Rapid influenza reinfection

Likely mechanisms and potential impacts during a pandemic

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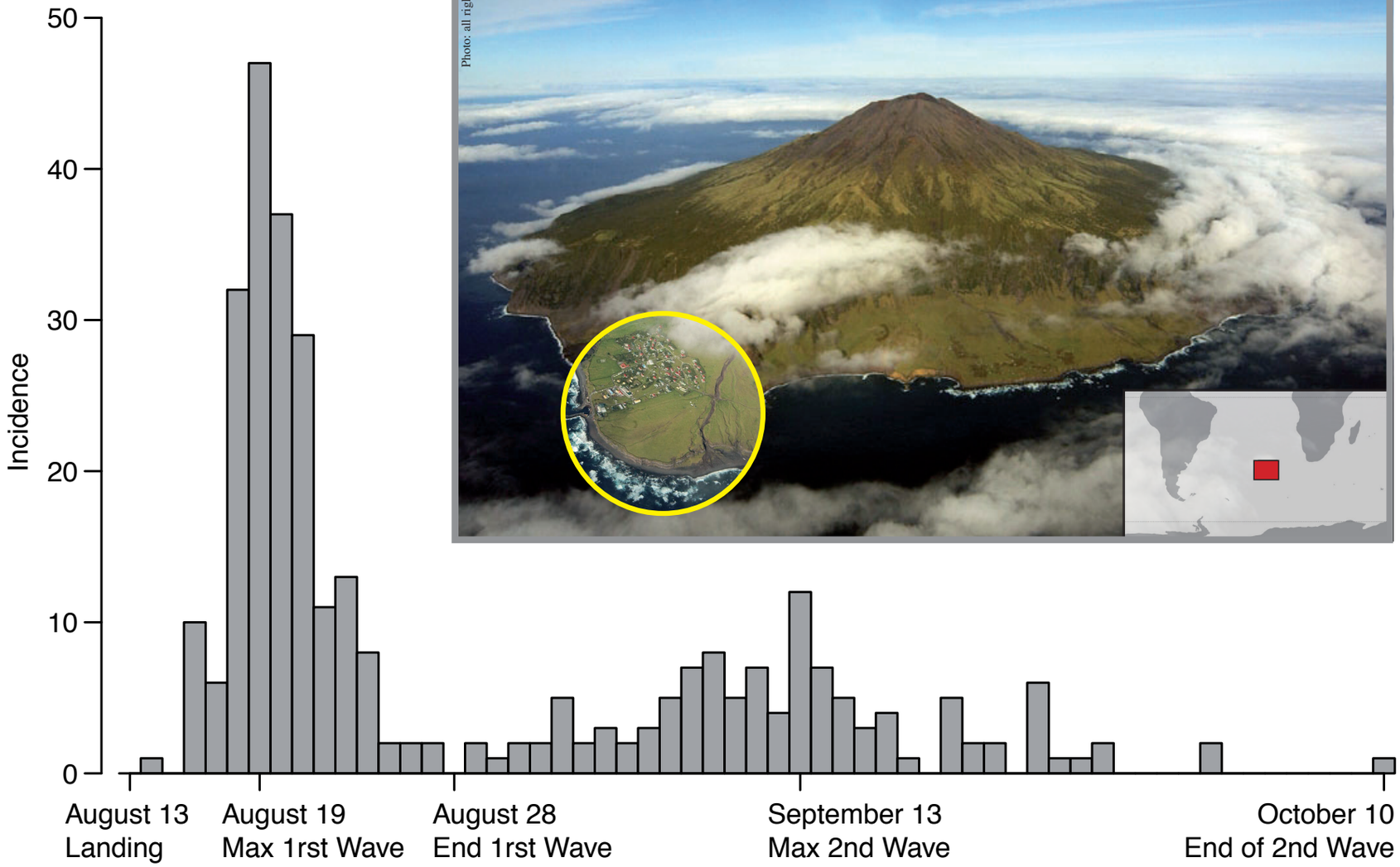
A two-wave epidemic on Tristan da Cunha (1971)



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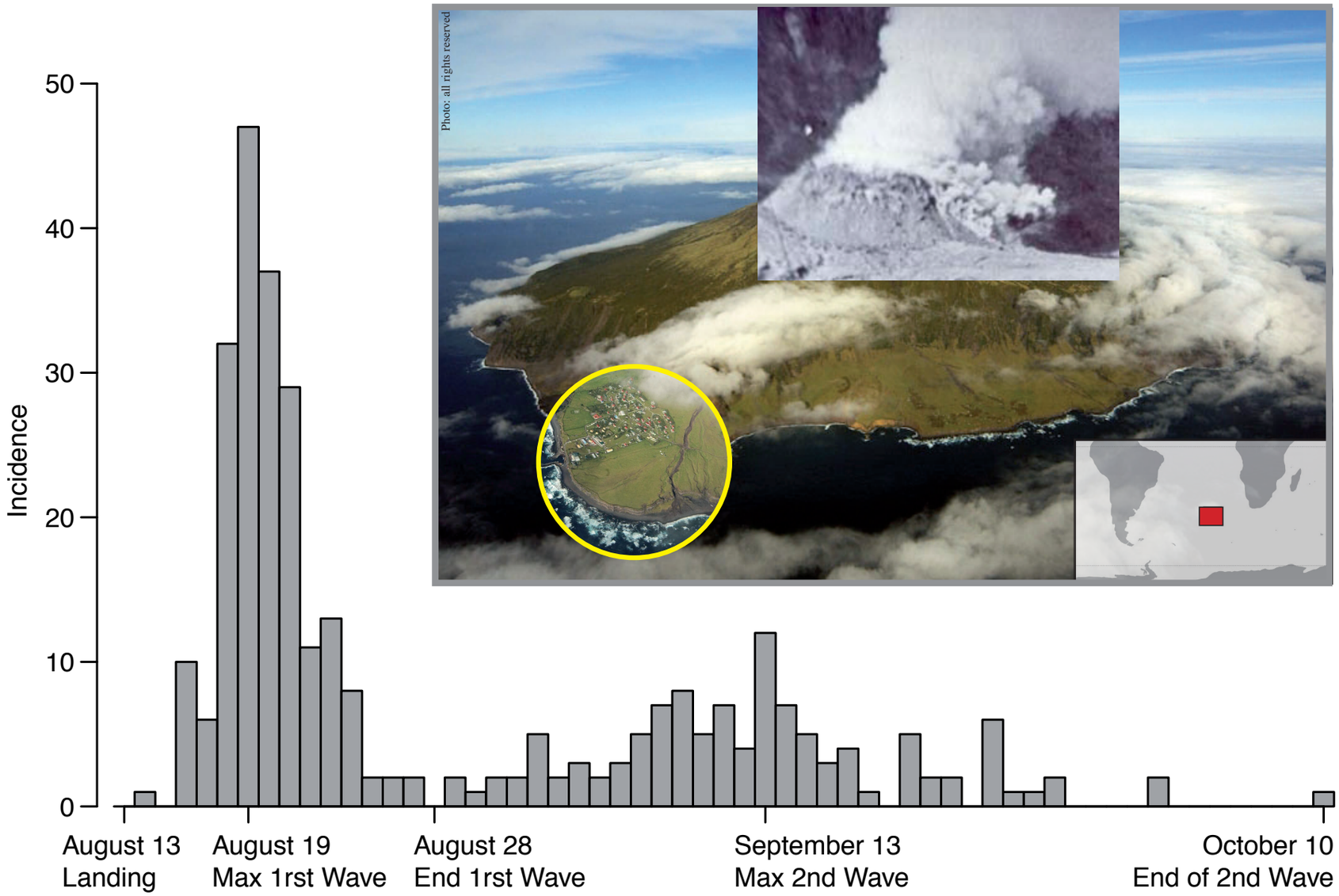

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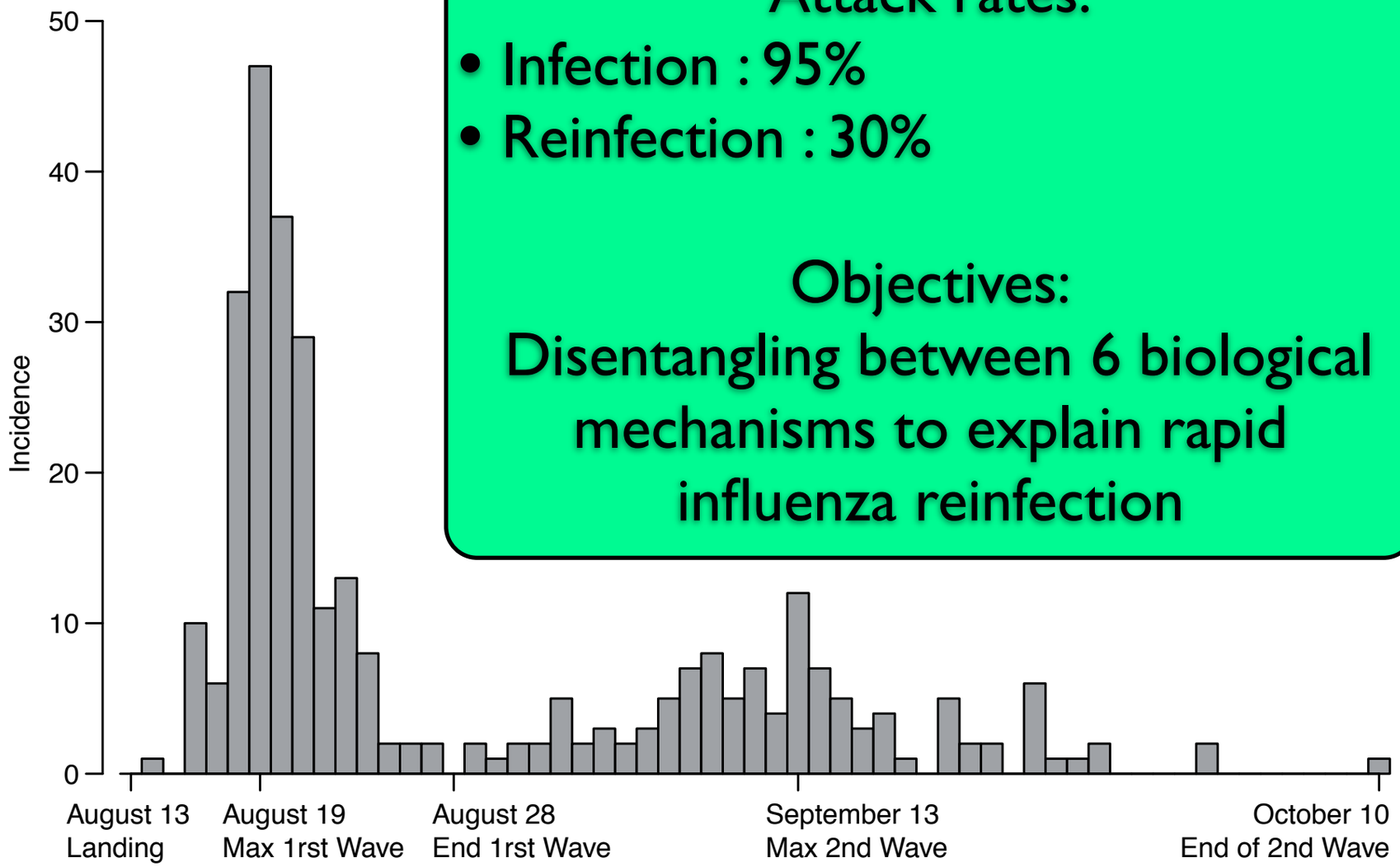


