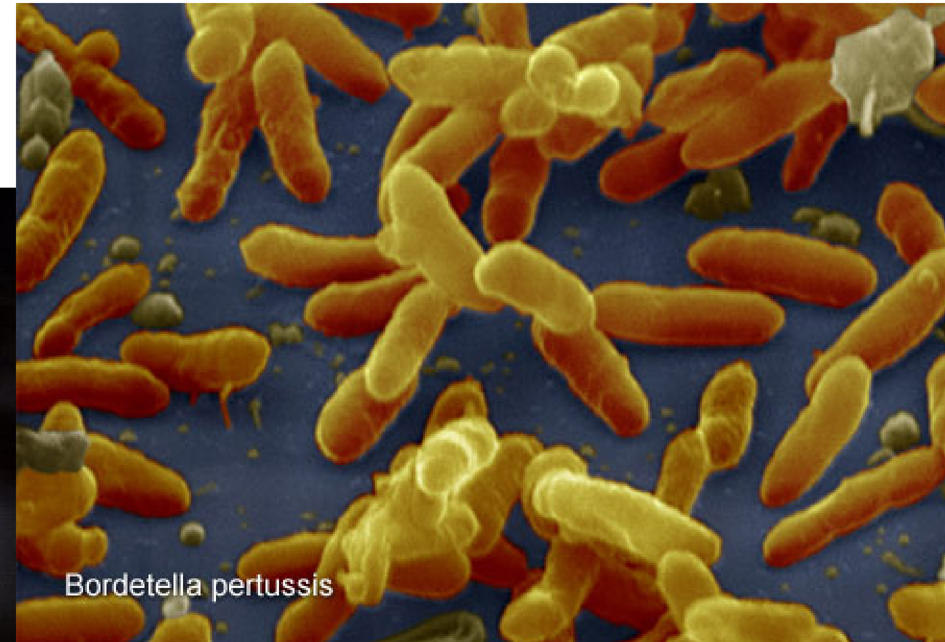
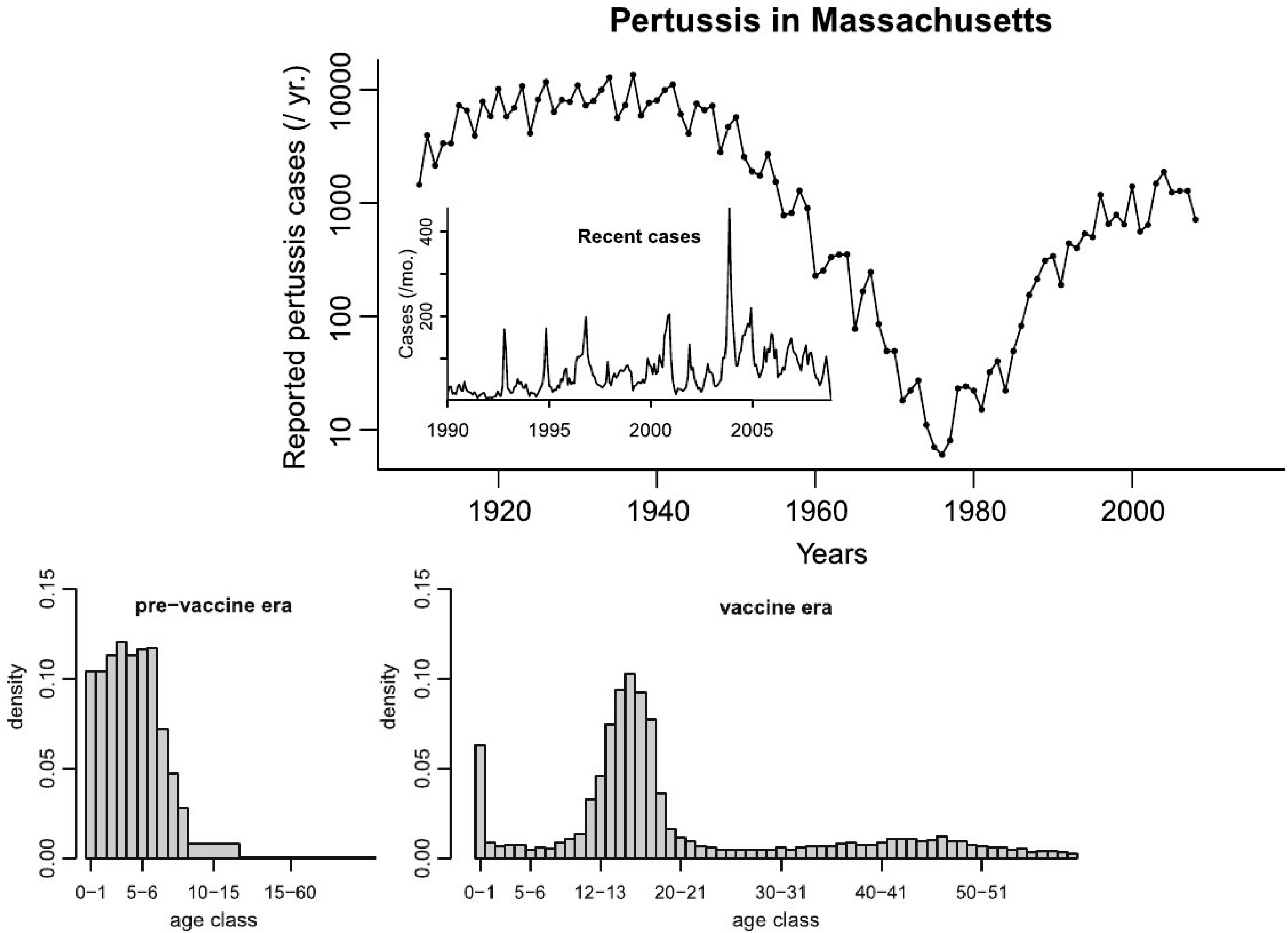
Ottar Bjørnstad

# Pertussis

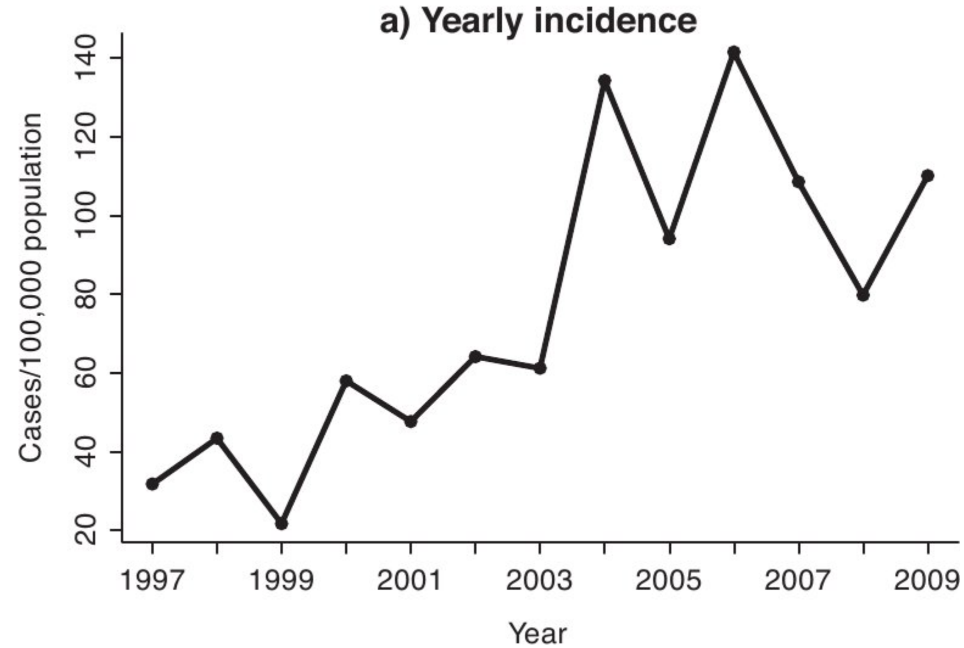


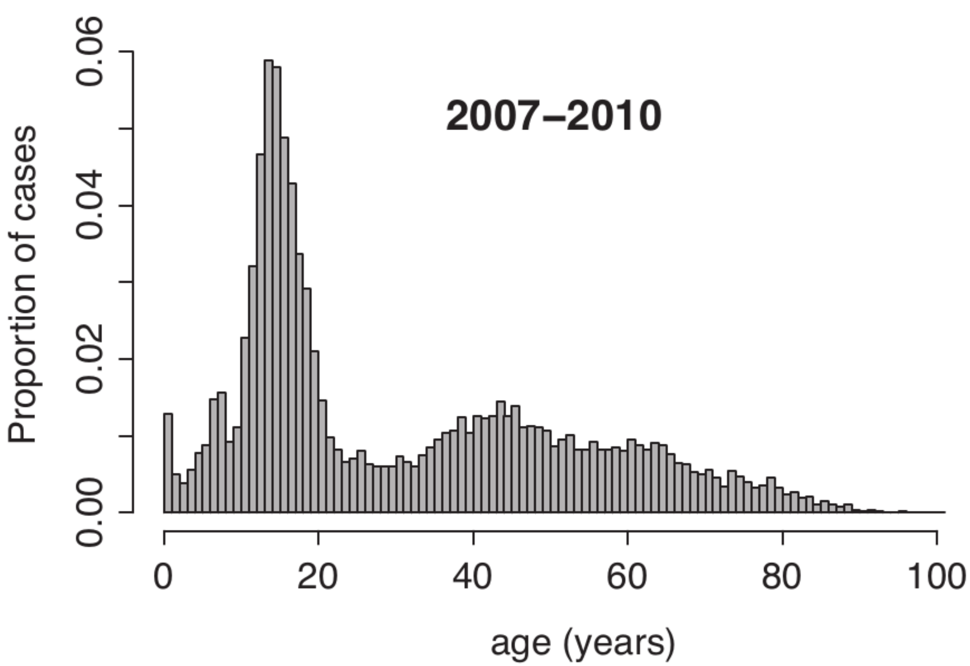

- aetiological agents: *Bordetella pertussis, B. parapertussis,* other *Bordetella* spp.
- worldwide, a leading cause of vaccine-preventable infant mortality
- resurgent in many developed countries despite (or perhaps due to) mass vaccination

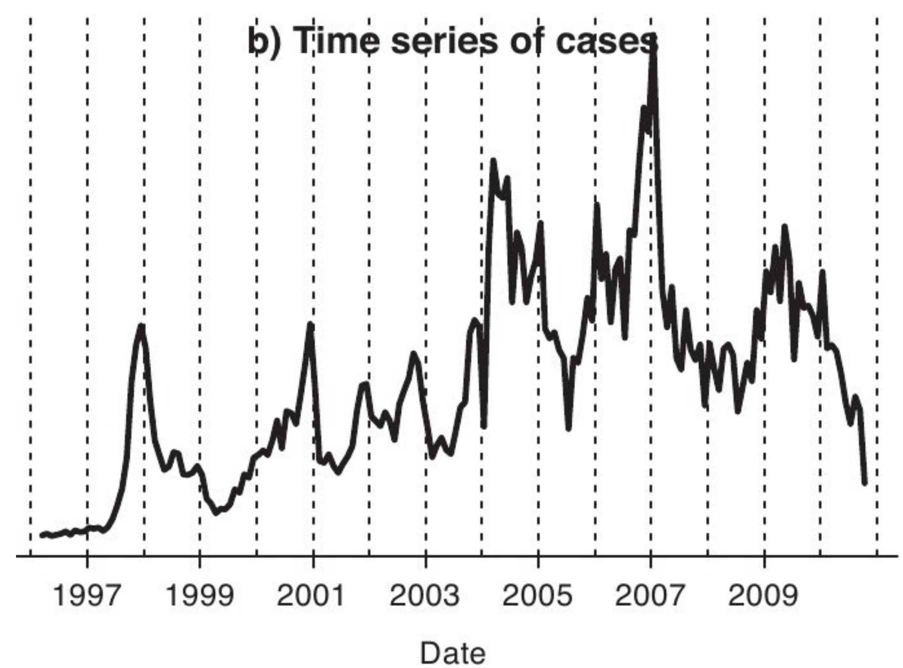


Pertussis in Massachusetts
Reported pertussis cases (/ yr.)
10000
1000
100
10
1920
1940
1960
1980
2000
Years
Recent cases
Cases (/mo.)
400
200
1990
1995
2000
2005
pre−vaccine era
density
0.15
0.10
0.05
0.00
0−1
5−6
10−15
15−60
age class
vaccine era
density
0.15
0.10
0.05
0.00
0−1
5−6
12−13
20−21
30−31
40−41
50−51
age class

# Pertussis in Norway



# Explaining the resurgence

- improved awareness and surveillance
- pathogen evolution
- vaccine failure
- loss of natural immune boosting

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**Key unknowns:**

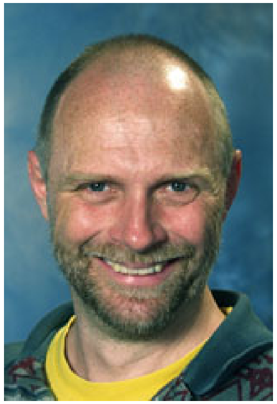
- how long does natural immunity last?
- how do infection- and vaccine-derived immunity differ?

# Overview

- the case for immune boosting: pre-vaccine data from Copenhagen
- evidence from Thailand's experiences with mass vaccination
- back to basics, focusing on the recent British resurgence

# The view from Denmark


Jennie Lavine

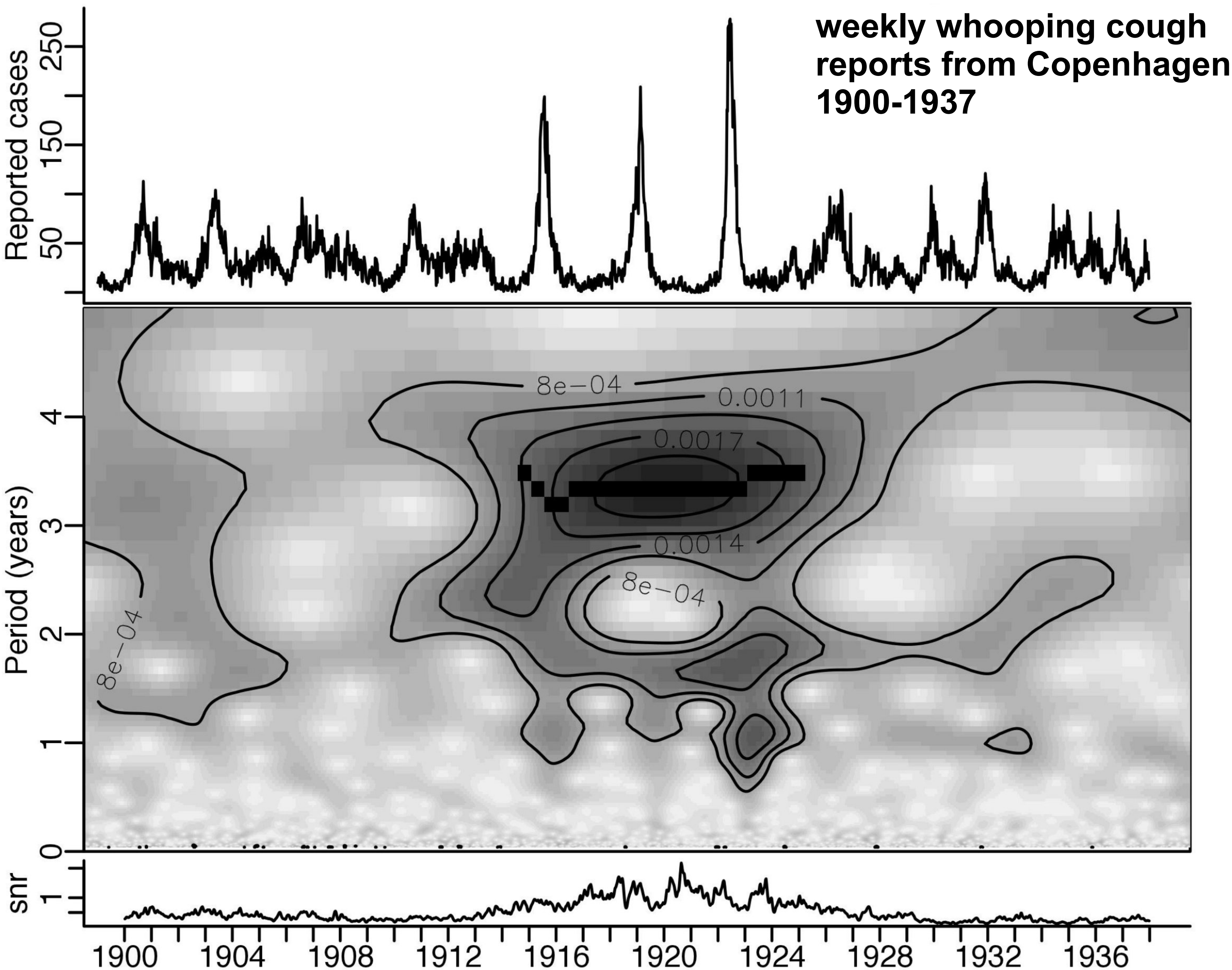

Viggo Andreasen

A unique set of high-quality data:

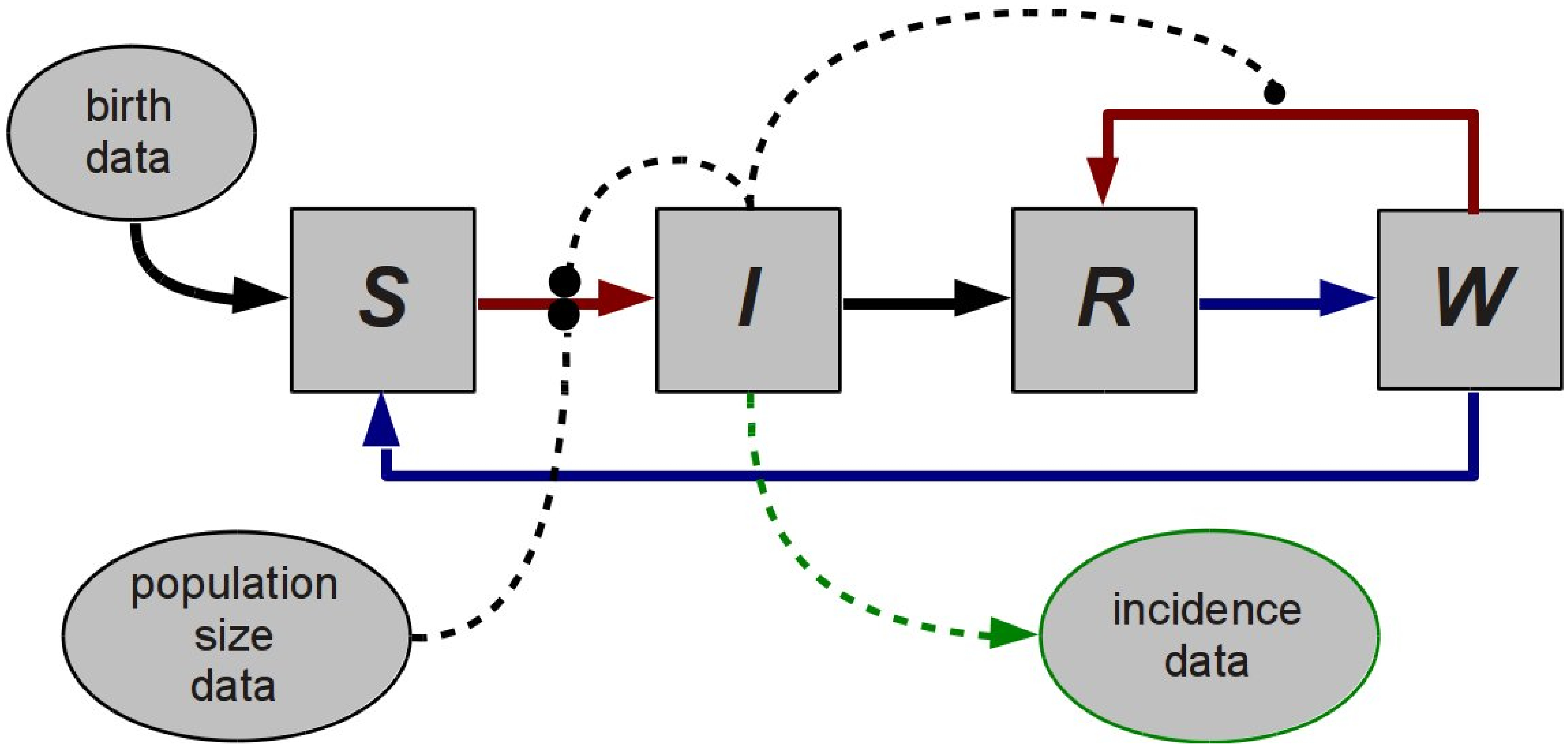
- weekly case reports
- weekly birth records
- 5 yr census intervals
- 1900–1937


Ottar Bjørnstad

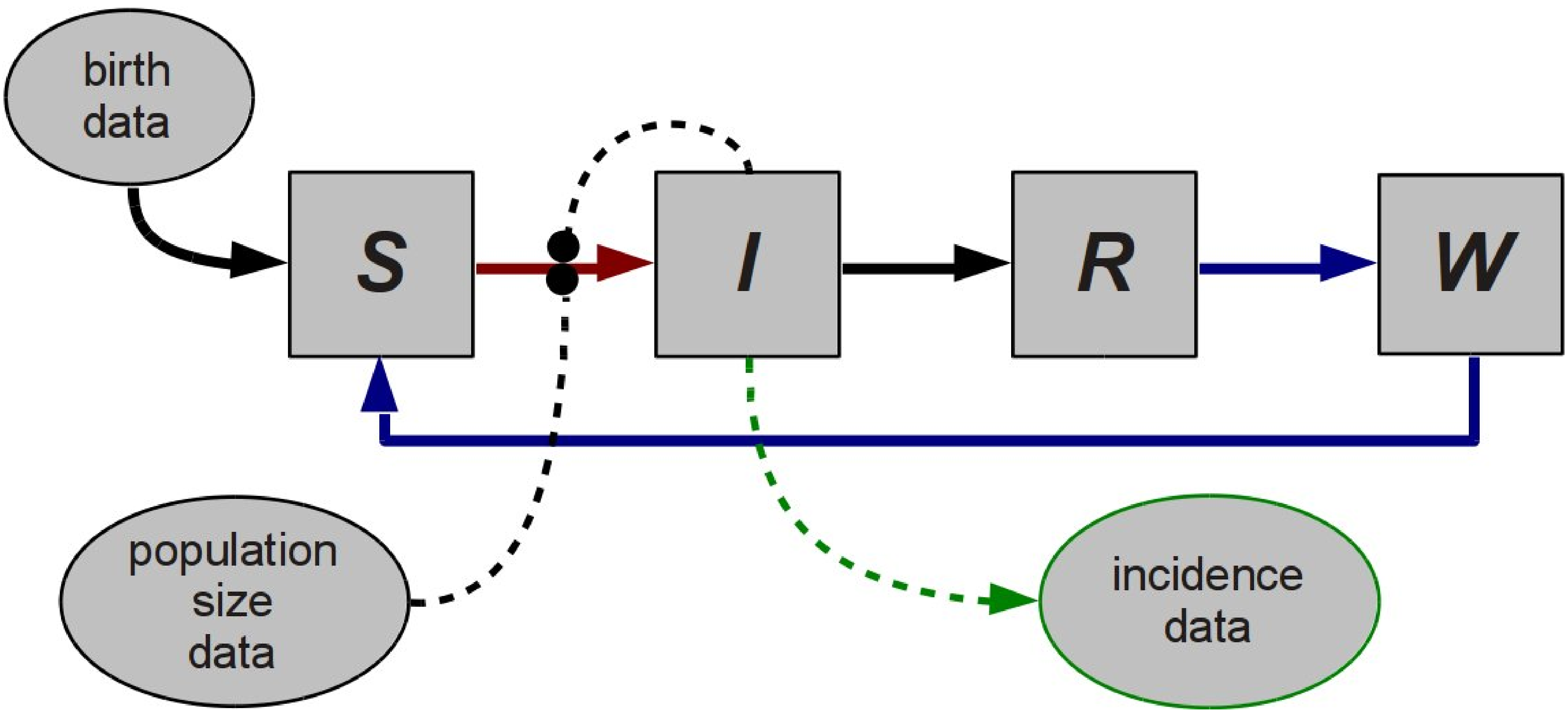
**Can we establish the immunological consequences of repeat natural infections?**


weekly whooping cough
reports from Copenhagen
1900-1937
Reported cases
50
150
250
Period (years)
0
1
2
3
4
8e−04
0.0011
0.0017
0.0014
snr
1
1900
1904
1908
1912
1916
1920
1924
1928
1932
1936

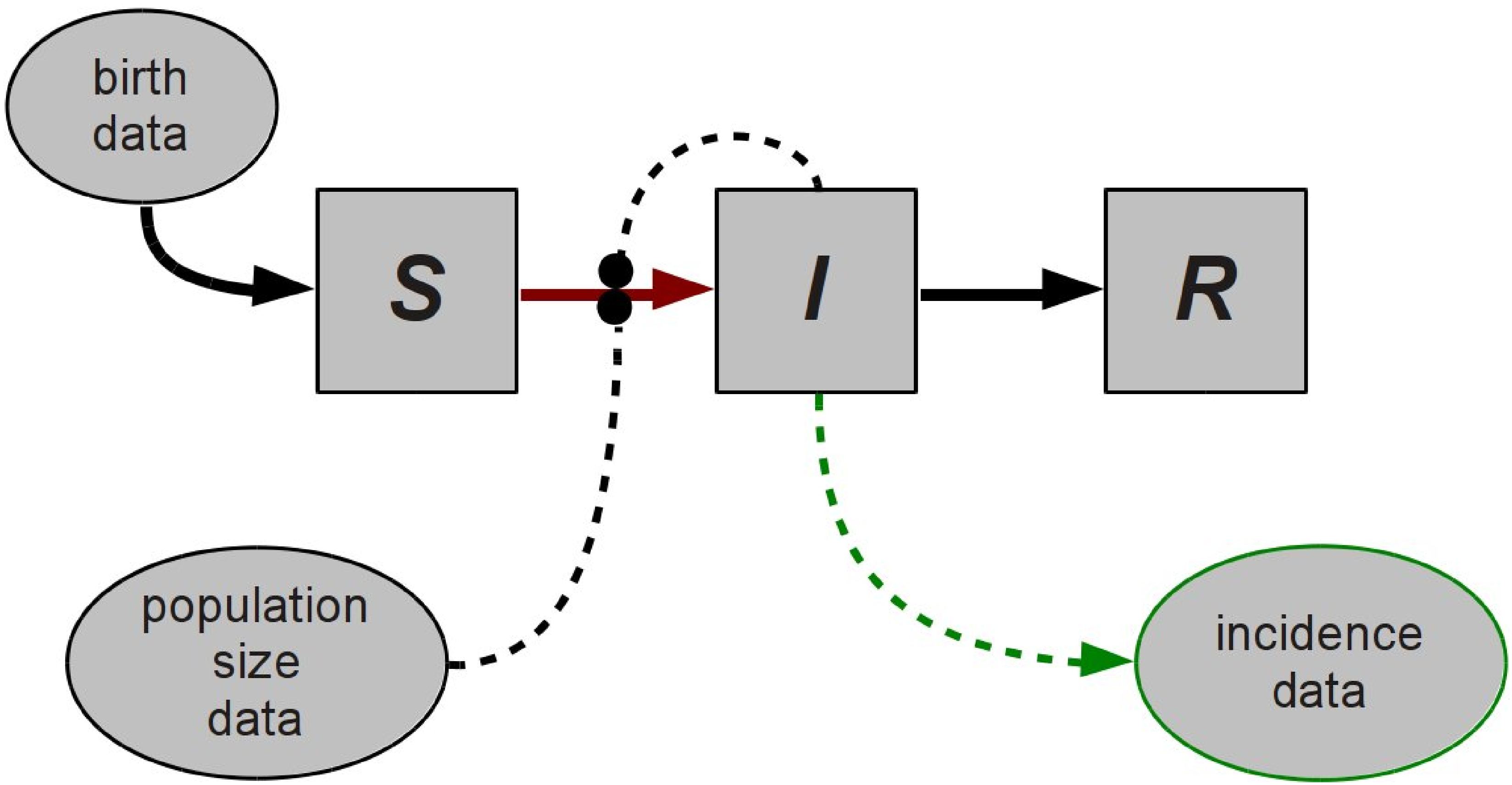
## SIRWS model
## (with waning and boosting of immunity)



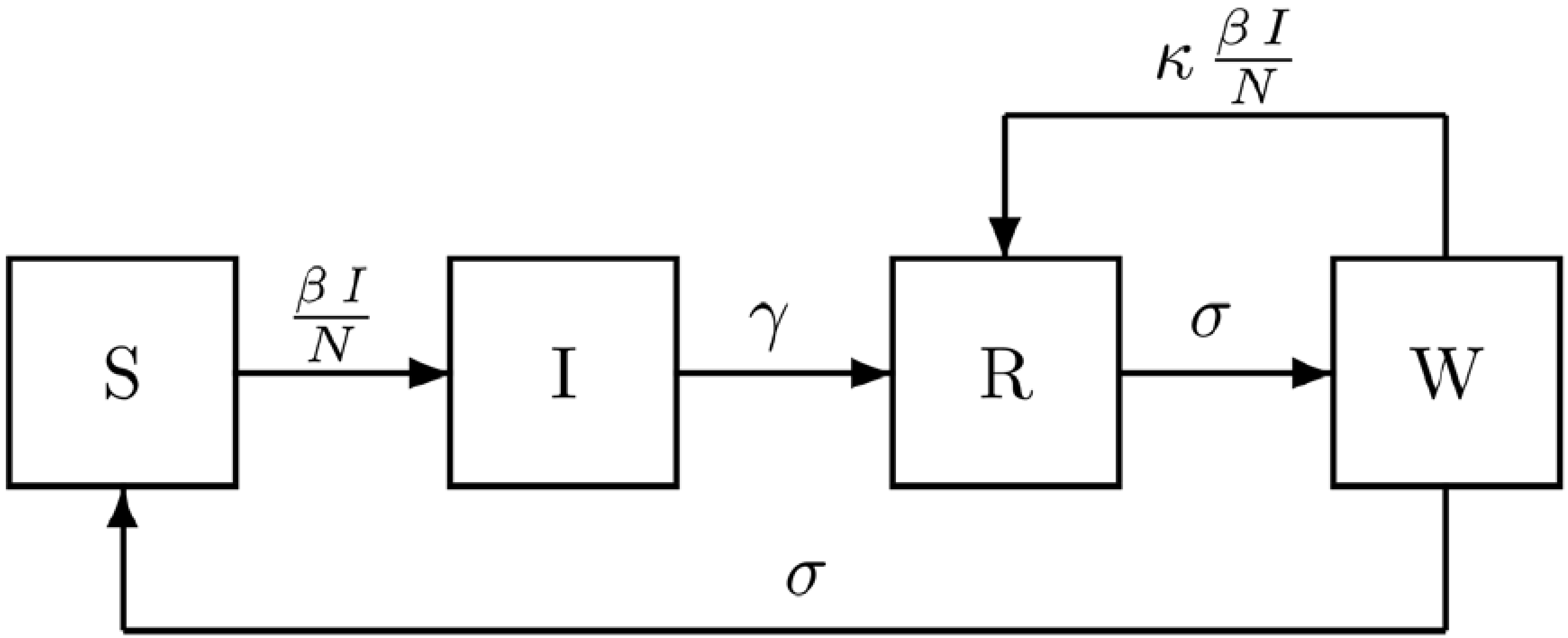
## SIRS model
## (passively waning immunity)