Attack rates:

- Infection : 95%
- Reinfection : 30%

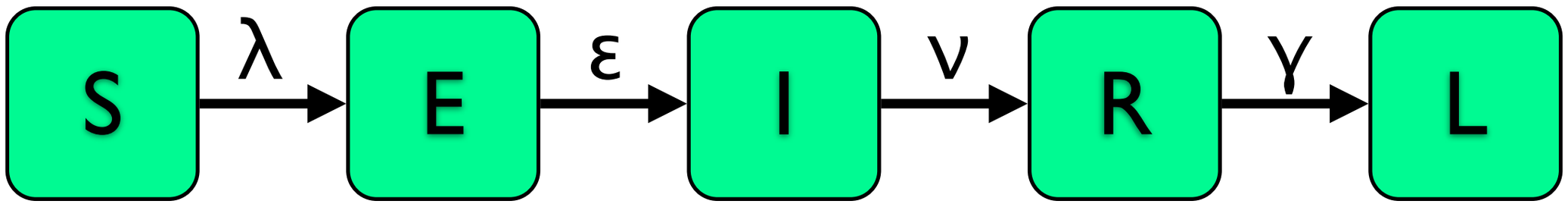
Objectives:
Disentangling between 6 biological mechanisms to explain rapid influenza reinfection

A simple mechanistic approach

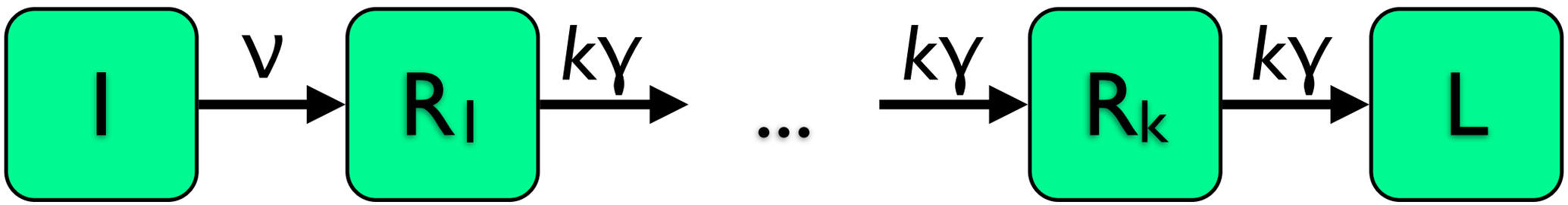
- $\lambda = \beta I/N$ mass-action
- $1/\varepsilon$: mean latent period
- $1/\nu$: mean infectious period
- $1/\gamma$: mean removed period

Long-term immunity

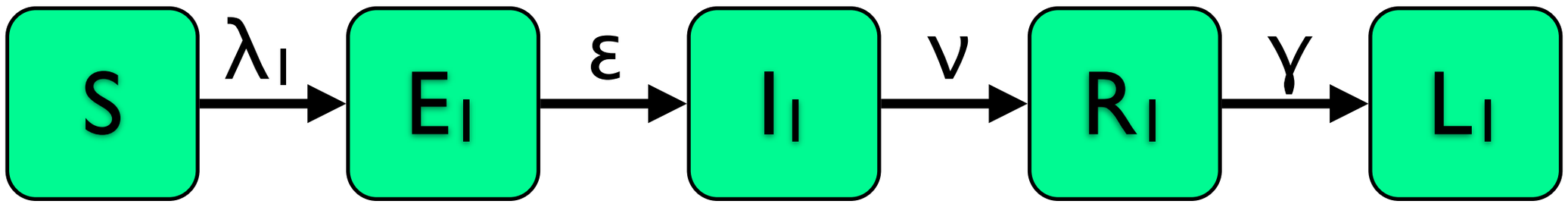
A simple mechanistic approach



Flexible distribution of the removed period: quarantine, non-specific protection, etc.



H1: the virus mutated during the first epidemic-wave



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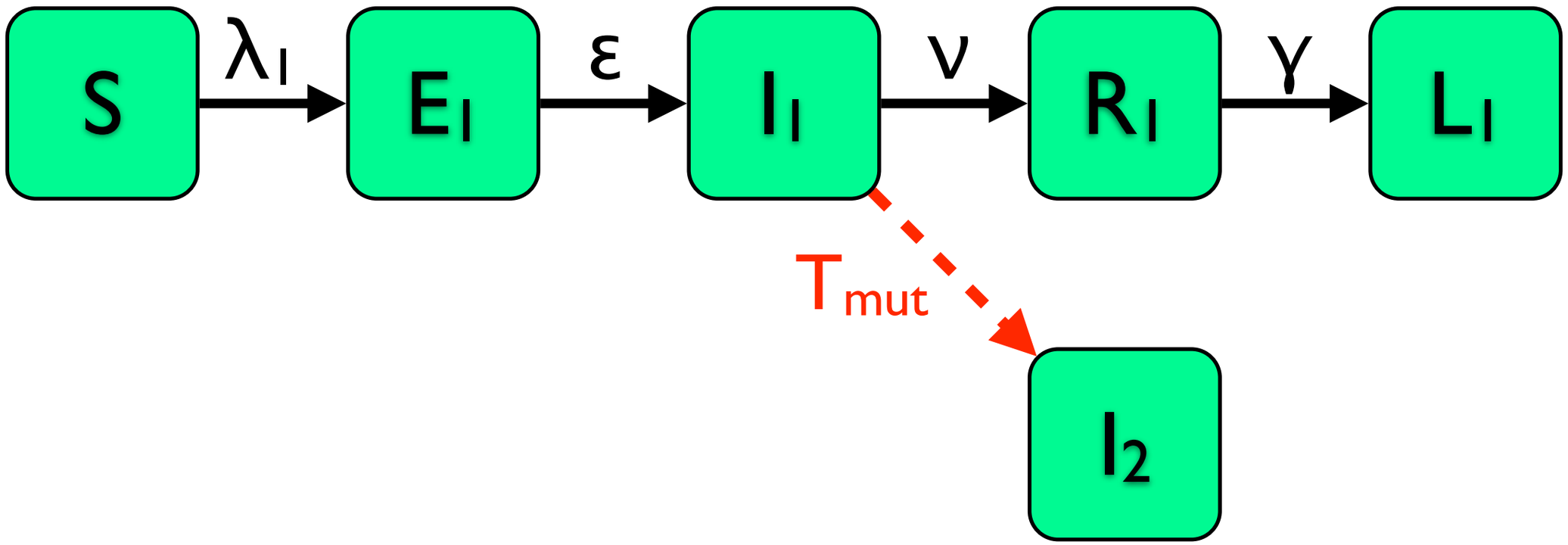

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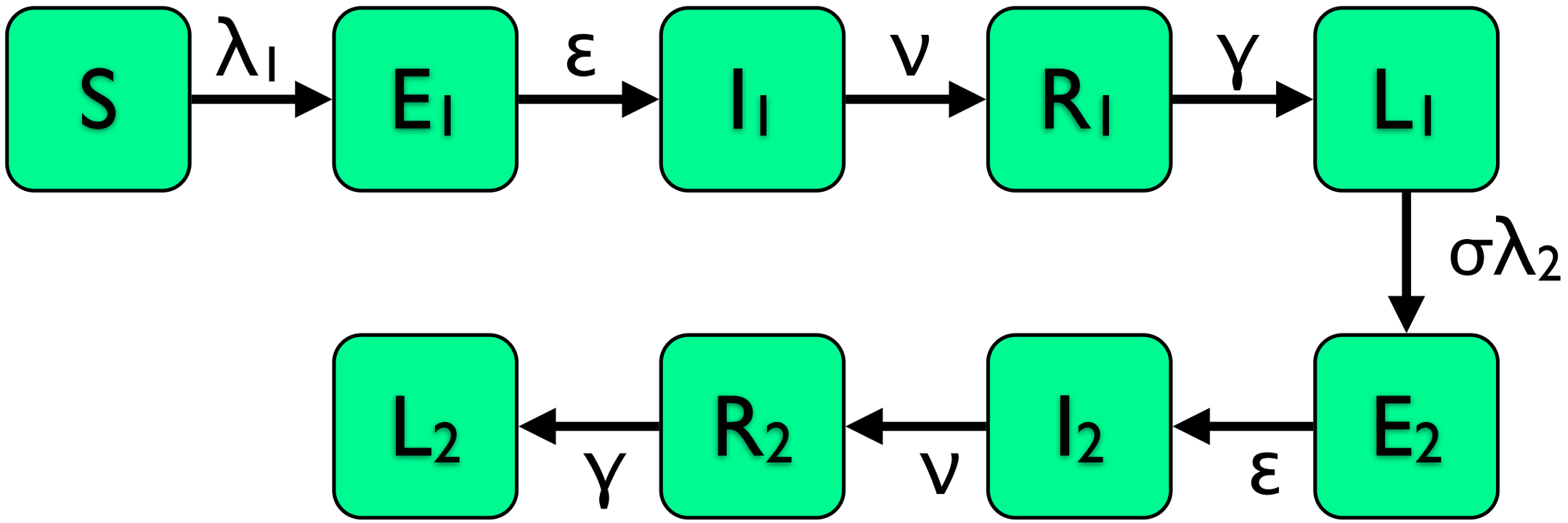
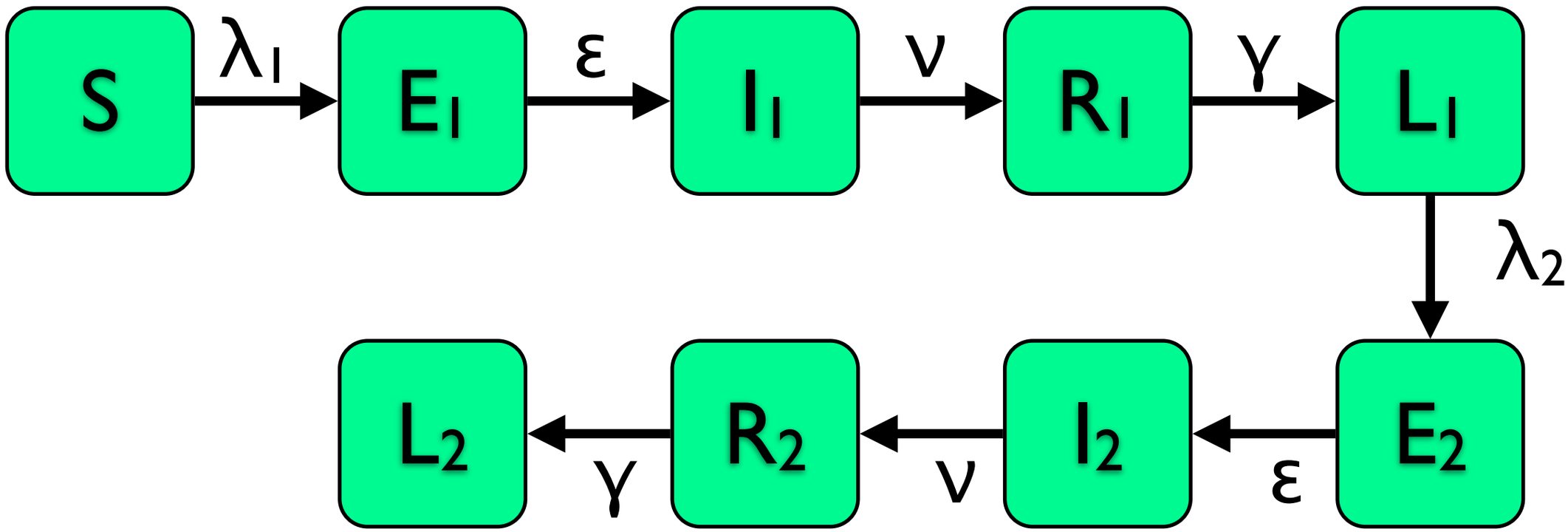