## SIR model (permanent immunity)



# SIRWS model
# (with waning and boosting of immunity)



# SIRWS model
# (with waning and boosting of immunity)

$$\frac{S_{t+1}}{m} = S_t + \mathrm{b}_{t+1} + \frac{\sigma}{\kappa\lambda_t + \sigma}(1 - e^{-(\sigma+\kappa\lambda)})W_t - \mathrm{d}_{t+1}$$

$$\frac{I_{t+1}}{m} = I_t + \mathrm{d}_{t+1} - (1 - e^{-\gamma})I_t$$

$$\frac{R_{t+1}}{m} = R_t + (1 - e^{-\gamma})I_t + \frac{\kappa\lambda_t}{\kappa\lambda_t + \sigma}(1 - e^{-(\sigma+\kappa\lambda)})W_t - (1 - e^{-\sigma})R_t$$

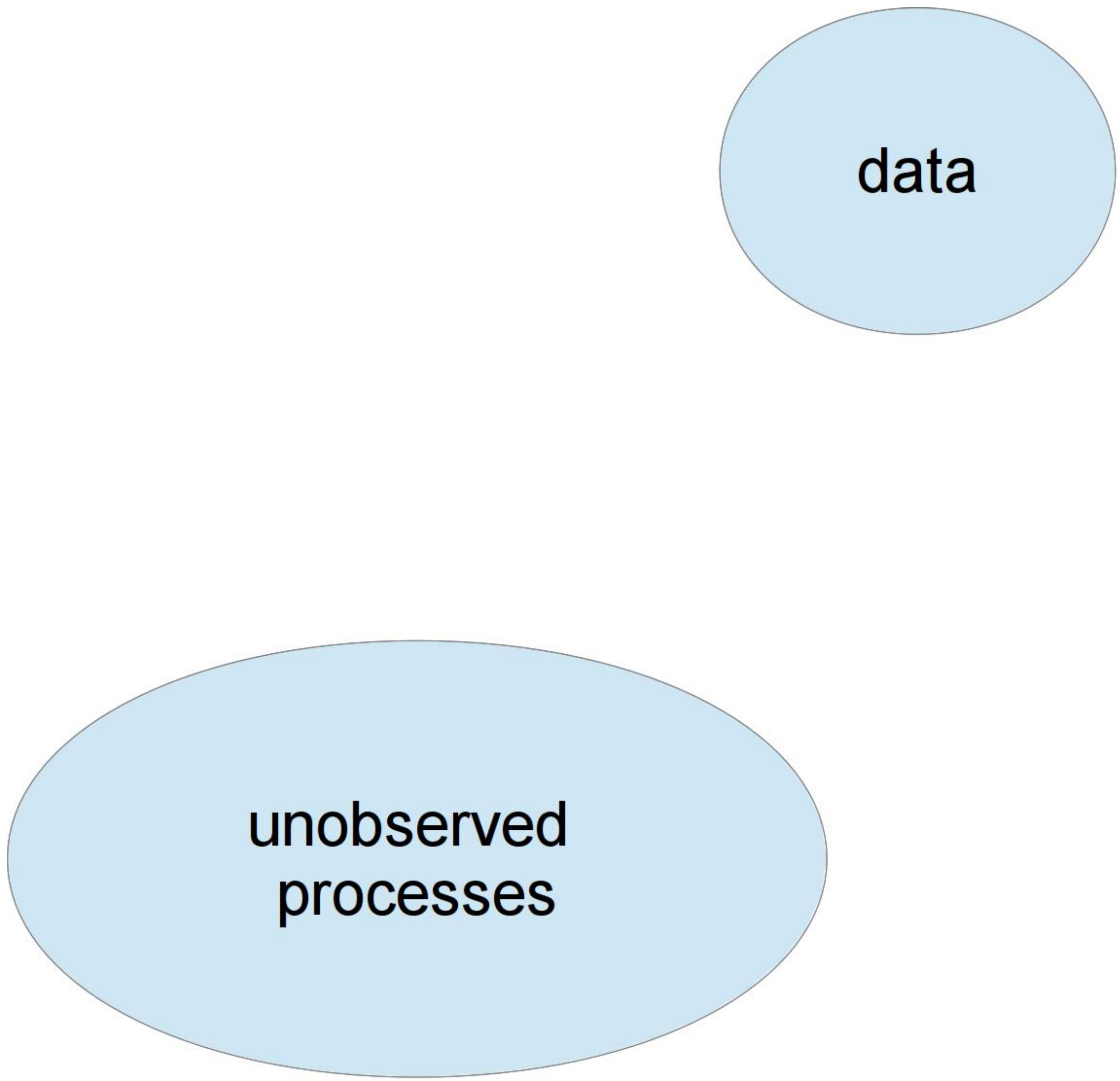
$$\frac{W_{t+1}}{m} = W_t + (1 - e^{-\sigma})R_t - (1 - e^{-(\sigma+\kappa\lambda_t)})W_t.$$

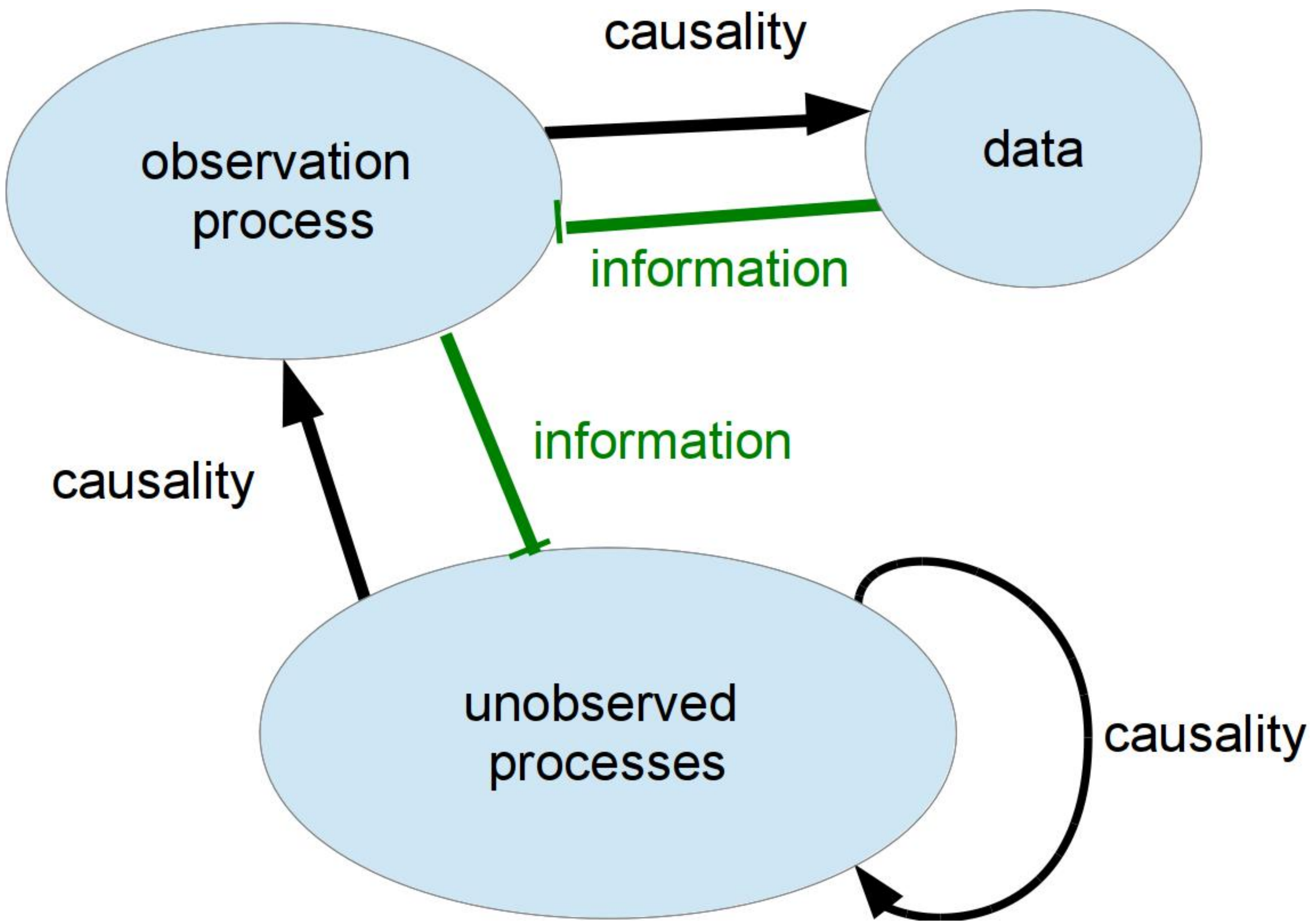
$$\mathrm{b}_{t+1} \sim \mathrm{Poisson}(b(t))$$

$$\mathrm{d}_{t+1} \sim \mathrm{binomial}(S_t, 1 - e^{-\lambda_t})$$

$$\lambda_t = \frac{\beta_t I_t Q_t}{N_t}.$$

$$Q_t \sim \mathrm{Gamma}\left(\frac{1}{\beta_{sd}^2}, \beta_{sd}^2\right).$$


data
unobserved processes




nonlinear, non-Gaussian state-space models -or-
partially-observed Markov processes

# Model-based inference

- Realism/tractability trade-off
- “Plug-and-play” methods
- Feature-matching methods
  - select summary statistics
  - match model and data summary statistics
- Full-information methods
  - compute likelihood function
  - maximum likelihood or Bayesian approaches

# model comparisons

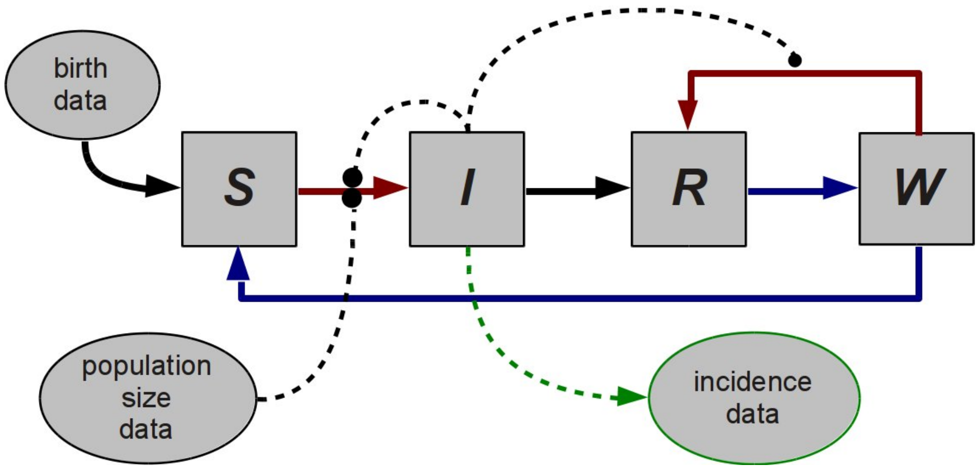
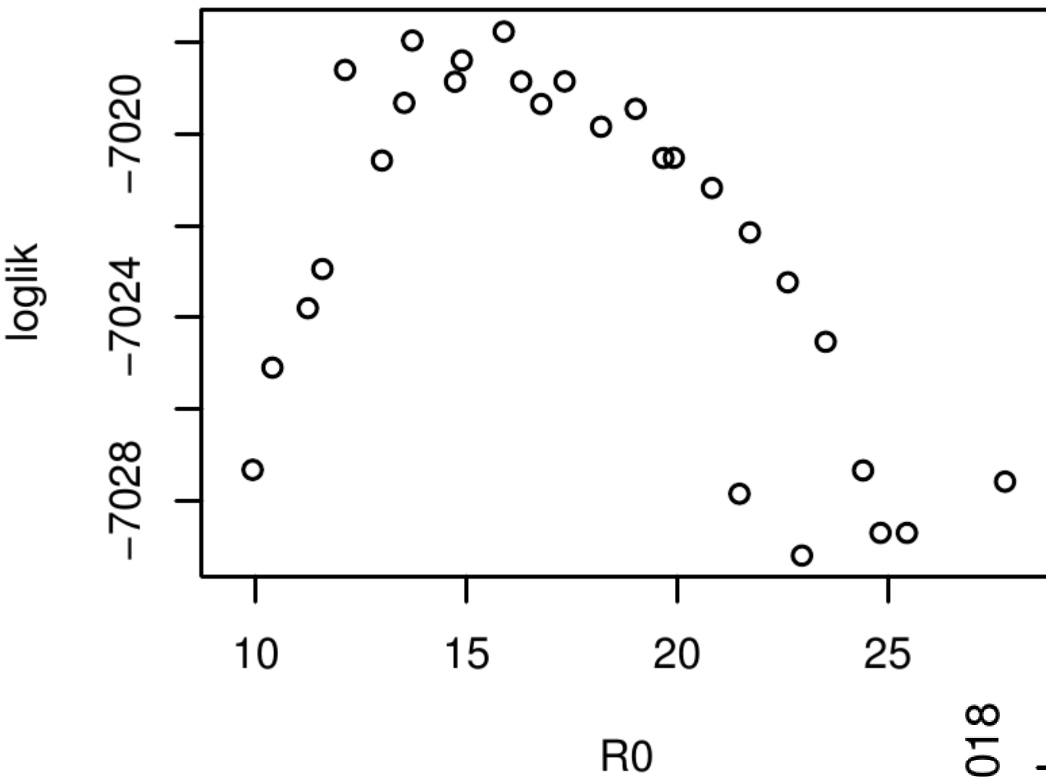



Table 1: Maximum likelihood parameter estimates for the three models and model comparison statistics (AICS weights, difference in AIC values from the SIRWS model, and p-values from likelihood ratio tests.

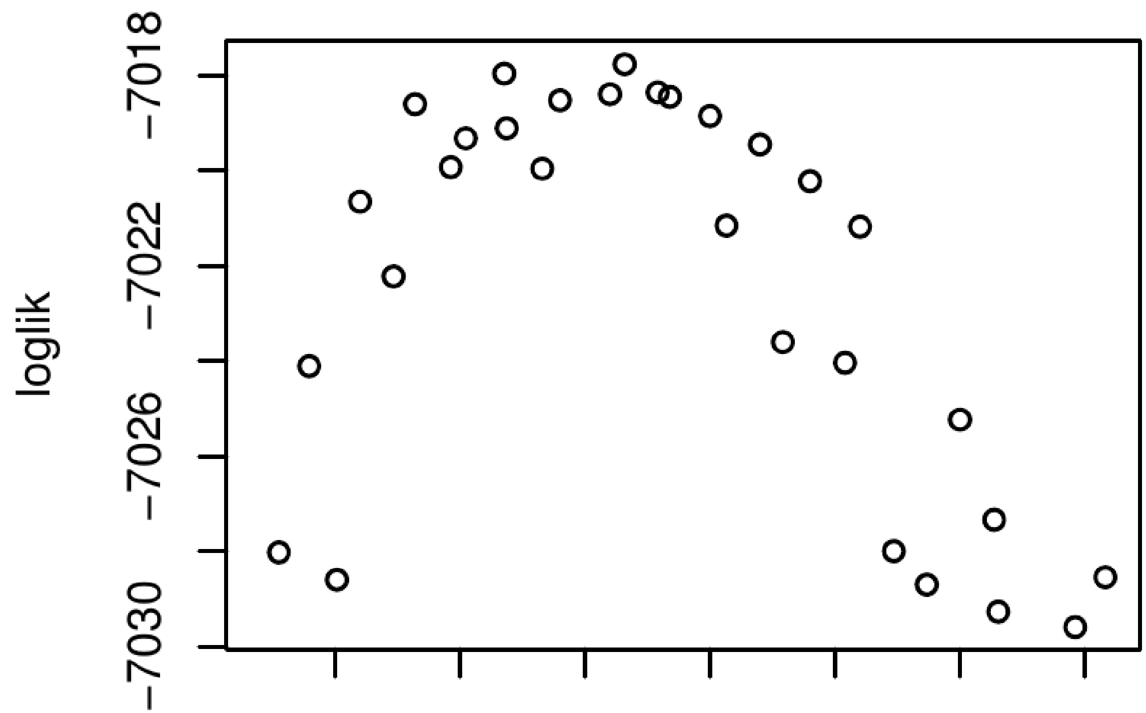
| | $R_0$ | Infectious period, $1/\gamma$ (wks) | Immune period, $2/\sigma/52$ (yrs) | Boosting coefficient, $\kappa$ | Observation probability | Weights ($\Delta$AIC) | p-val from LRT |
|---|---|---|---|---|---|---|---|
| Full SIRWS | 16(12, 19) | 3.7(2.8, 4.2) | 34(17, 66) | 6.6(0.66, 69) | 0.15(.15, .16) | 0.95 (0) | - |
| Waning SIRS | 18(16,19) | 3.6(3.1,3.8) | 192(178,192) | – | 0.15(.15, .16) | 0.05 (6) | 0.012 |
| Life-long SIR | 17(16,17) | 3.4(3.0,3.4) | – | – | 0.17 | 0.00 (30) | $<$0.0001 |

37% lose immunity before death

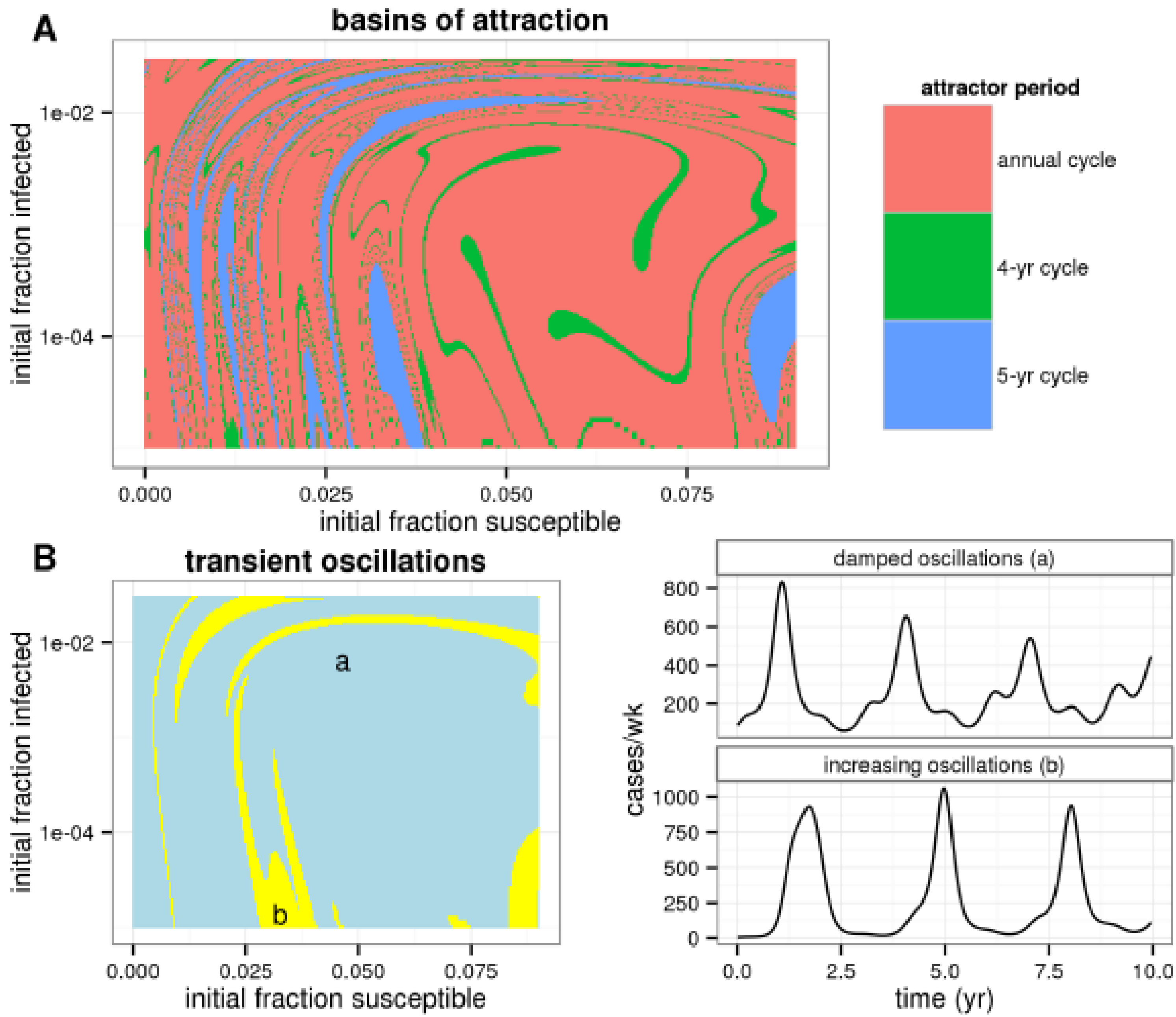



**$R_0$ profile likelihood**

**infectious period profile likelihood**

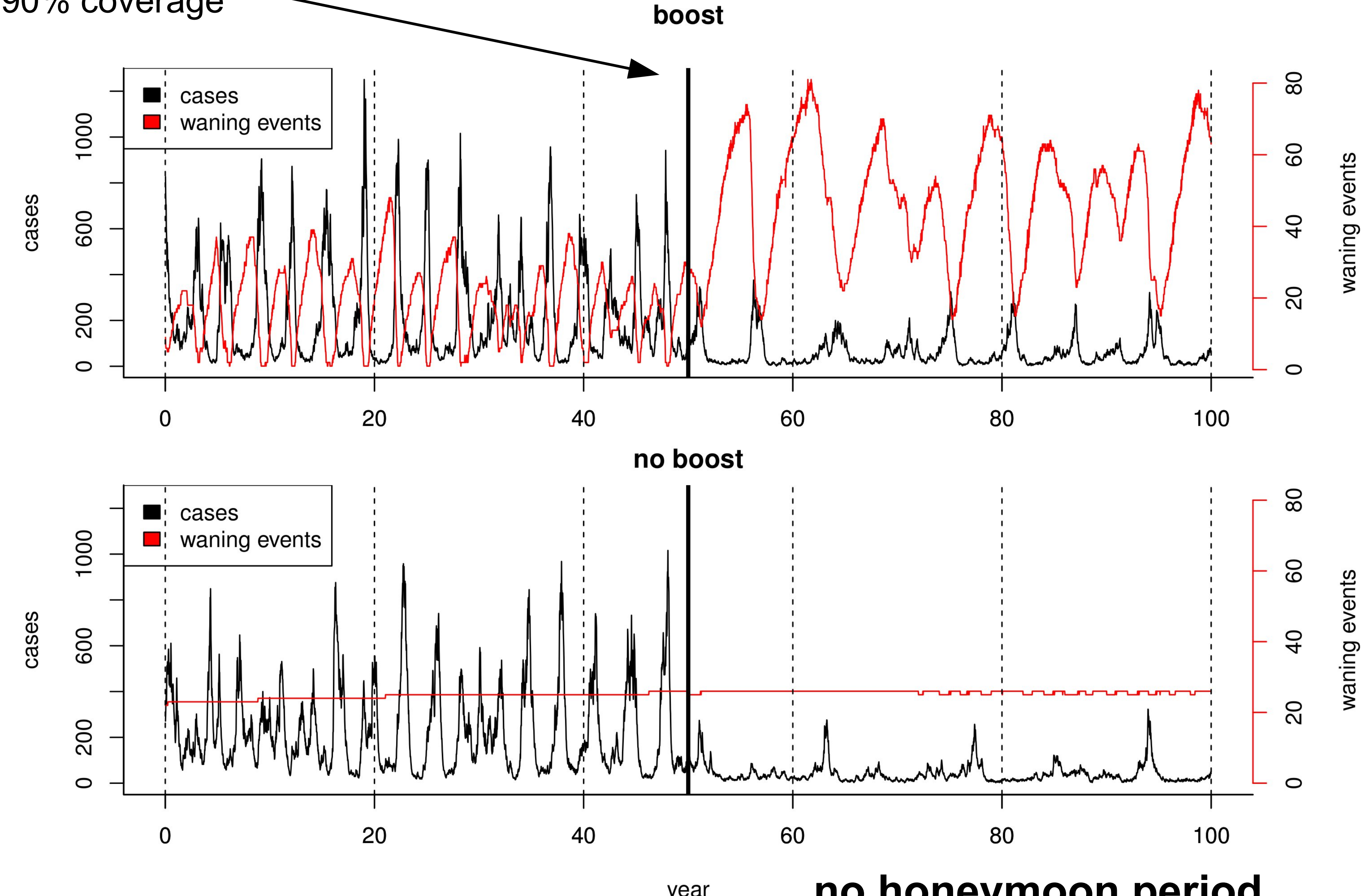


# Complex transient dynamics



# implications

start of mass vaccination, 90% coverage

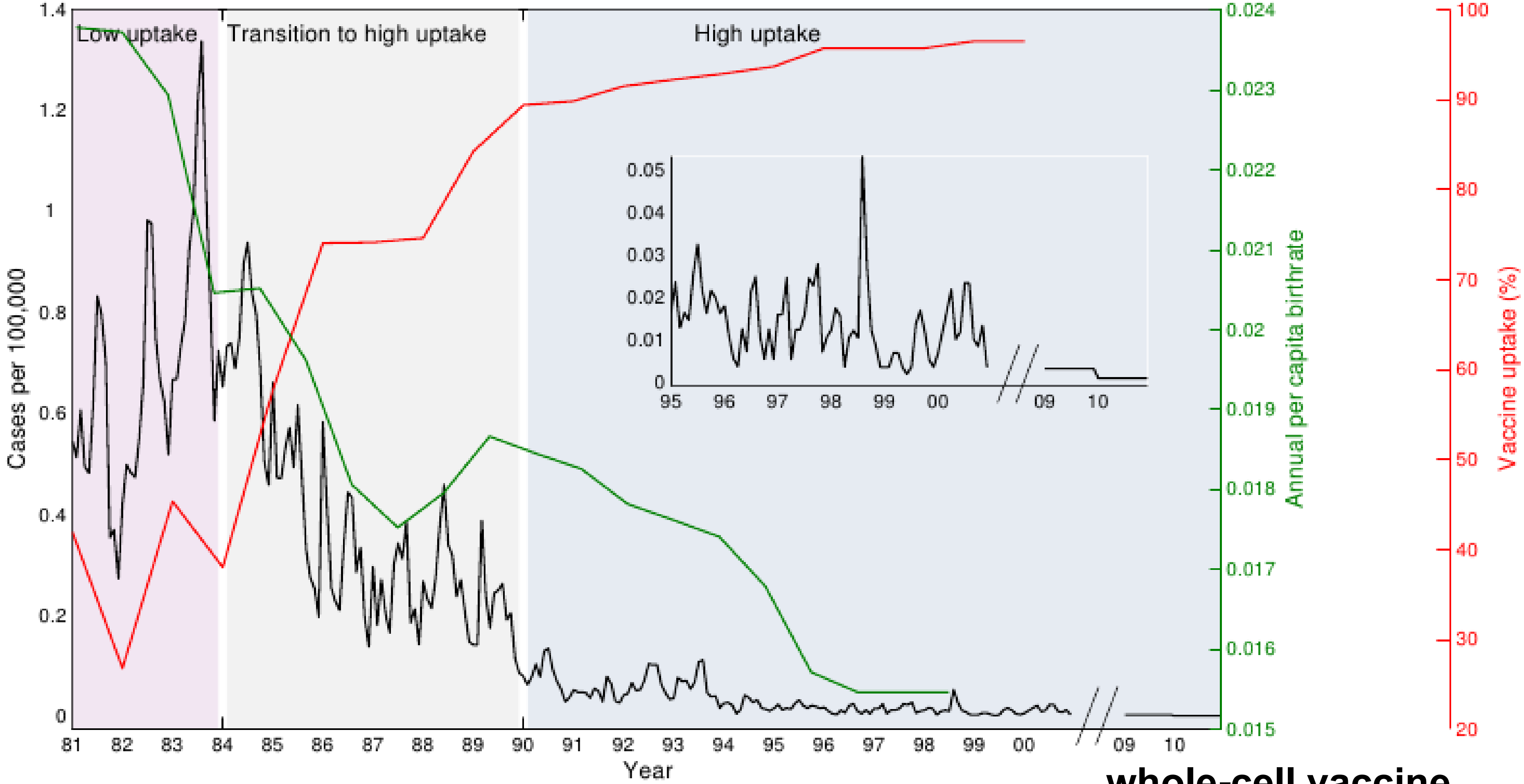



**no honeymoon period predicted**

# The Thai experience

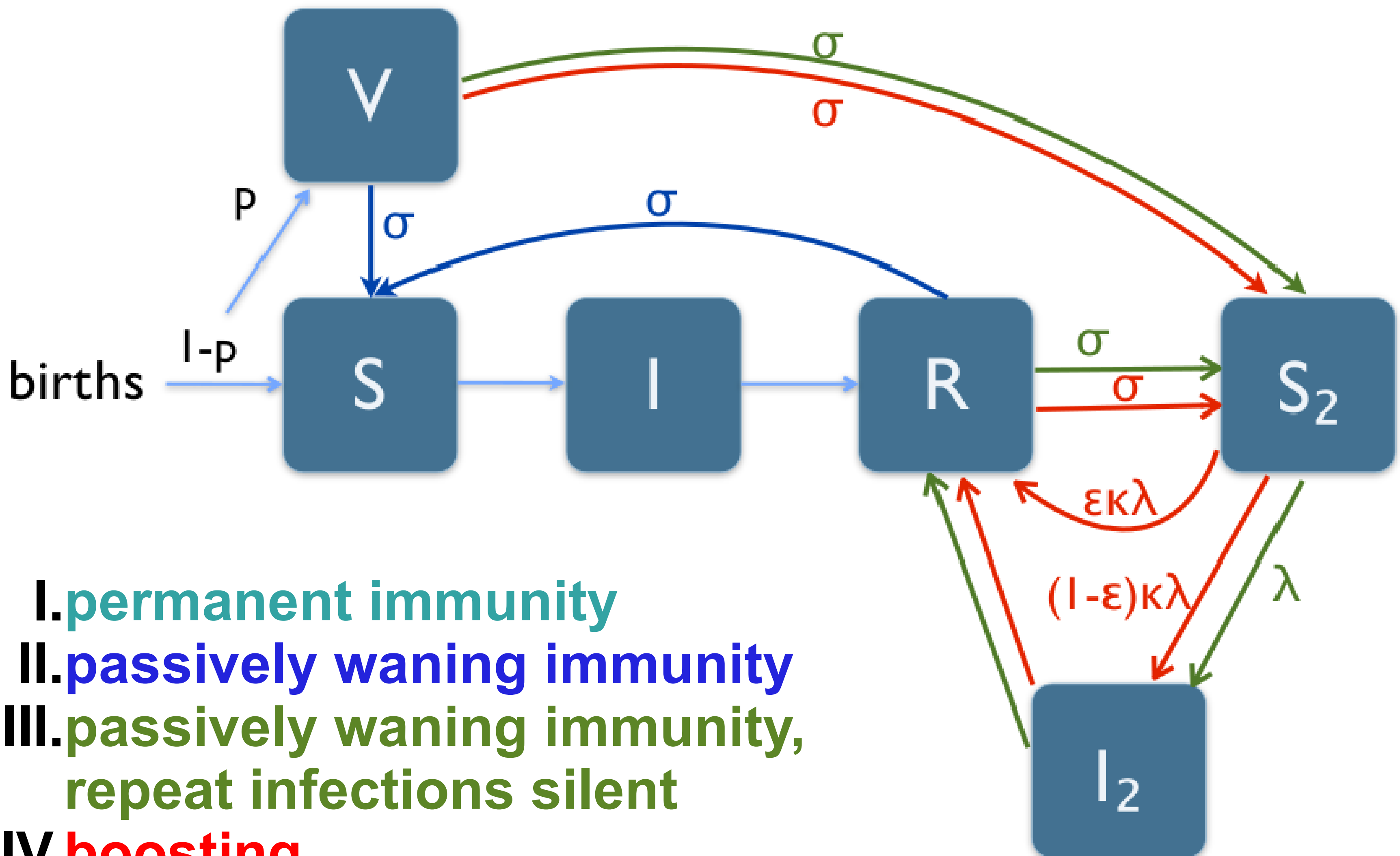
Julie Blackwood

Pej Rohani




**whole-cell vaccine**

# nested models




I. permanent immunity
II. passively waning immunity
III. passively waning immunity, repeat infections silent
IV. boosting