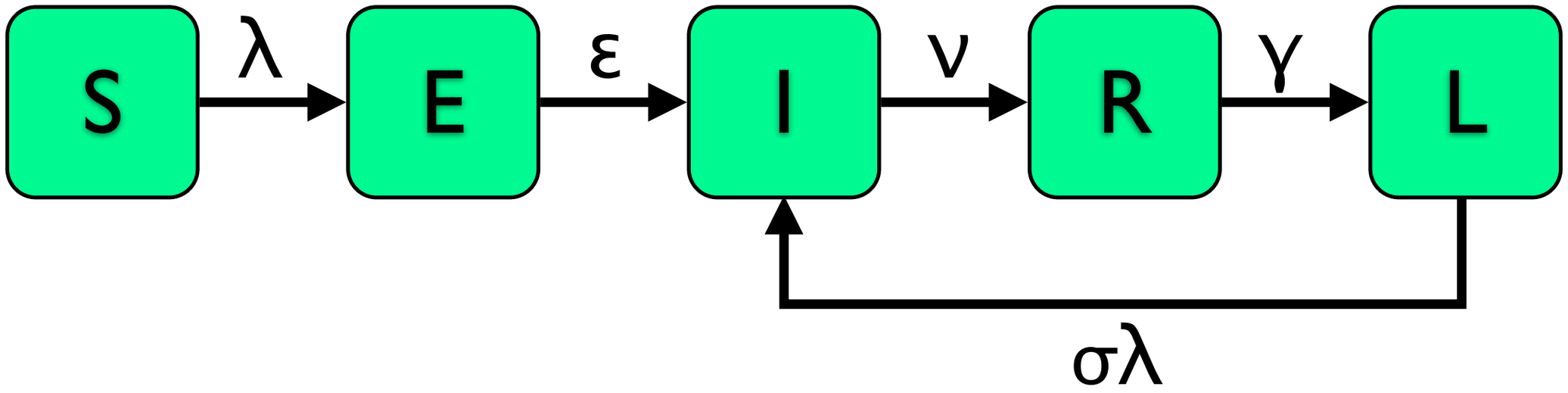
- σ ∈*[0,1]* cross-immunity
- 2-strain history-based model (Rios-Doria & Chowell 2009)

H2: two different viruses at the beginning



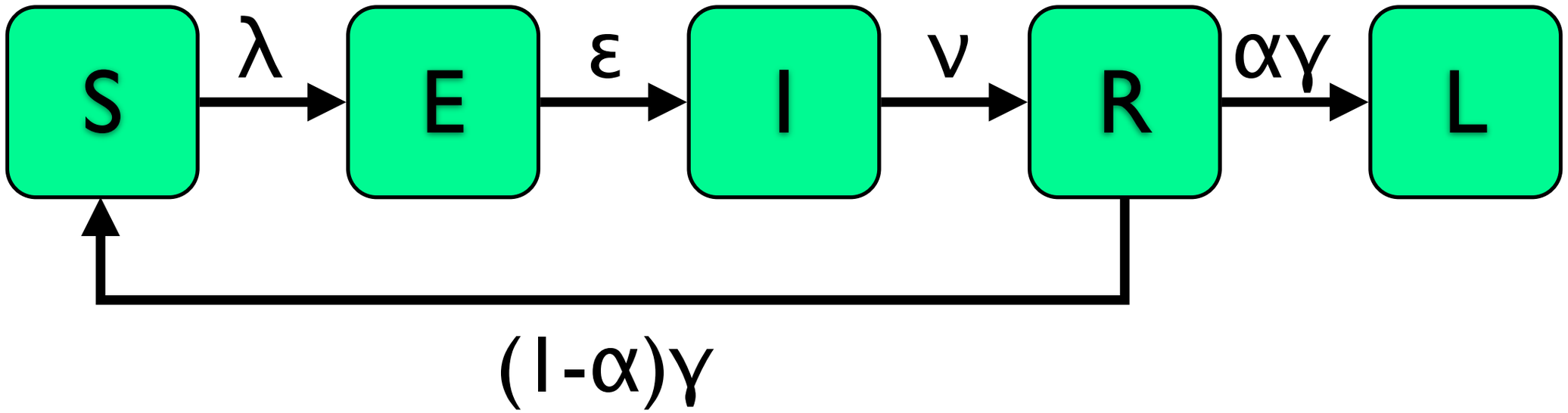
- no cross-immunity
- 2-virus history-based model

H3: partially-protective immunity



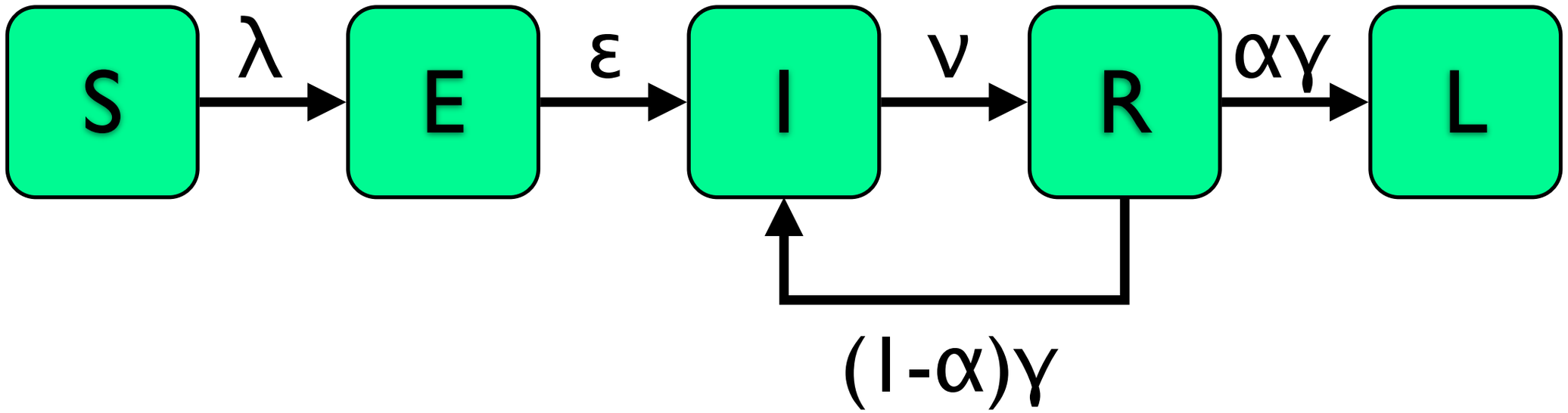
σ ∈*[0, 1]*: probability to be reinfected
(Gomes et al. 2004)

H4: All-or-Nothing



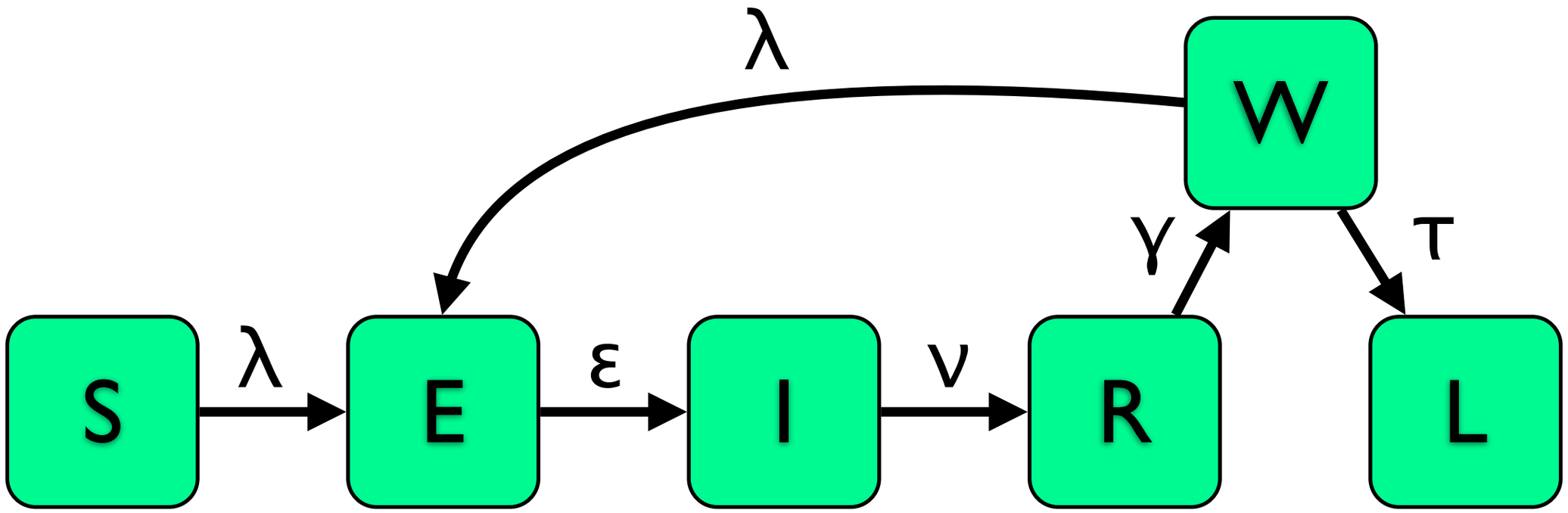
α: the probability to develop long-term immunity (Mathews et al. 2007)