# model comparisons

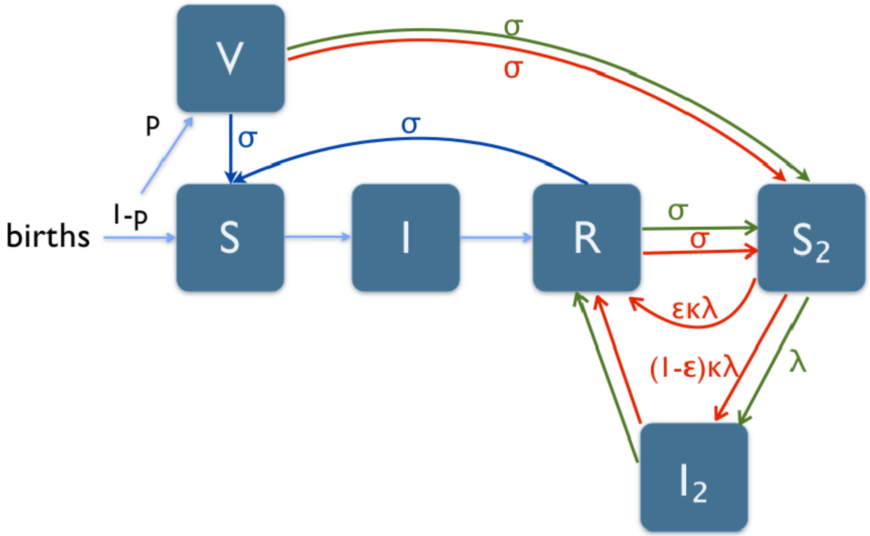
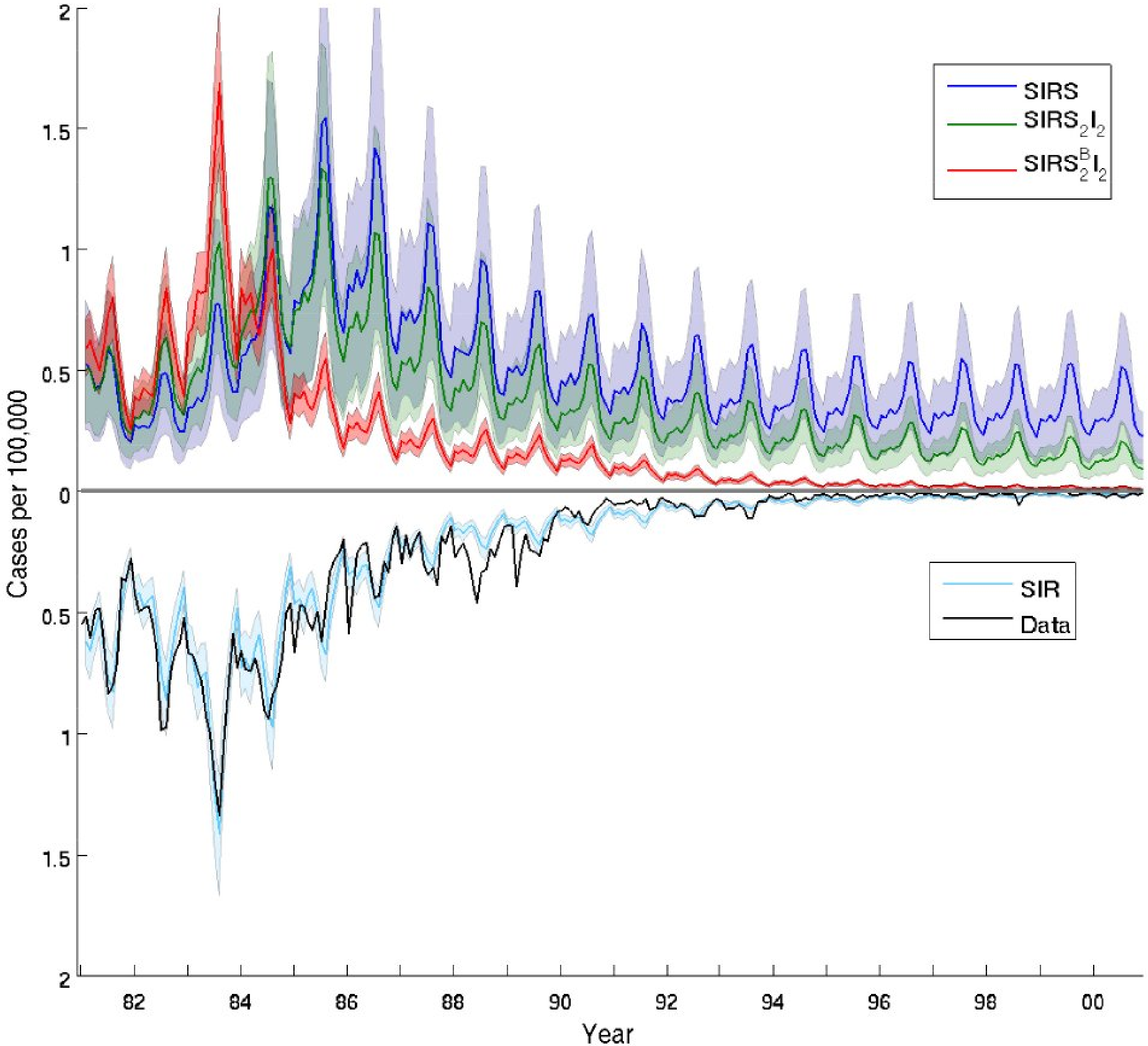


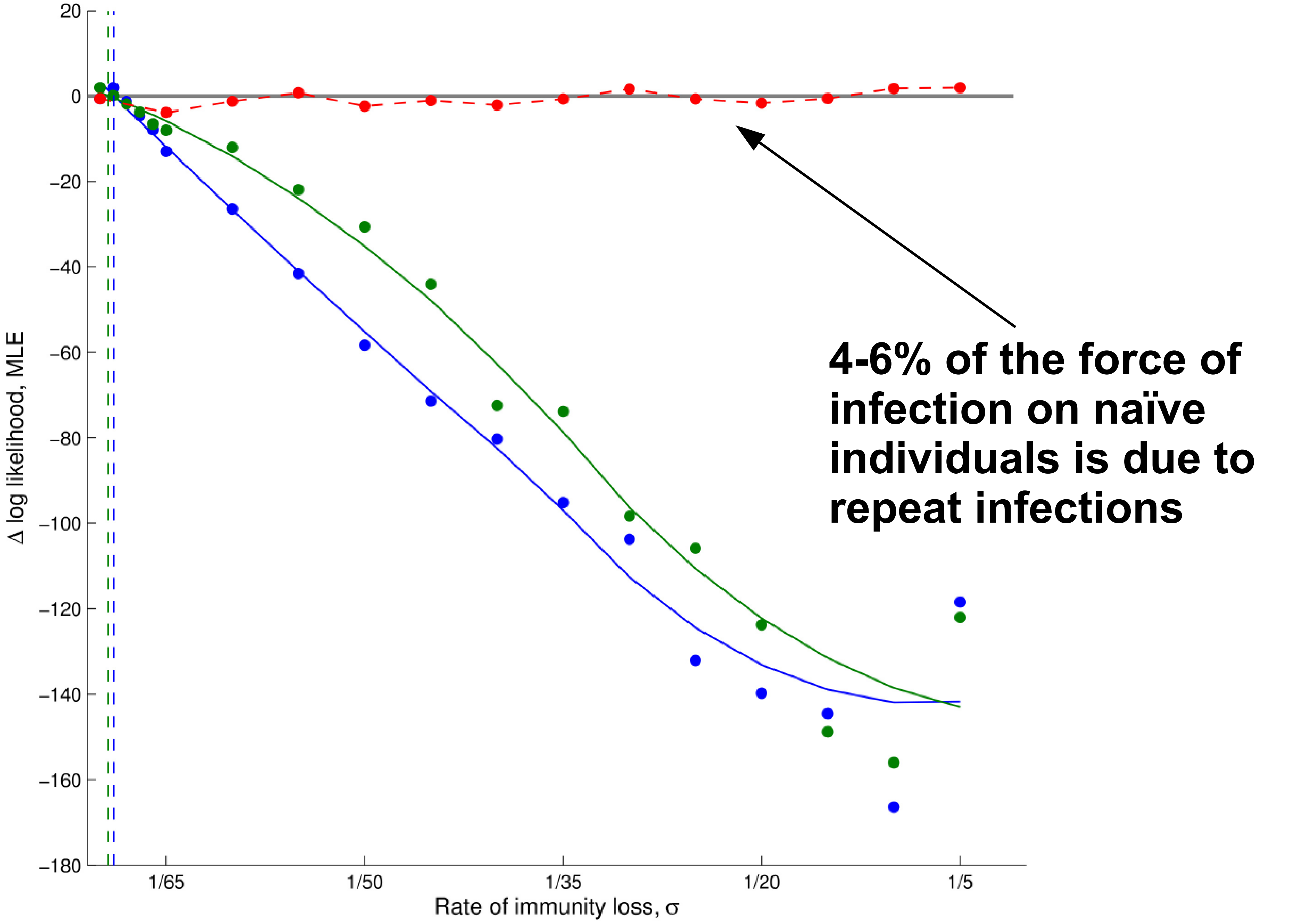

**Table 1.** Fitting results for each model

| Model | Description | MLE | AIC | ΔAIC |
|---|---|---|---|---|
| I | $SIR$ | -1059.8 | 2151.6 | 0 |
| II | $SIRS$ | -1597.2 | 3228.4 | 1076.8 |
| III | $SIRS_2I_2$ | -1480.3 | 2998.6 | 847 |
| IV | $SIRS_2^BI_2$ | -1060.3 | 2168.6 | 17 |

# model comparisons



# how long does immunity last?



# tentative conclusions

- no careful direct comparison of the Copenhagen and Thai data has yet been done
- both studies are consistent with a small role for natural immune boosting, if it is present at all

# Explaining the resurgence

- ~~improved awareness and surveillance~~
- pathogen evolution
- vaccine failure
- loss of natural immune boosting

**Key unknowns:**

- how long does natural immunity last?
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# Explaining the resurgence

- improved awareness and surveillance
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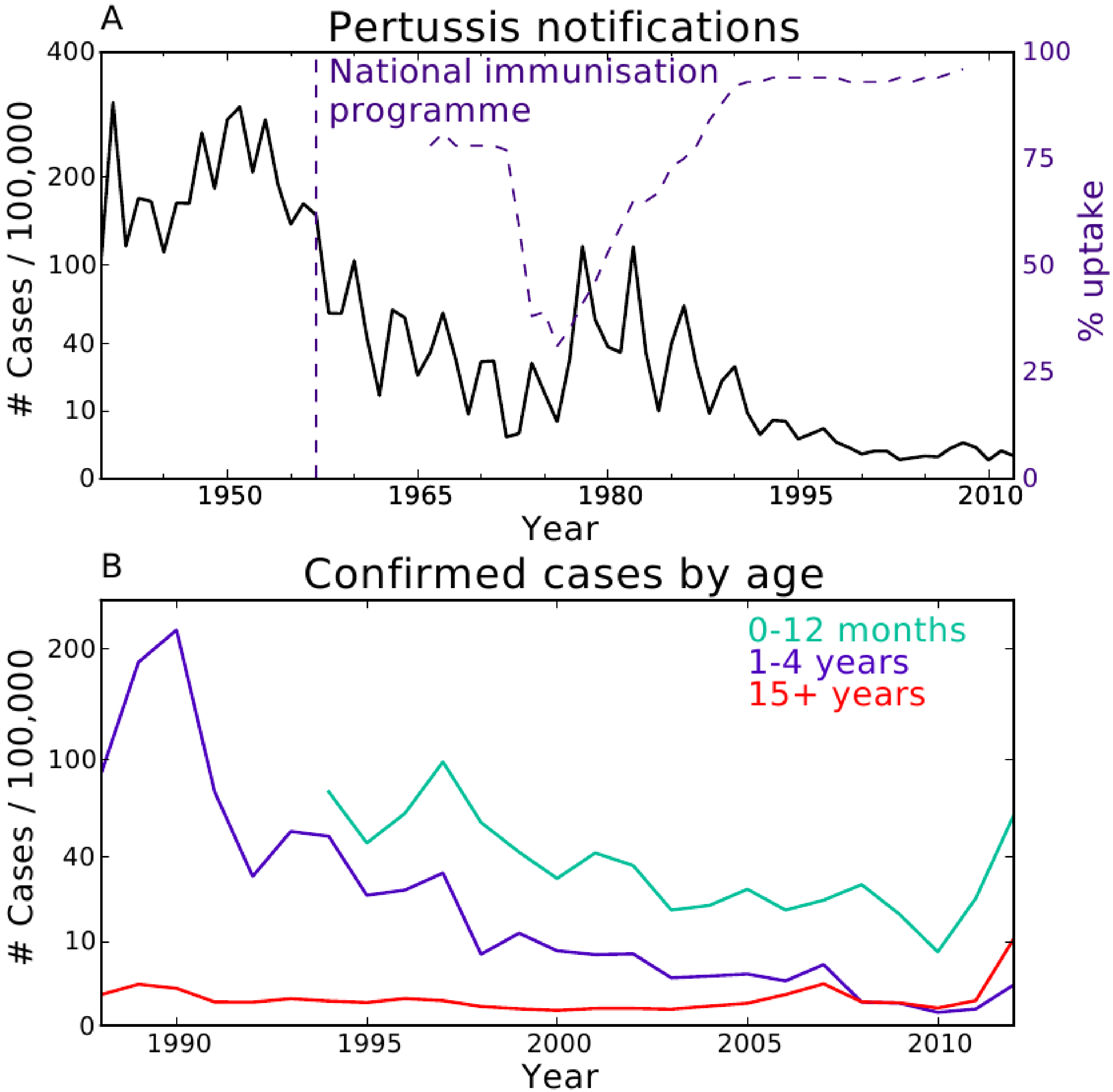
**to what extent are complex explanations for this phenomenon called for?**

**how well can we account for resurgence with the simplest models?**

**Key unknowns:**

- how long does natural immunity last?
- how do infection- and vaccine-derived immunity differ?

# The British story




Maria Riolo

Pej Rohani

# an age-structured model

$$\frac{dS_i}{dt} = w_V V_i' + w_R R_i' - \lambda_i(t) S_i + (bN - aS_0)\delta_{i,0} + (1 - eu(t))aS_0\delta_{i,1}$$

$$\frac{dE_i}{dt} = \lambda_i(t) S_i - \gamma E_i + aE_0(\delta_{i,1} - \delta_{i,0})$$

$$\frac{dI_i}{dt} = \gamma E_i - rI_i + aI_0(\delta_{i,1} - \delta_{i,0})$$

$$\frac{dR_i}{dt} = rI_i - w_R R_i + aR_0(\delta_{i,1} - \delta_{i,0})$$

$$\frac{dR_i'}{dt} = w_R R_i - w_R R_i' + aR_0'(\delta_{i,1} - \delta_{i,0})$$

$$\frac{dV_i}{dt} = eu(t)aS_0\delta_{i,1} - w_v V_i + aV_0(\delta_{i,1} - \delta_{i,0})$$

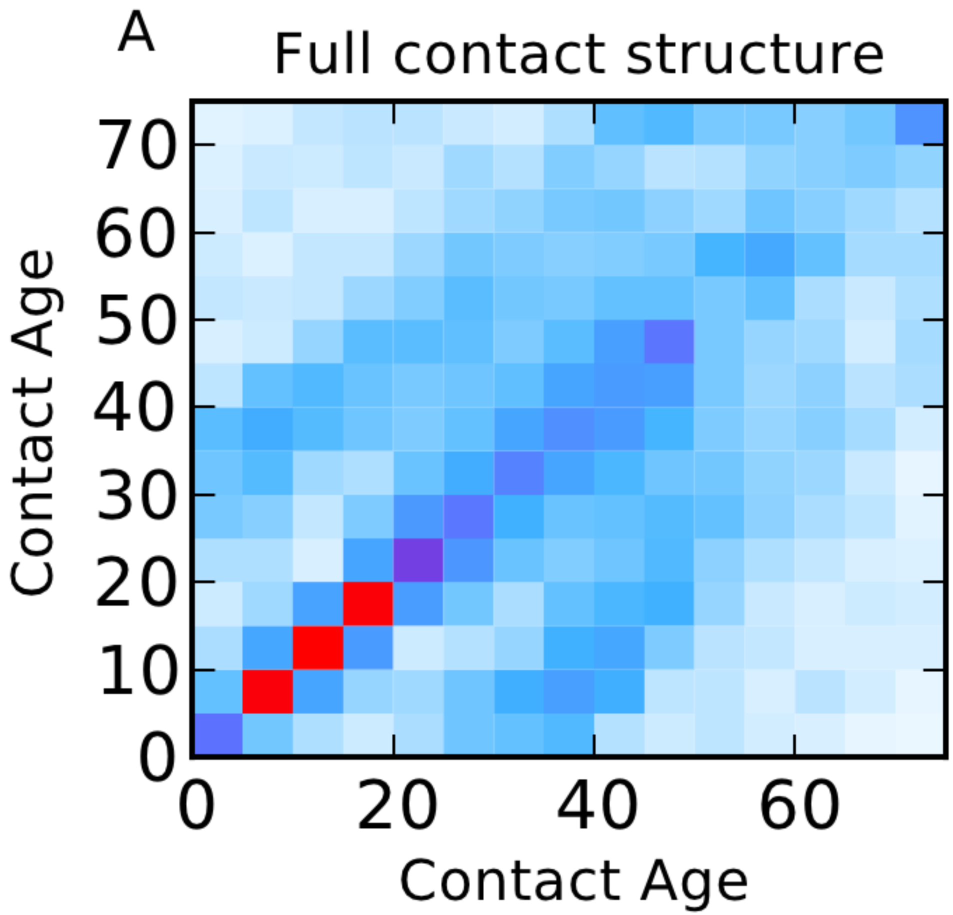
$$\frac{dV_i'}{dt} = w_V V_i - w_V V_i' + aV_0'(\delta_{i,1} - \delta_{i,0})$$

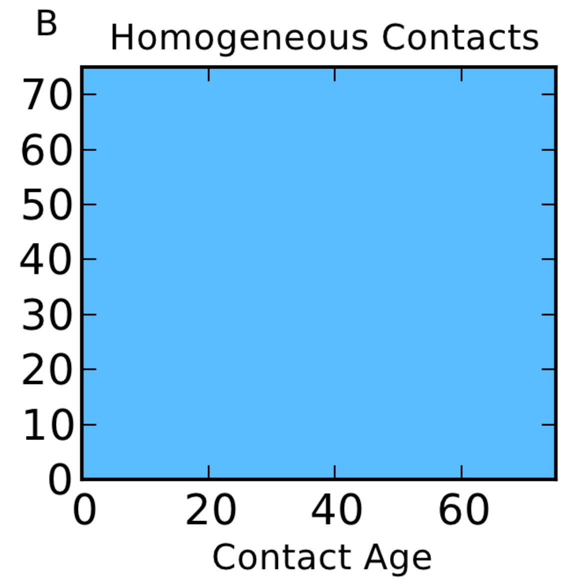
# an age-structured model

- everyone lives to age 75 and then dies
- 2 infant age classes, vaccination at 6 mo
- both natural- and vaccine-induced immunity wane according to a Γ(2) distribution, though potentially with different rates
- vaccination uptake follows the data, efficacy 75–95%
- school-term seasonality among schoolchildren
- age-specific force of infection determined by a contact matrix

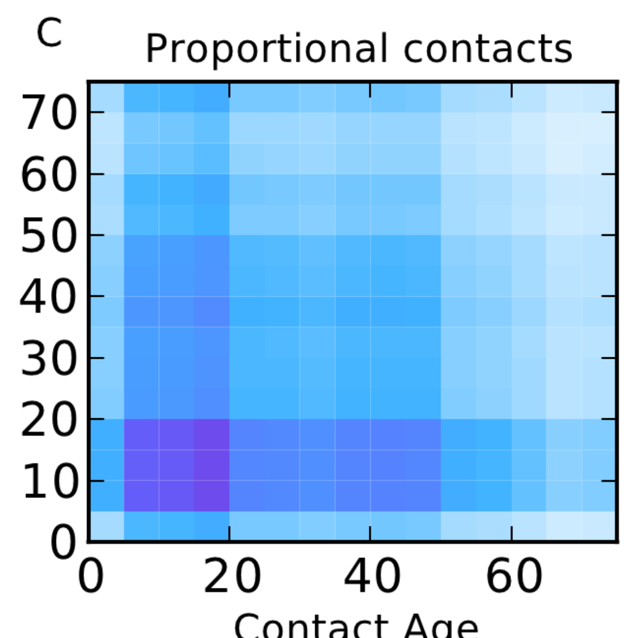
$$\lambda_i(t) = q\Sigma_k F_{hk}(t) c_{hk} \frac{\tilde{I}_k}{\tilde{N}_k}$$

# age-specific contact rates

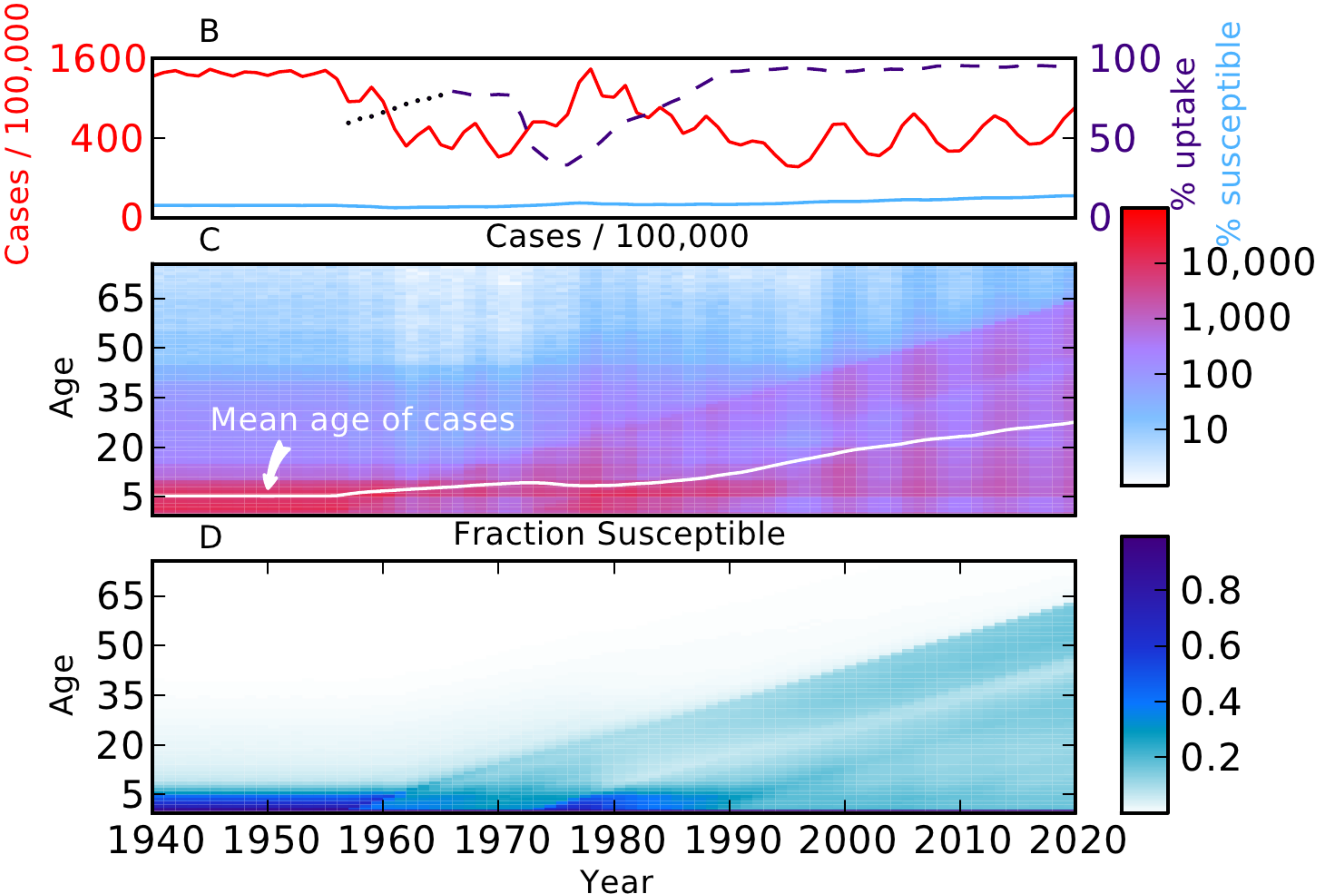


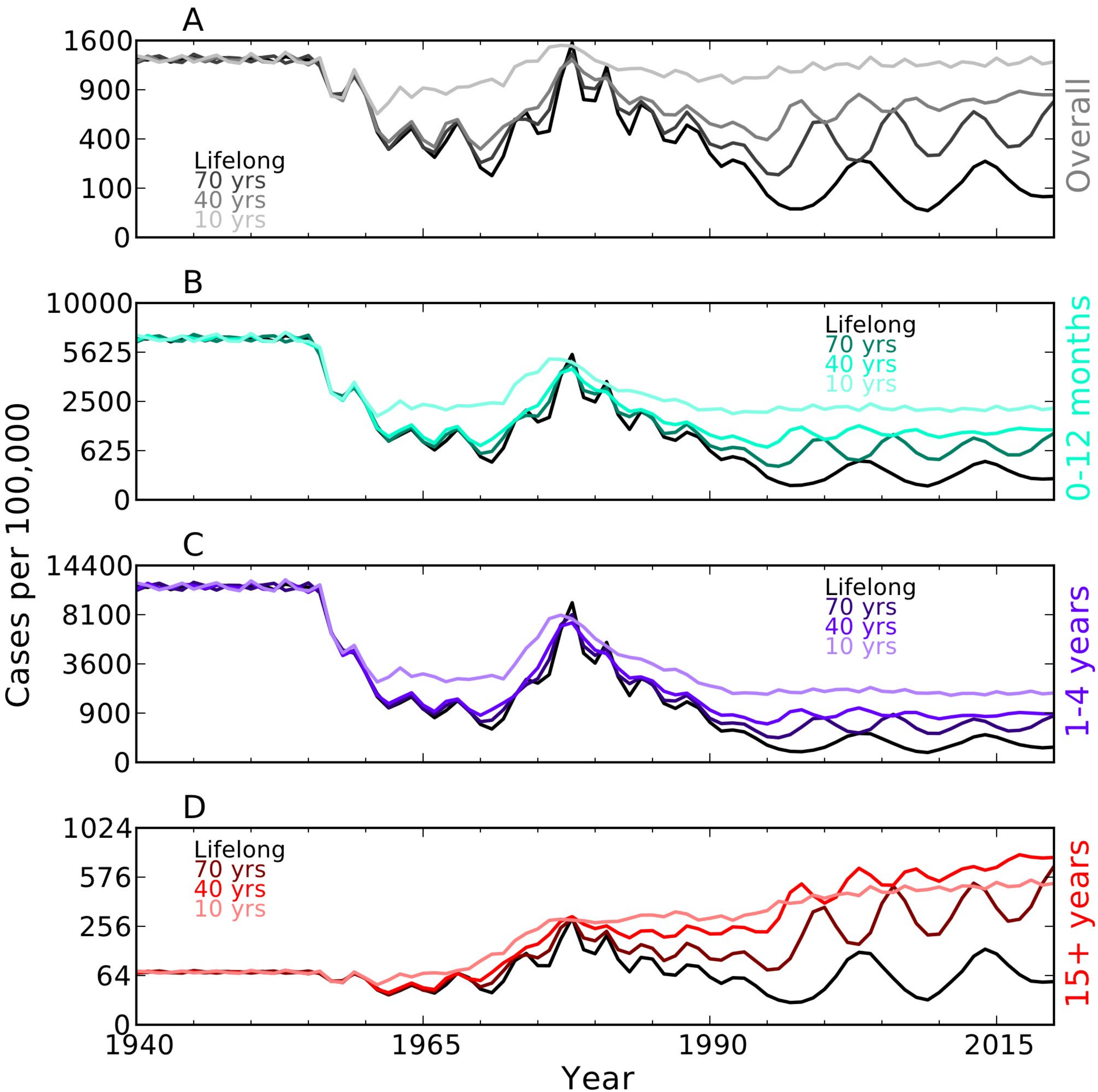




data from the POLYMOD study (Mossong 2008)