H5: intra-host recrudescence of infection



α: the probability to clear the viral load

H6: window-of-reinfection



1/τ: the mean duration of the window of susceptibility before developing immunity

Likelihood-based inference

For a given time series: $y_{1:T} = (y_1, y_2, ..., y_T)$
and a state space model completely specified by:

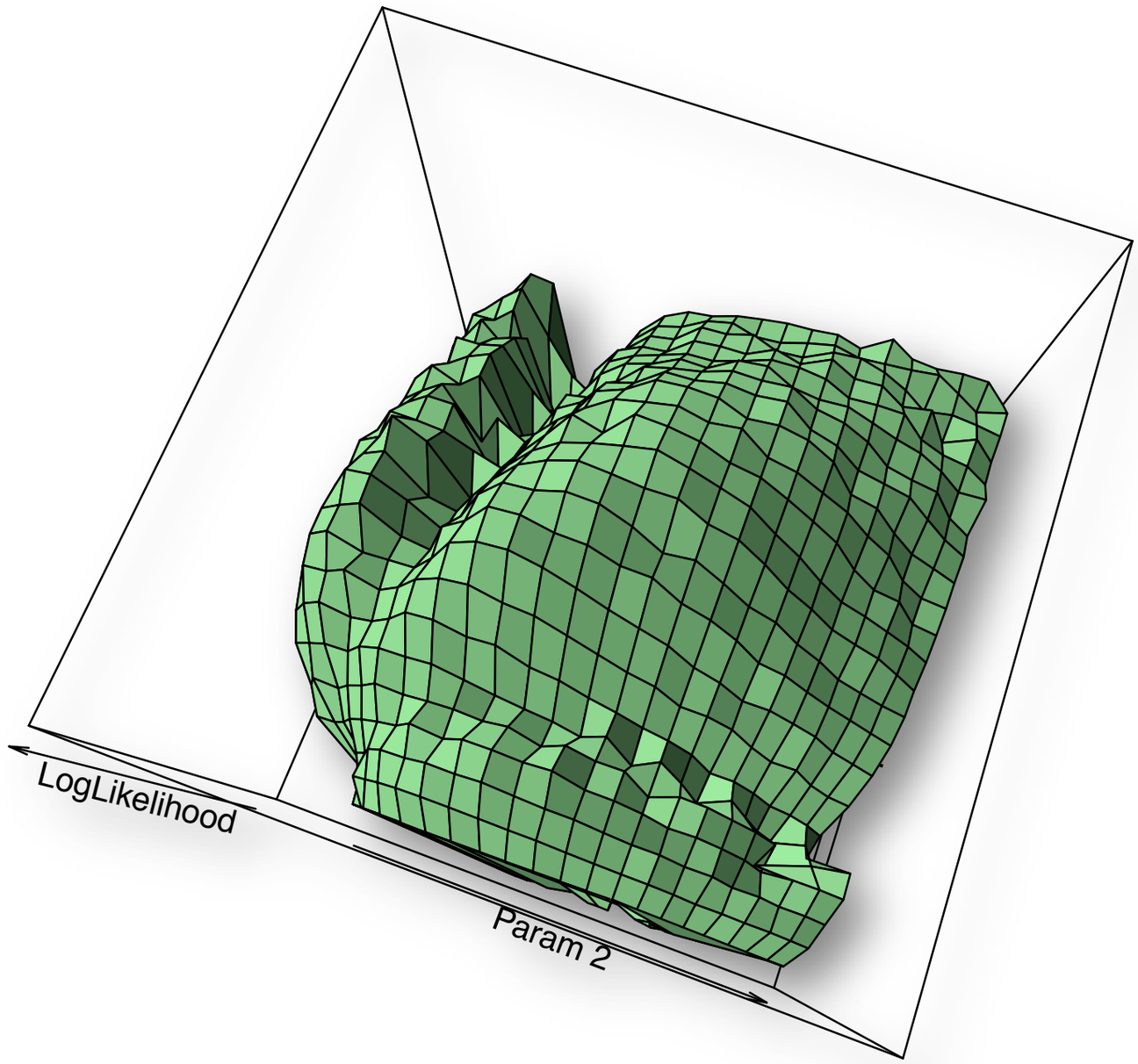
$$M : \begin{cases} f(x_t|x_{t-1}, \theta) & \text{the conditional transition density} \\ f(y_t|x_t, \theta) & \text{the conditional distribution} \\ & \text{of the observation process} \\ f(x_0|\theta) & \text{the initial density} \end{cases}$$

the likelihood is given by the identity:

$$f(y_{1:T}|\theta) = \prod_{t=1}^{T} f(y_t|y_{1:t-1}, \theta)$$

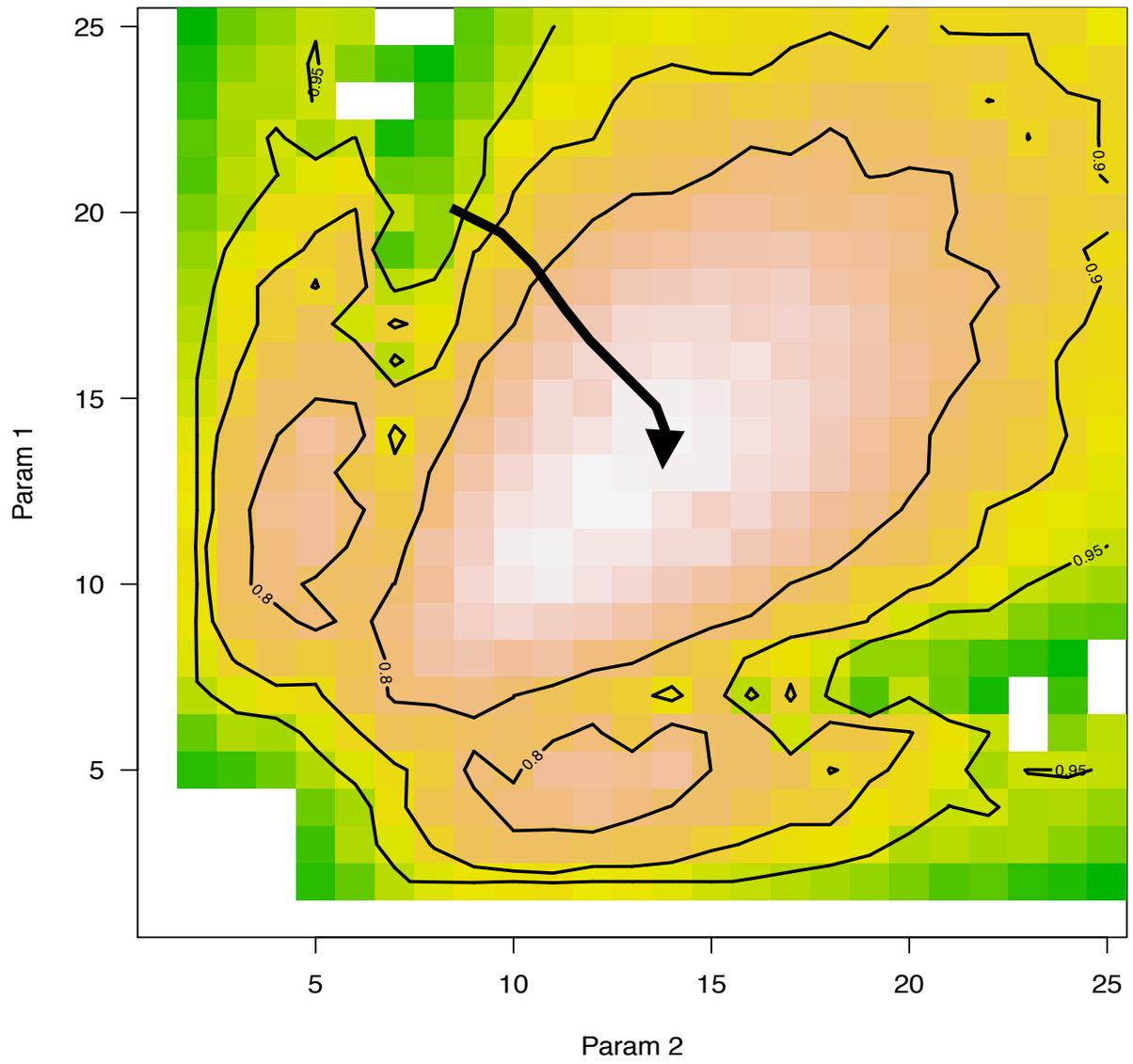
where x_t is the unobserved Markov process, θ is the unknown vector of parameters and $f(.|.)$ is a generic density specified by its arguments

Exploring the likelihood surface



Exploring the likelihood surface with MIF (Ionides *et al.* 2006)