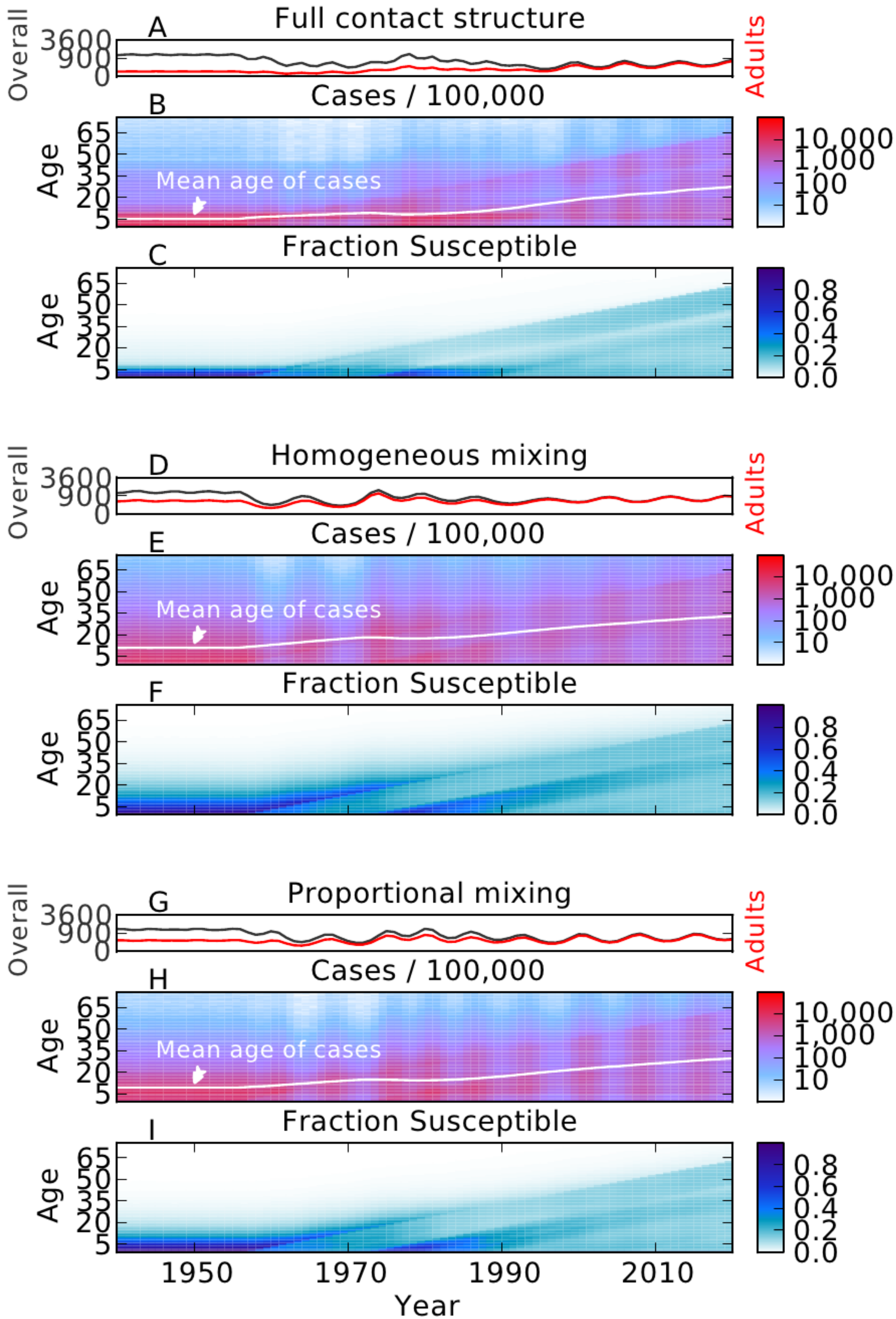


# a typical realization

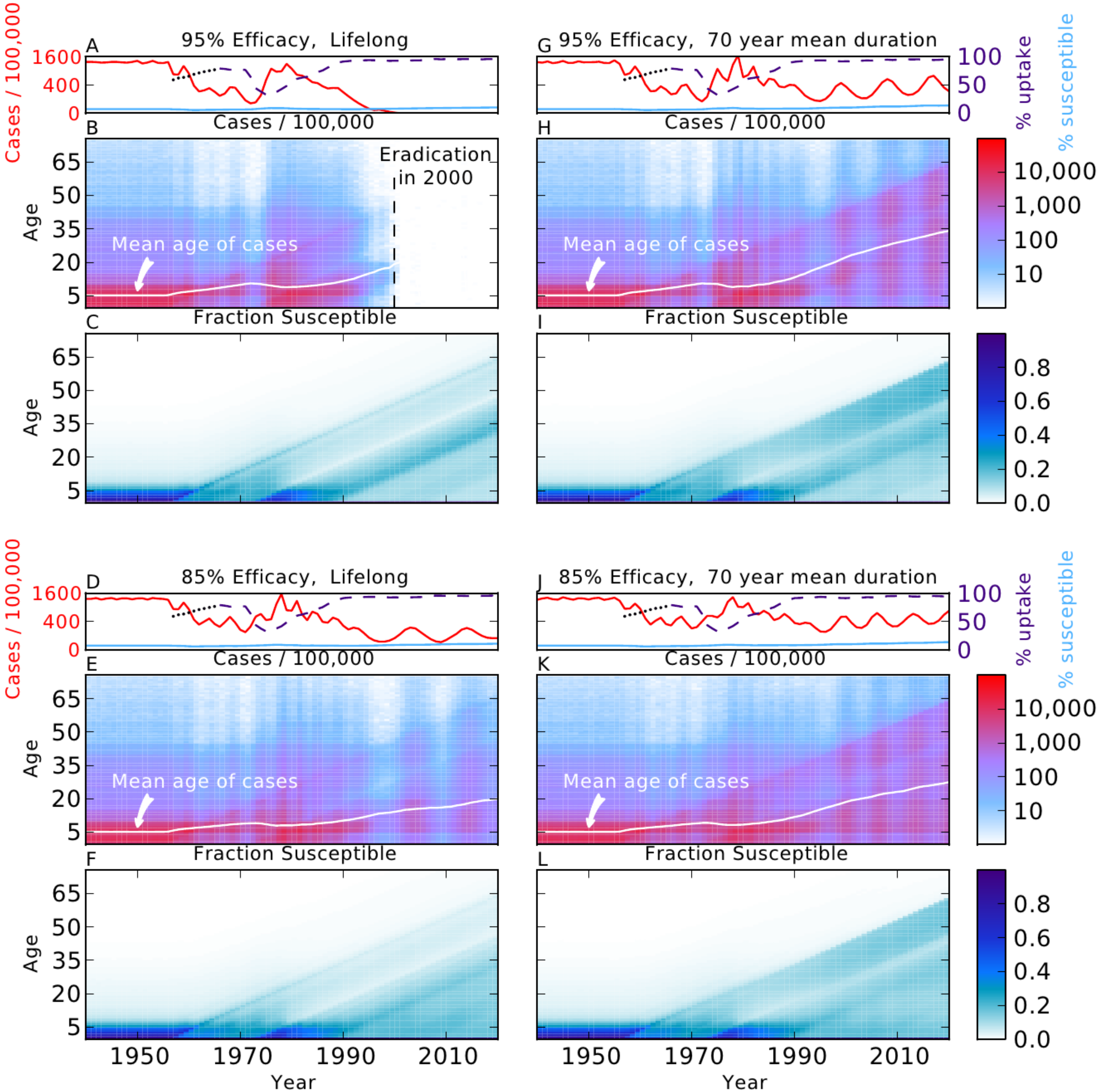




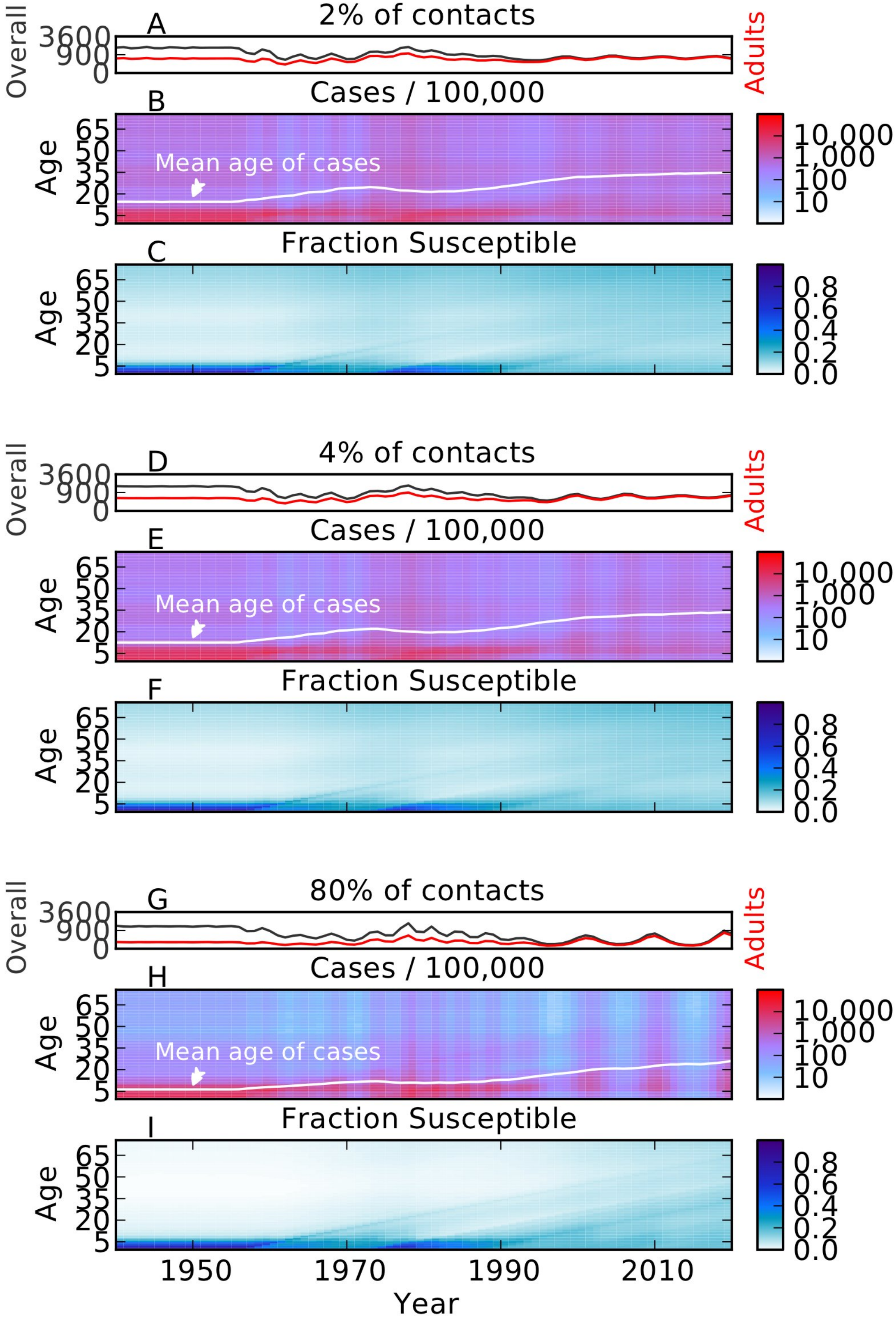

lifelong natural immunity




# varying the contact matrix



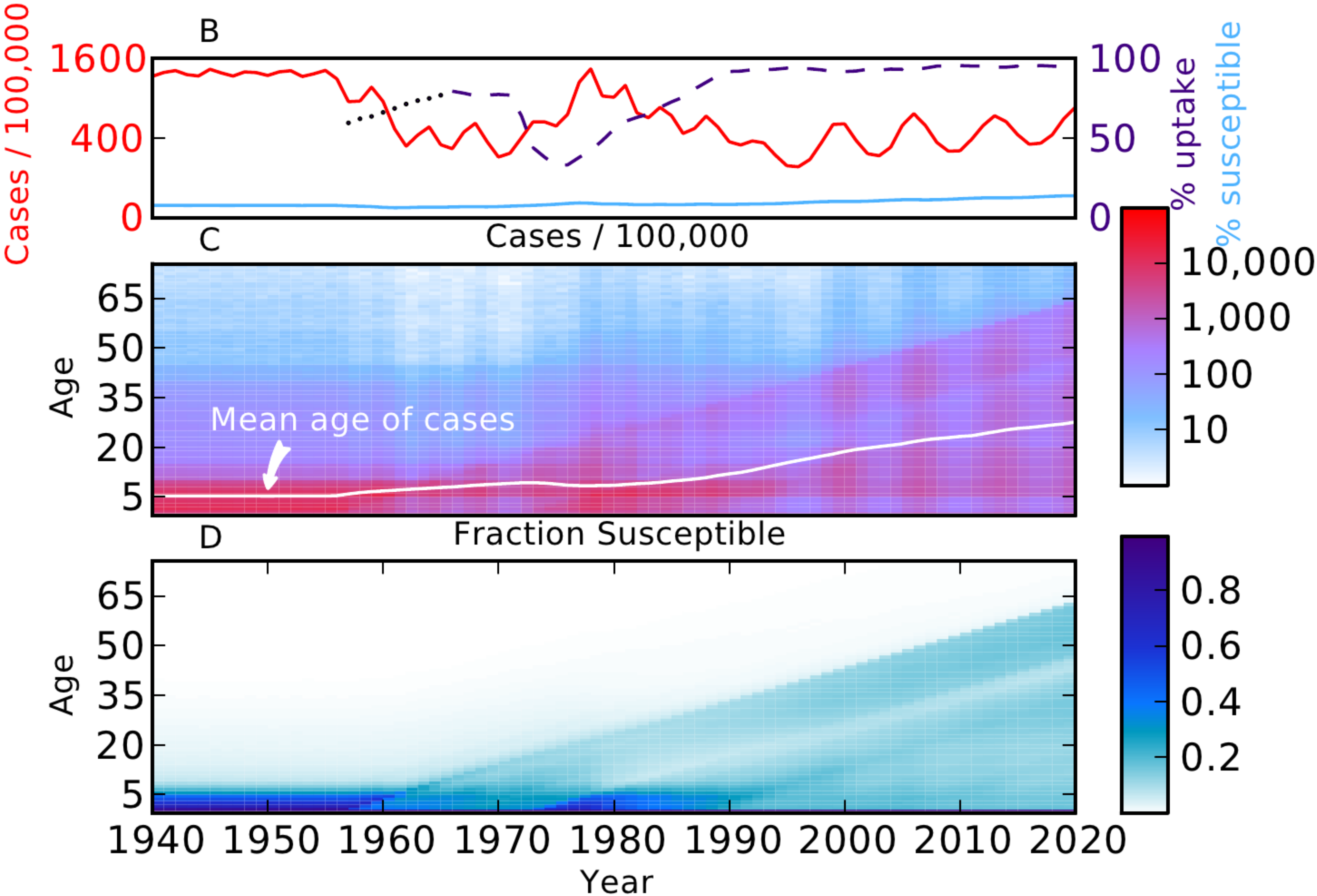

varying vaccine efficacy & duration of vaccine-induced immunity




with boosting of immunity

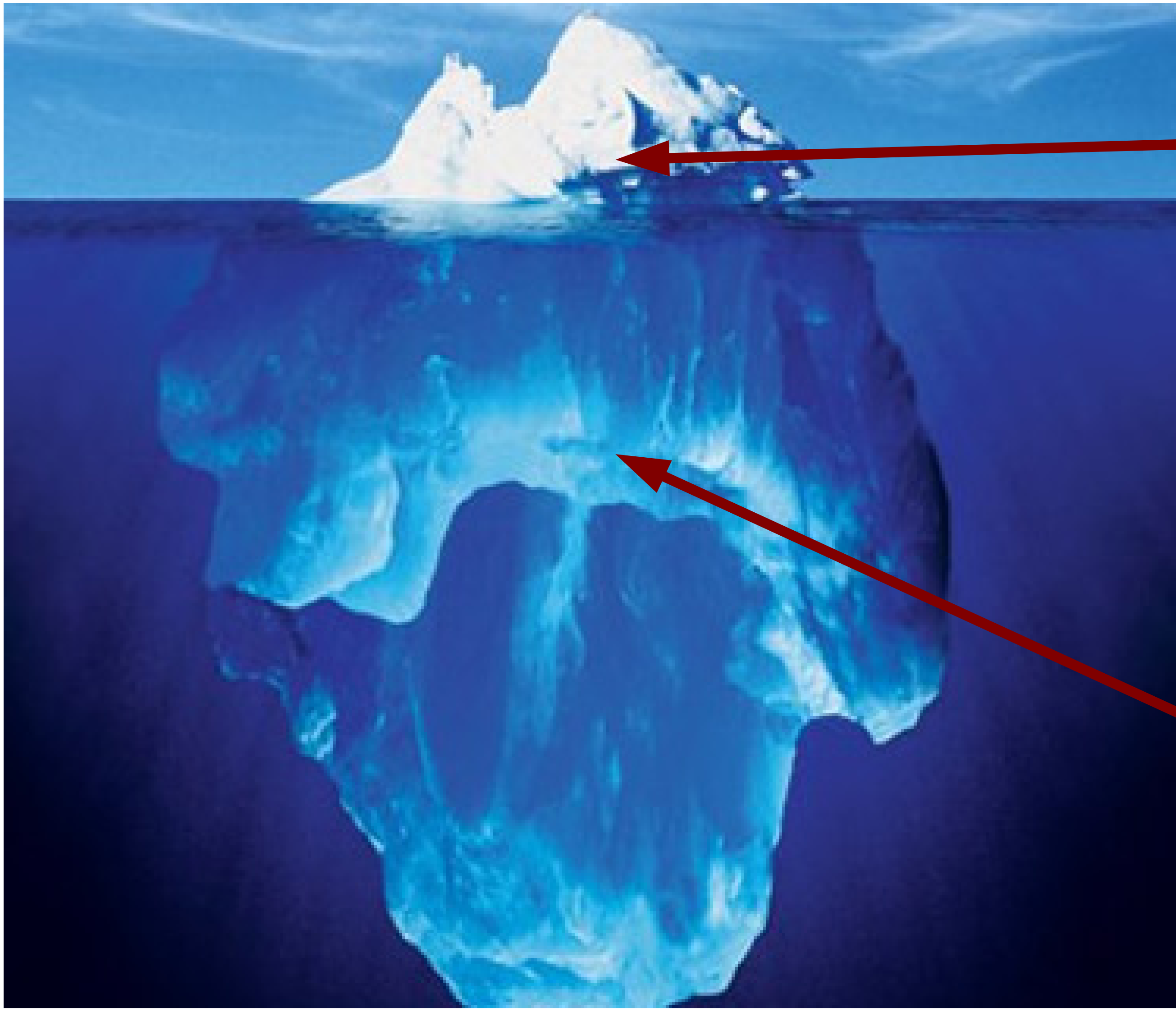
compare with
κ = 0.5, 1, 20

# the honeymoon effect



# tentative conclusions

- data are consistent with *effectively* lifelong infection-induced immunity
- natural immune boosting is probably a weak effect at best
- legacy of imperfect vaccination is long-lived
- recent resurgence might be understandable as the end of a long honeymoon period
- more effective vaccines and vaccination will be needed if we are to regain the upper hand

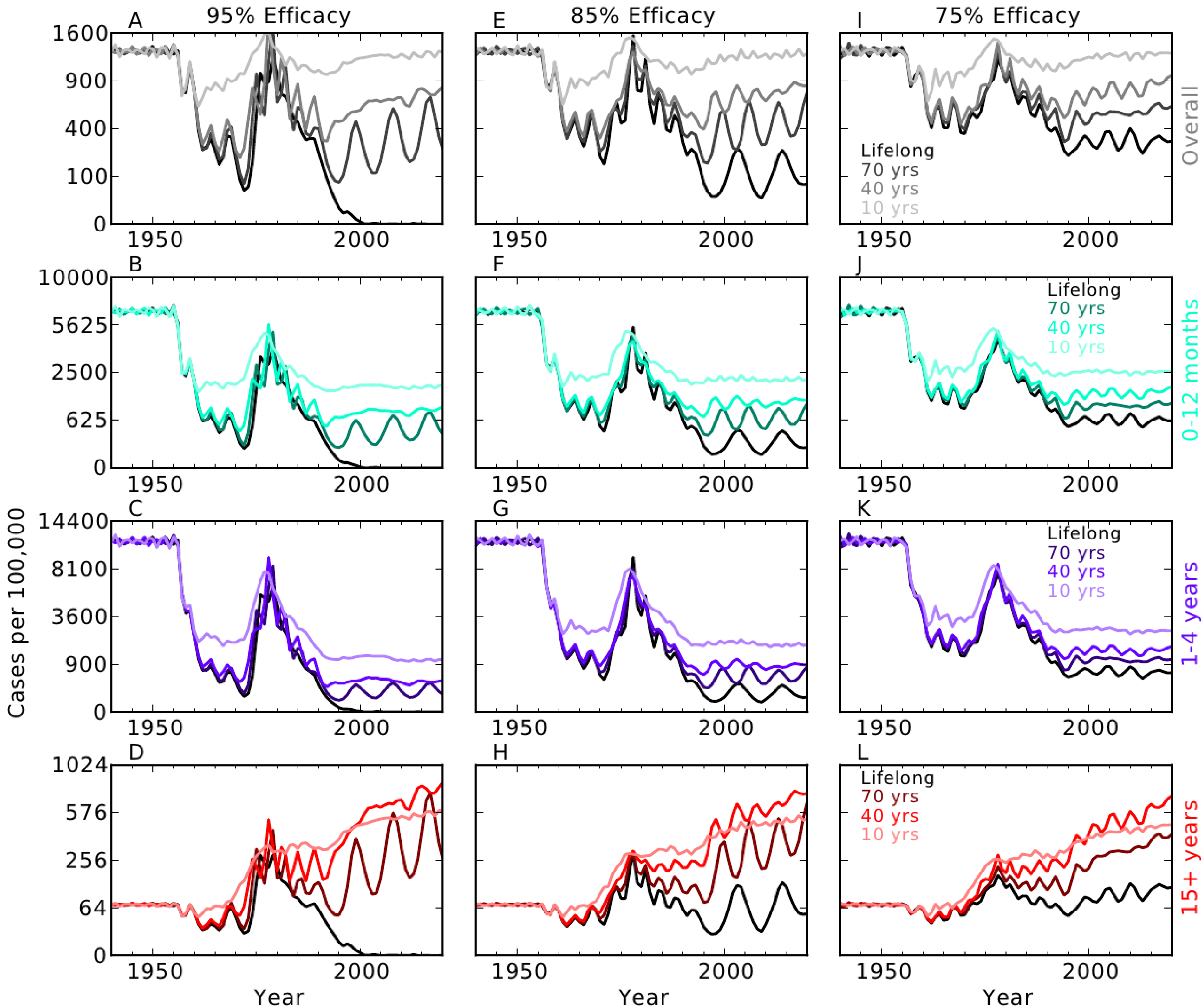


**Clinical and epidemiological studies (focus on disease)**

**Subclinical infection, effects on transmission and immunity (focus on ecology)**

# Thanks

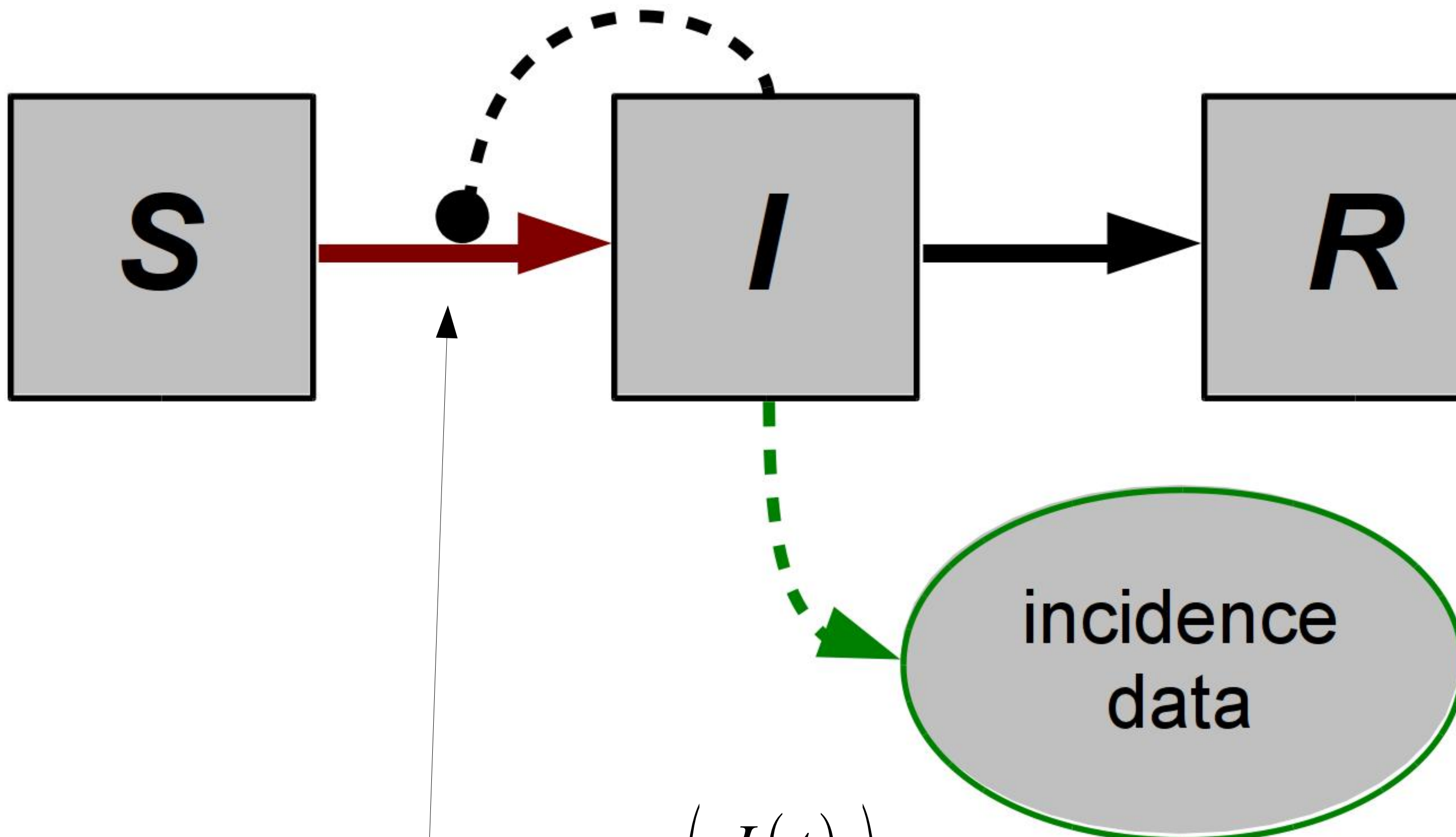
- Joint NIH/DHS Research and Policy in Infectious Disease Dynamics (RAPIDD)
- National Institutes of Health
- National Center for Ecological Analysis & Synthesis


95% Efficacy
85% Efficacy
75% Efficacy
A
B
C
D
E
F
G
H
I
J
K
L
Overall
0-12 months
1-4 years
15+ years
Lifelong
70 yrs
40 yrs
10 yrs
Cases per 100,000
Year
1600
900
400
100
0
10000
5625
2500
625
14400
8100
3600
1024
576
256
64
1950
2000

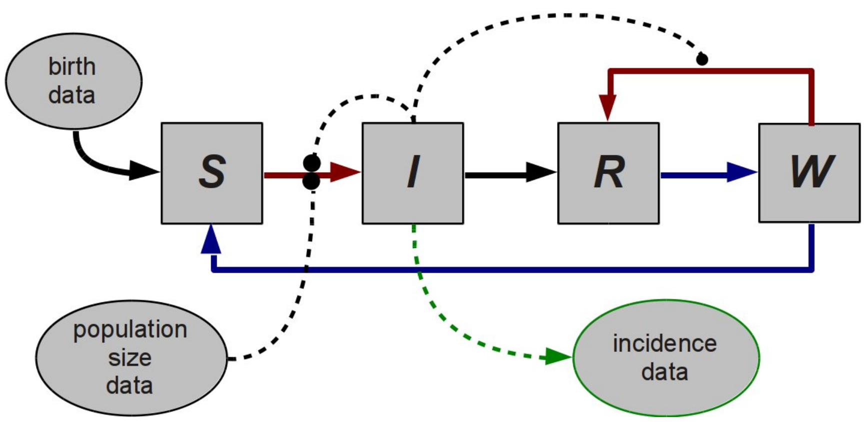
# Complexities of disease ecology

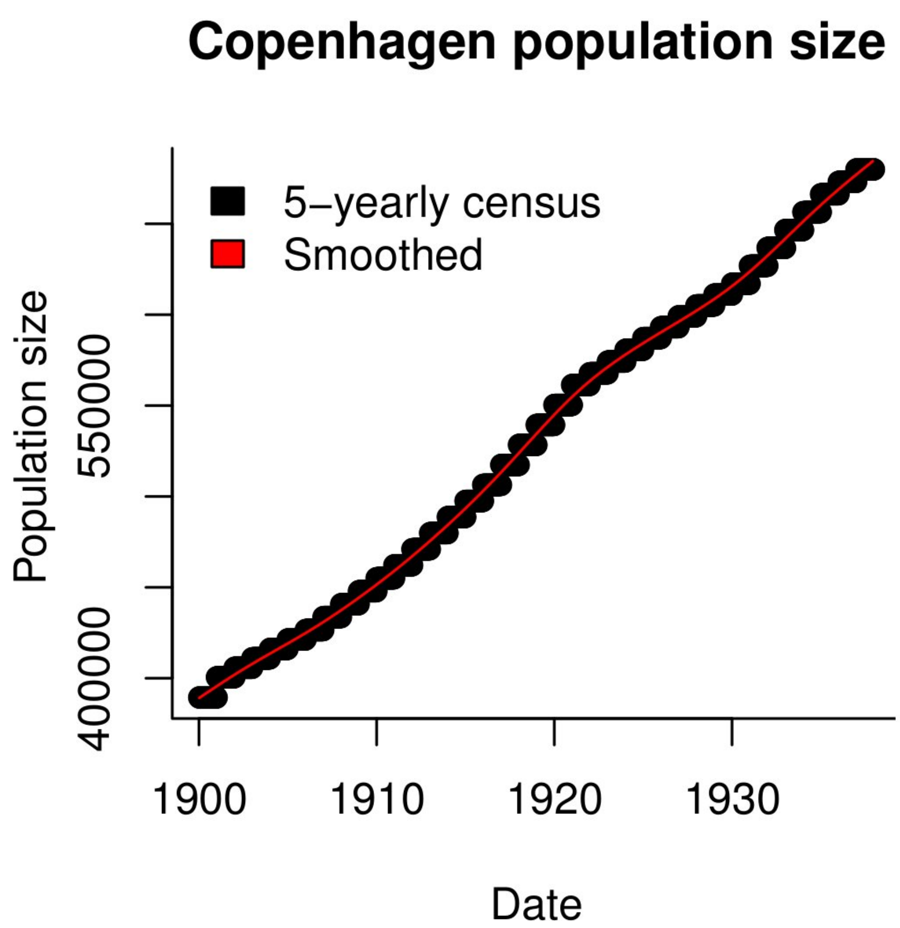
- multiplicity of antigenic strains
- temporary immunity
- complex demography
- age structured transmission/immunity
- spectrum of disease severity

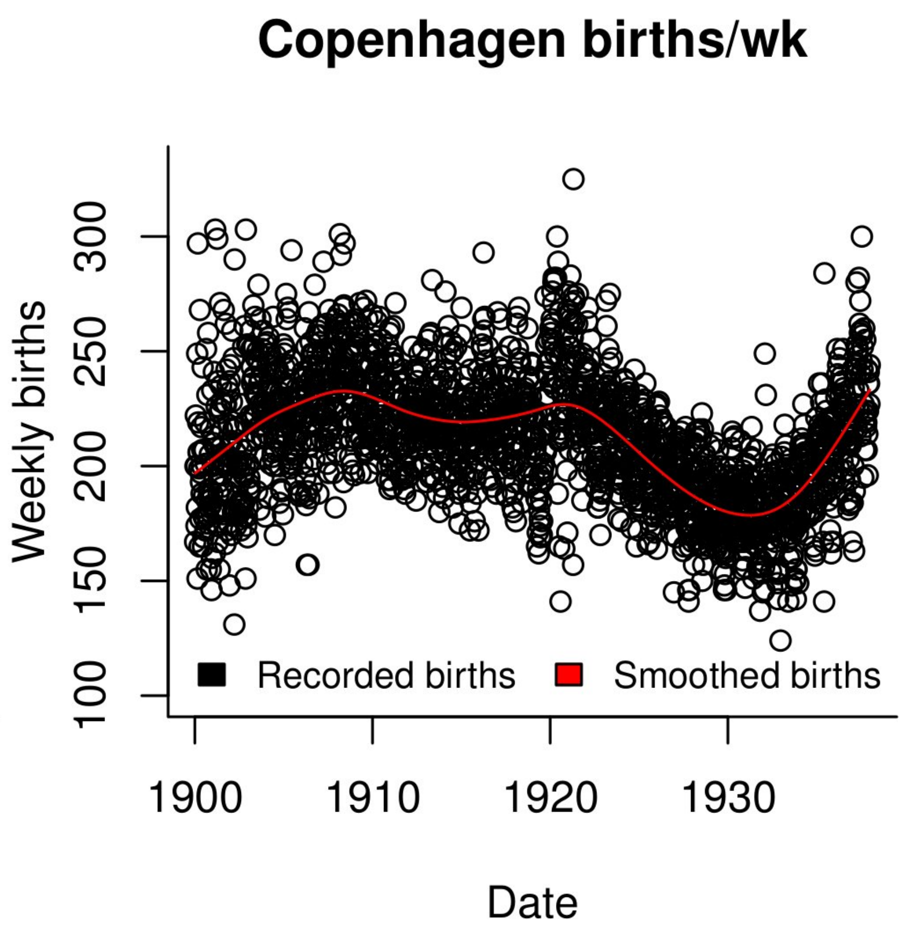
## compartmental models




$$\textit{force of infection} = \lambda = \beta(t)\left(\frac{I(t)}{N(t)}\right)$$


birth data
S
I
R
W
population size data
incidence data


Copenhagen population size
5−yearly census
Smoothed
Population size
400000
550000
1900
1910
1920
1930
Date


Copenhagen births/wk
Weekly births
100
150
200
250
300
Recorded births
Smoothed births
1900
1910
1920
1930
Date