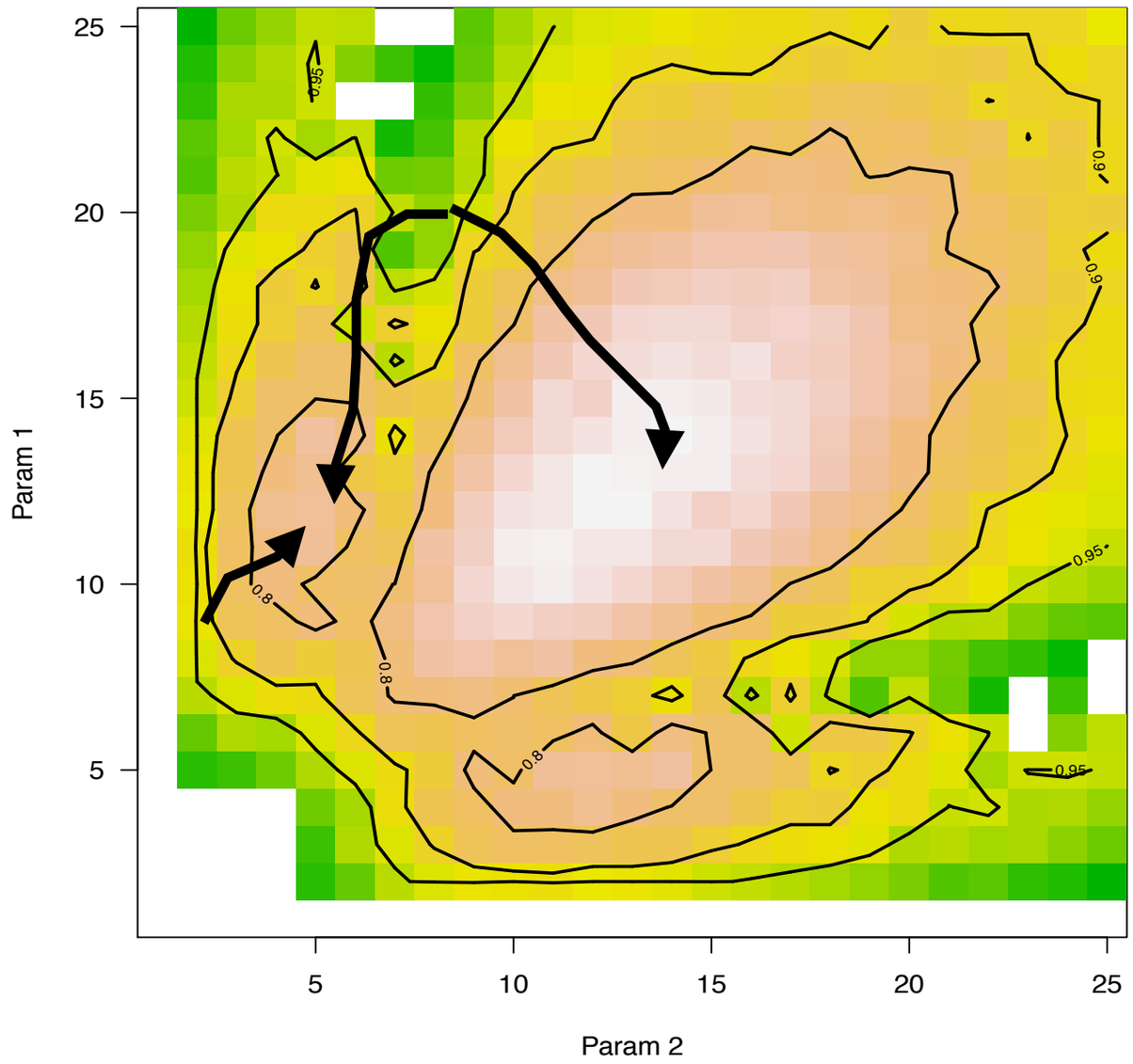
- 3 local maxima
- 1 global maximum



Global convergence

Exploring the likelihood surface with MIF (Ionides *et al.* 2006)

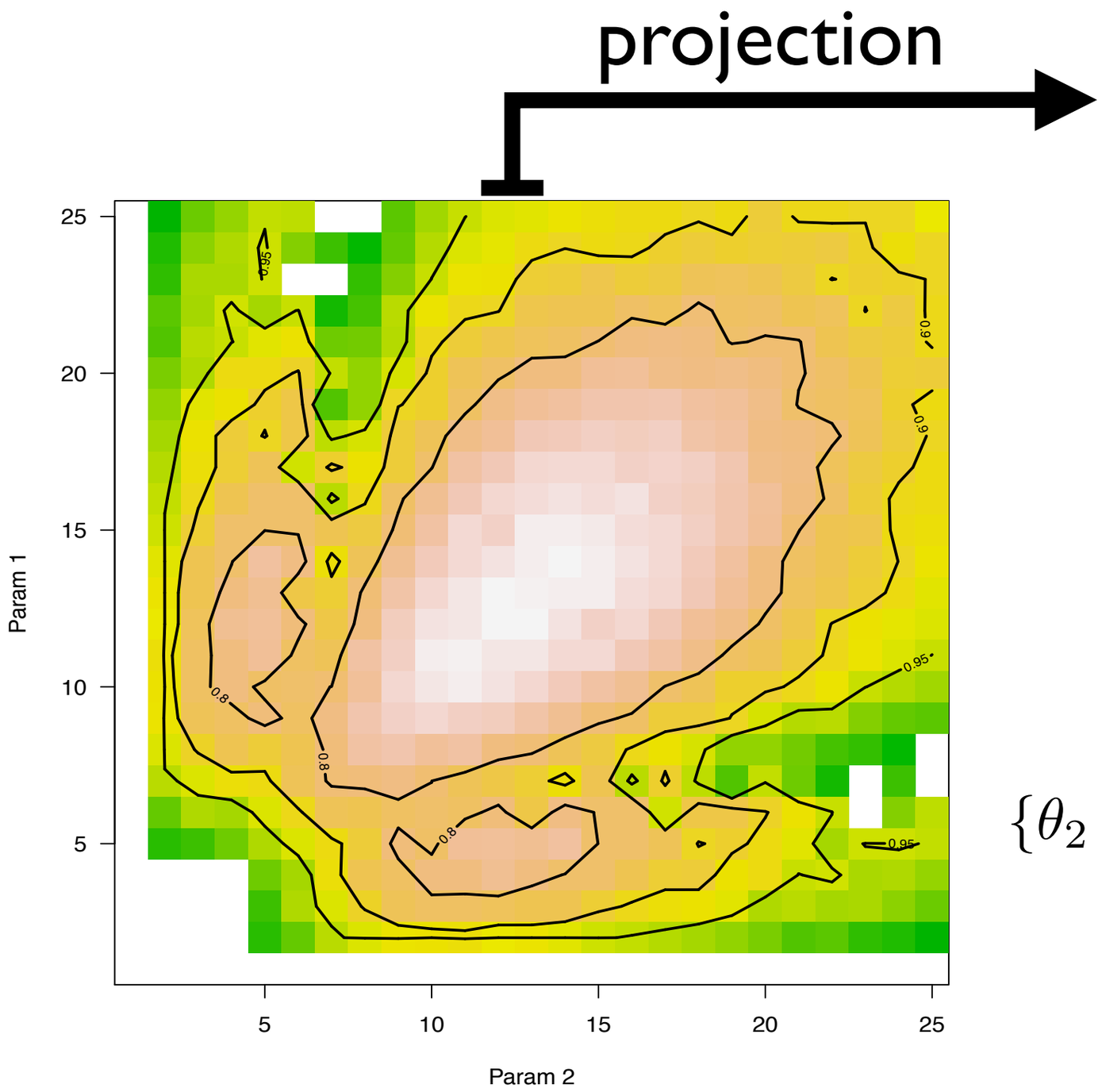
- 3 local maxima
- 1 global maximum

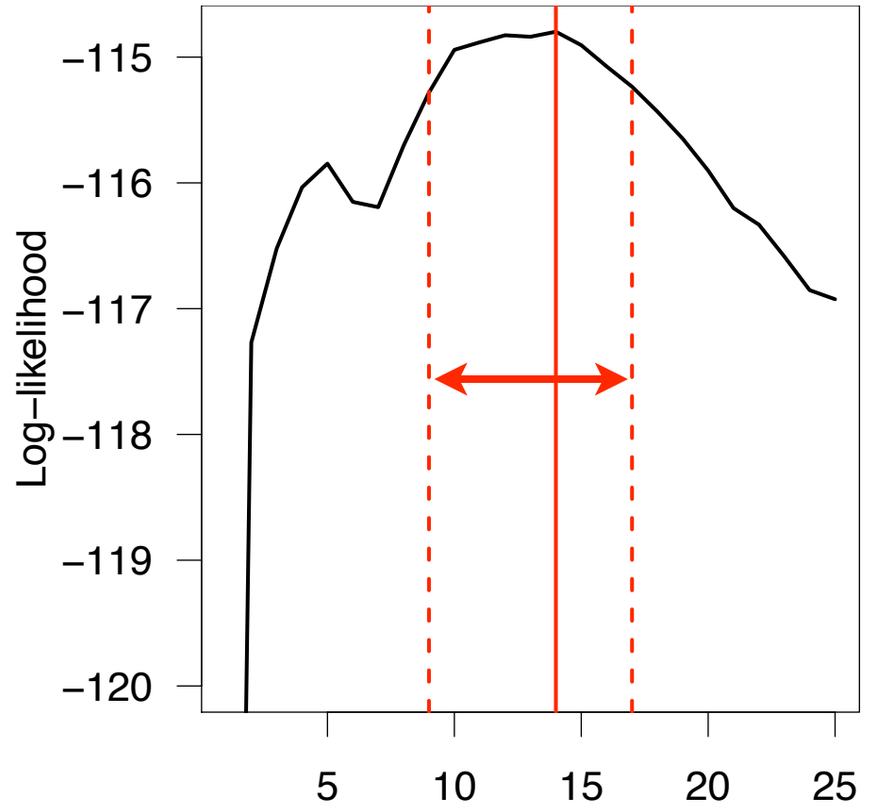


Local trap:

- initial θ
- MIF parametrization

Log-likelihood profile



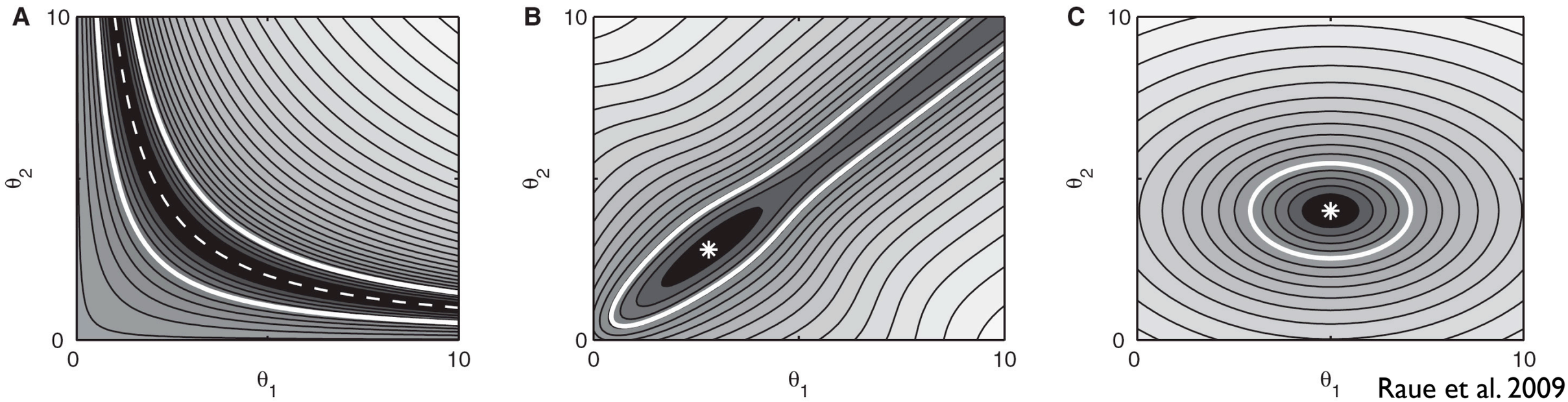


95% confidence interval:

$$\{\theta_2 : 2[l_{(p)}(\hat{\theta}_2) - l_{(p)}(\theta_2)] < \chi^2_{0.95}(1)\}$$

with $\hat{\theta}_2 = \text{argmax}\ l_{(p)}(\theta_2)$

Parameter identifiability



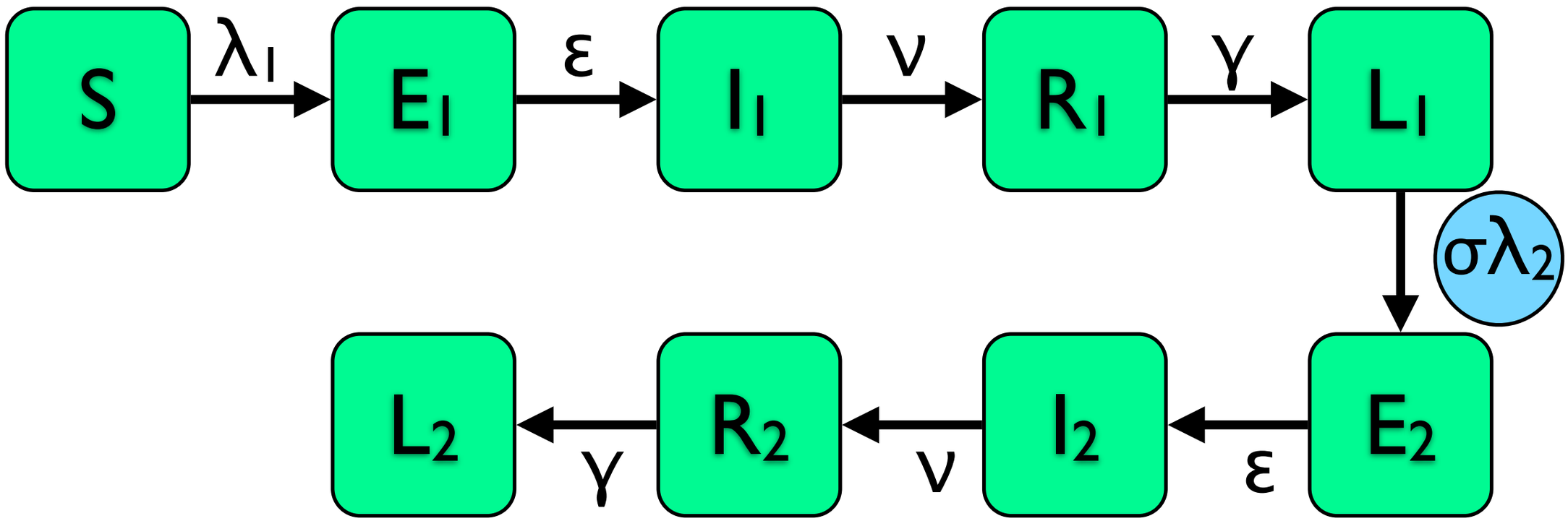
Raue et al. 2009

Structural non-identifiability

Practical non-identifiability

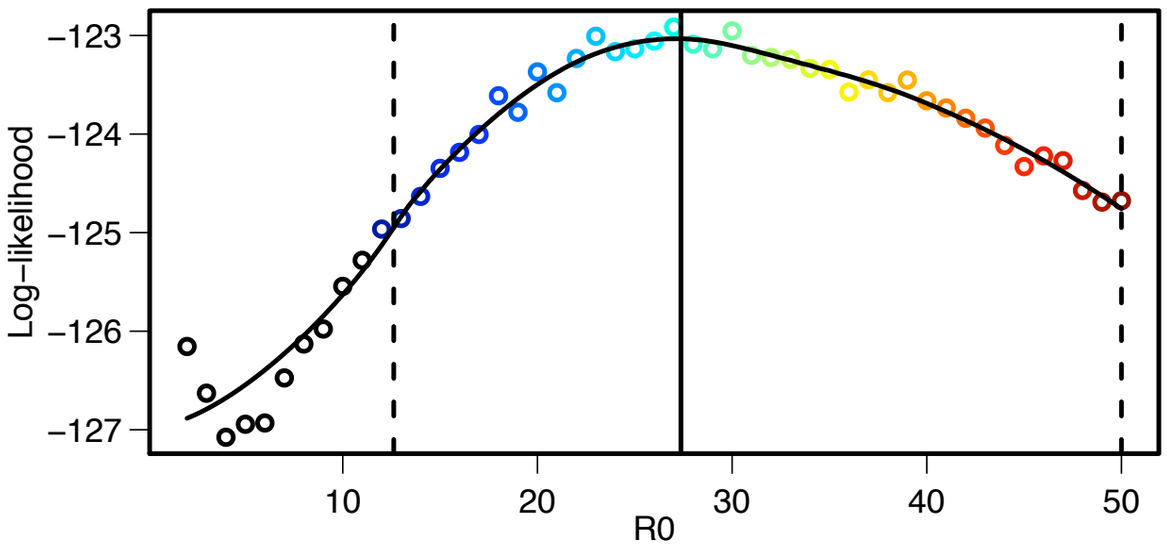
Identifiability

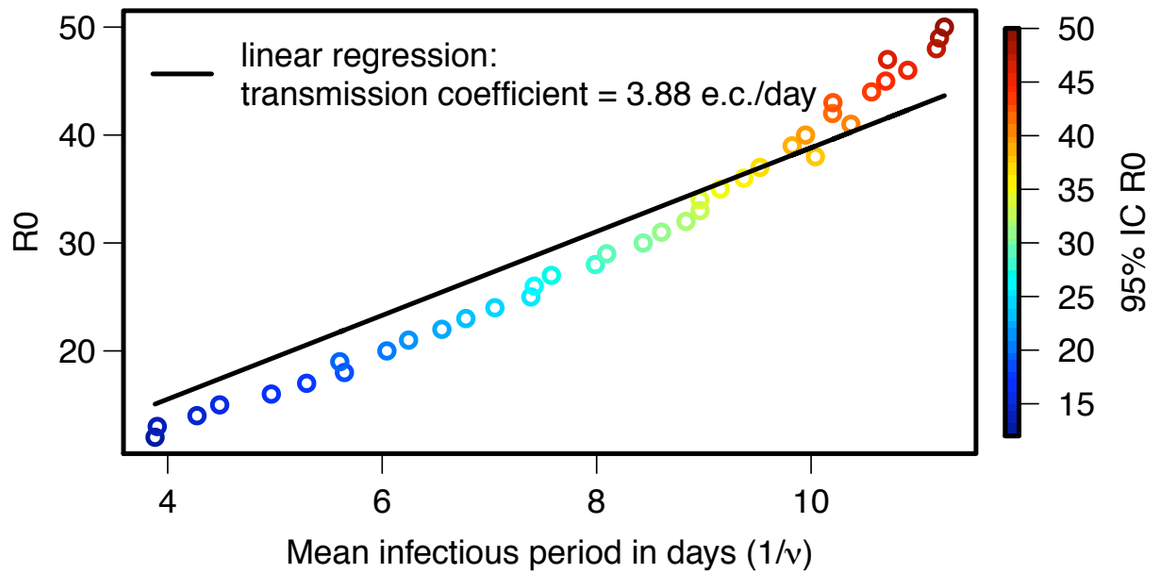
Structural non-identifiability (Mutation: H I)

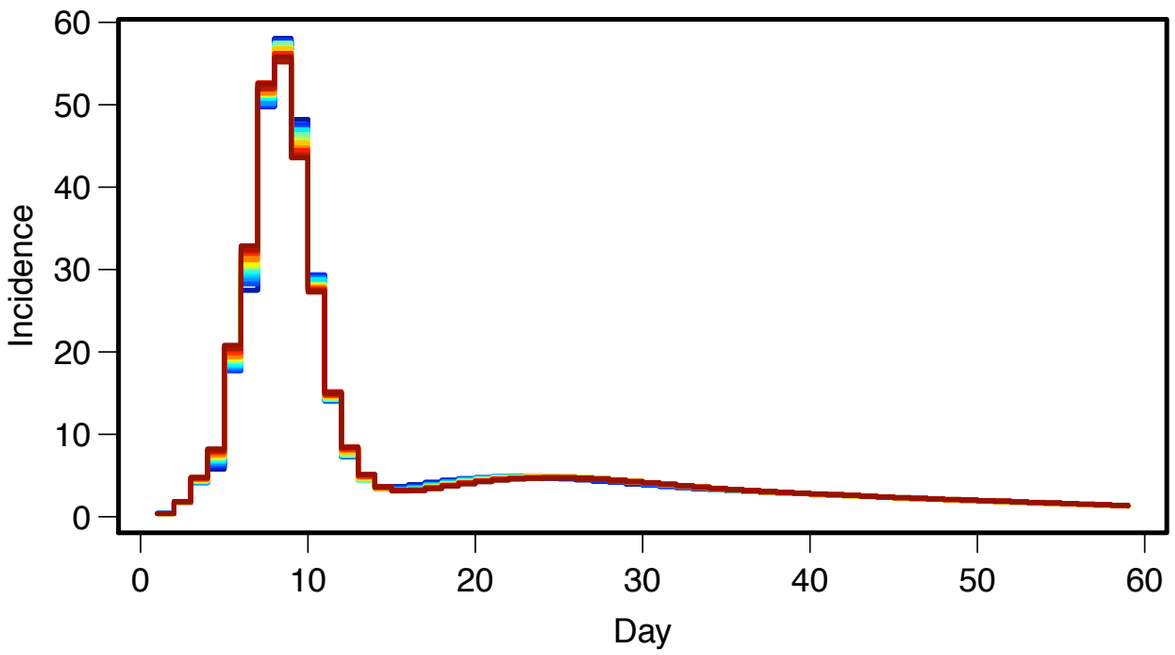


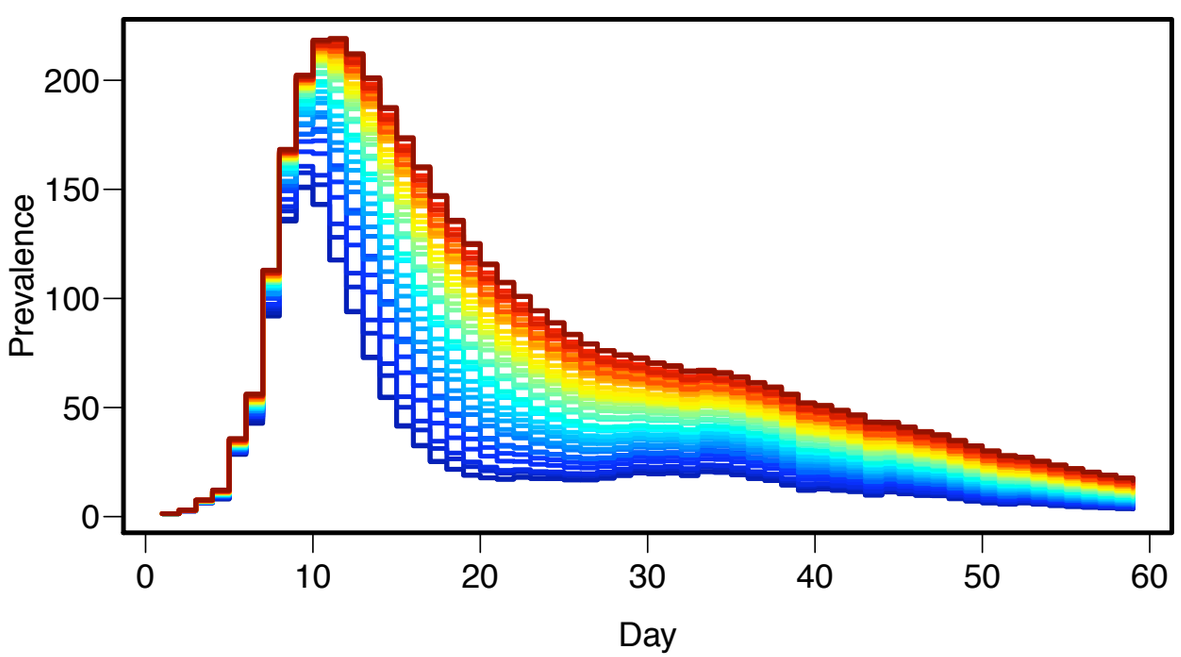
Structural non-identifiability between σ and $\beta_2 \Rightarrow \beta_2 = \beta_1$

Practical non-identifiability (In-Host: H5)









Model selection: Akaike information criterion

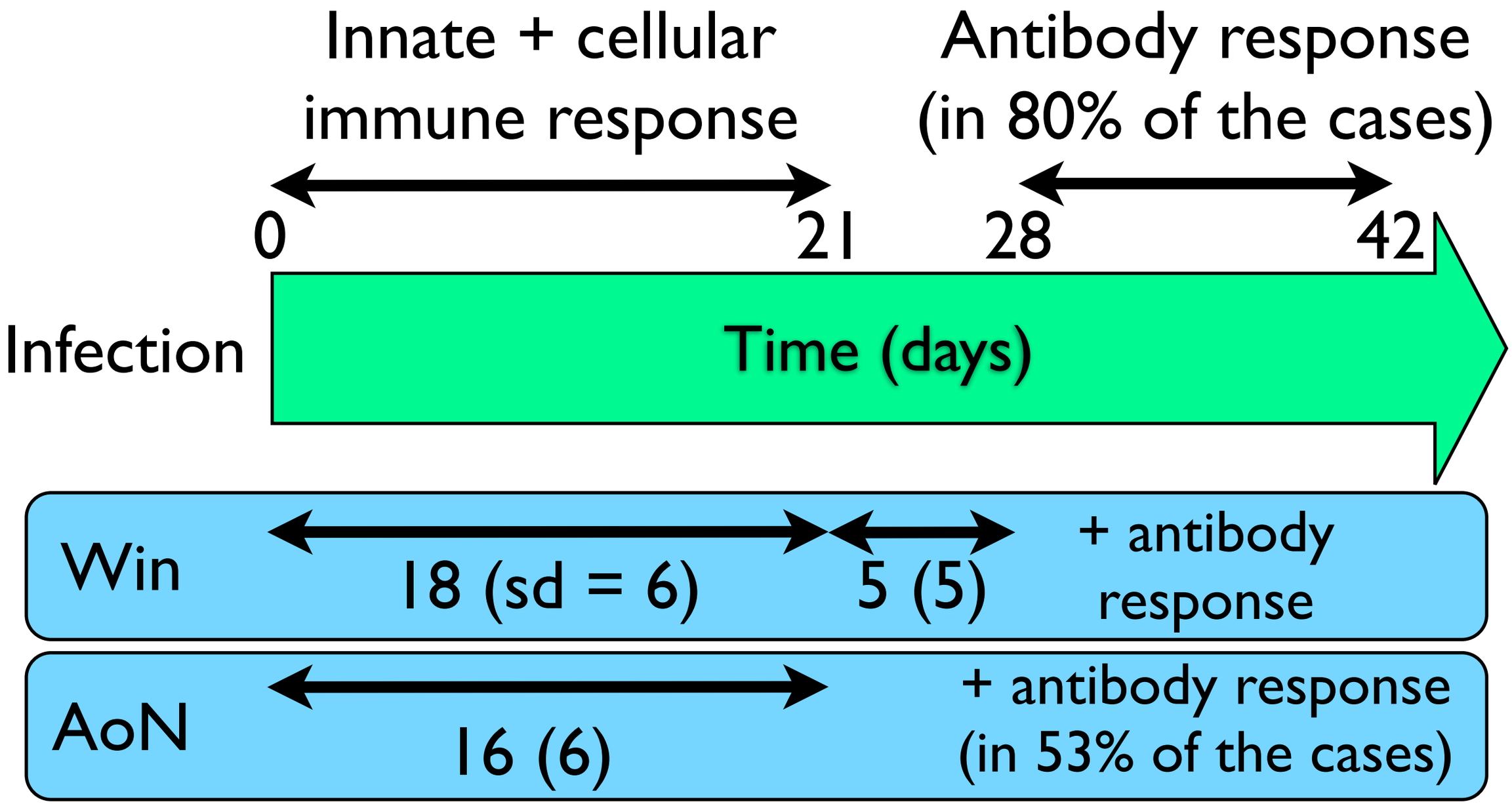
$$AIC_c = -2\mathcal{L}(\theta_{MLE}) + 2k + \frac{2k(k+1)}{T-k-1} \text{ with } k = ||\theta||$$

Model	Win	AoN	2Vi	Mut	In-Host	PPI
k	9	9	10	10	9	9
Log-Like	-112.52	-112.78	-114.75	-115.20	-117.50	-118.44
ΔAIC_c	0	0.52	7.37	8.27	9.96	11.84

Maximum likelihood parameters

Parameter	Win	AoN
$R_0 = \beta/\nu$	10.38	11.27
Mean latent period (days)	2.14	2.11
Mean infectious period (days)	2.01	2.43
Mean removed period (days)	13.58 (shape 5)	11.62 (shape 4)
Reinfection window (days)	4.86	-
Probability of long-term immunity	-	0.53

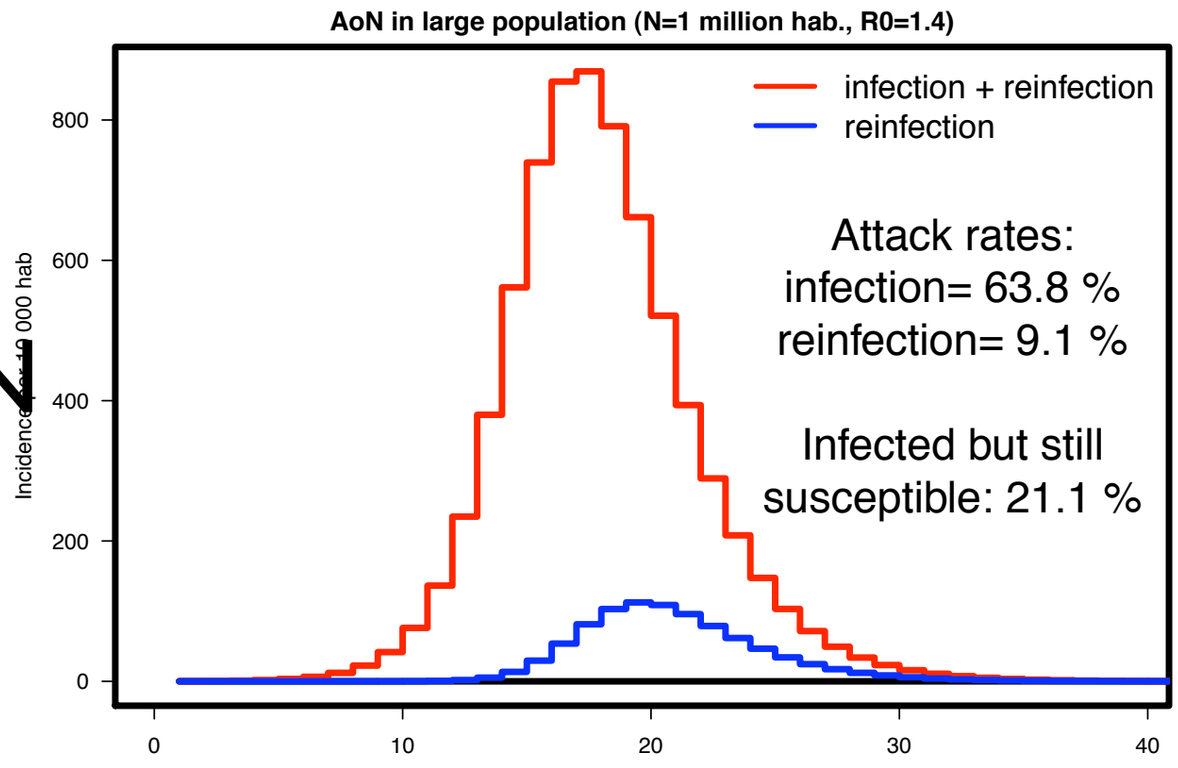
Immunological support: primary influenza infection

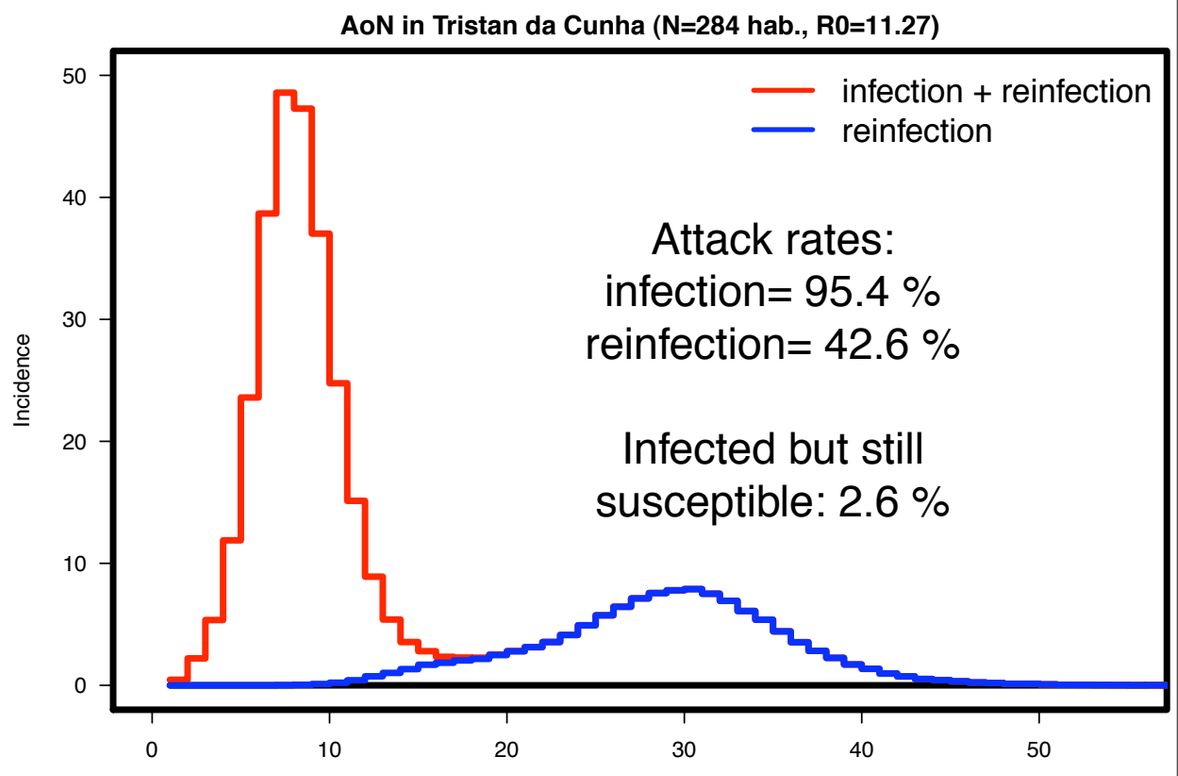


Large pop:
N = 1 million hab.
R_0 = 1.4 ($2009\ pH_1N_1$)

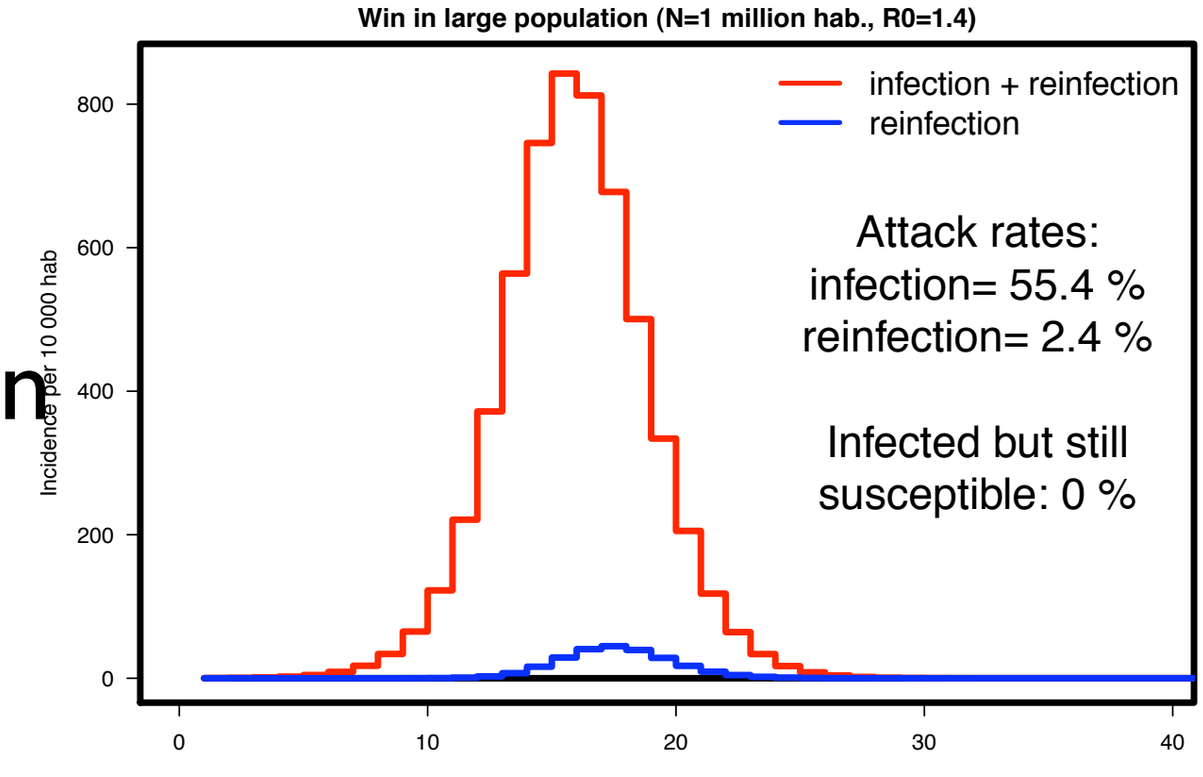
Tristan da Cunha:
N = 284 hab.
$R_0 \approx 11$

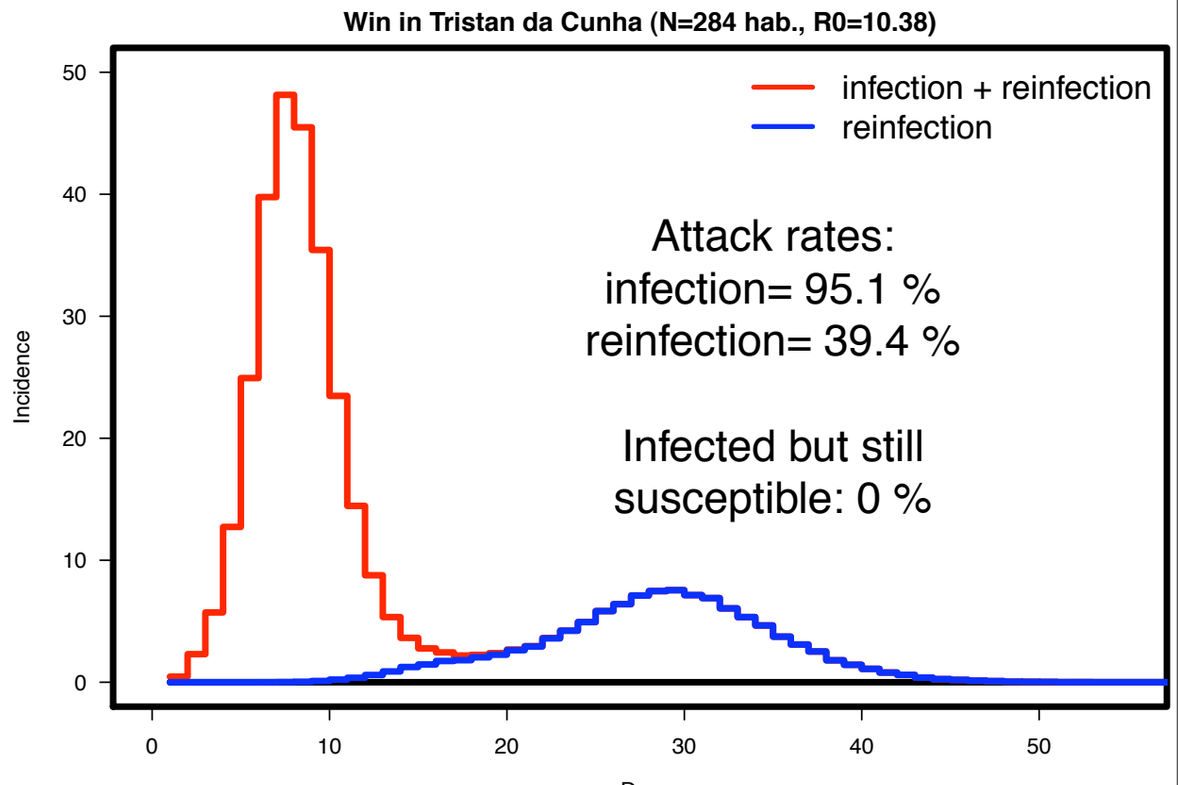
AoN





Win





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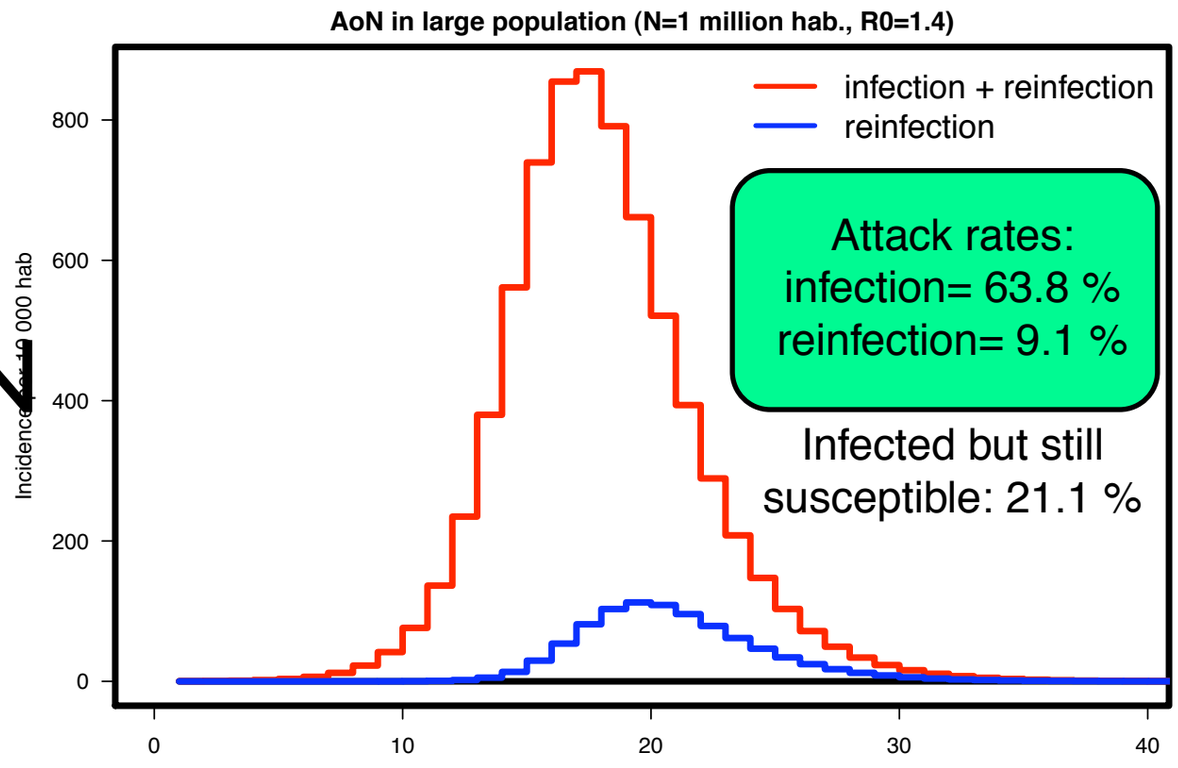

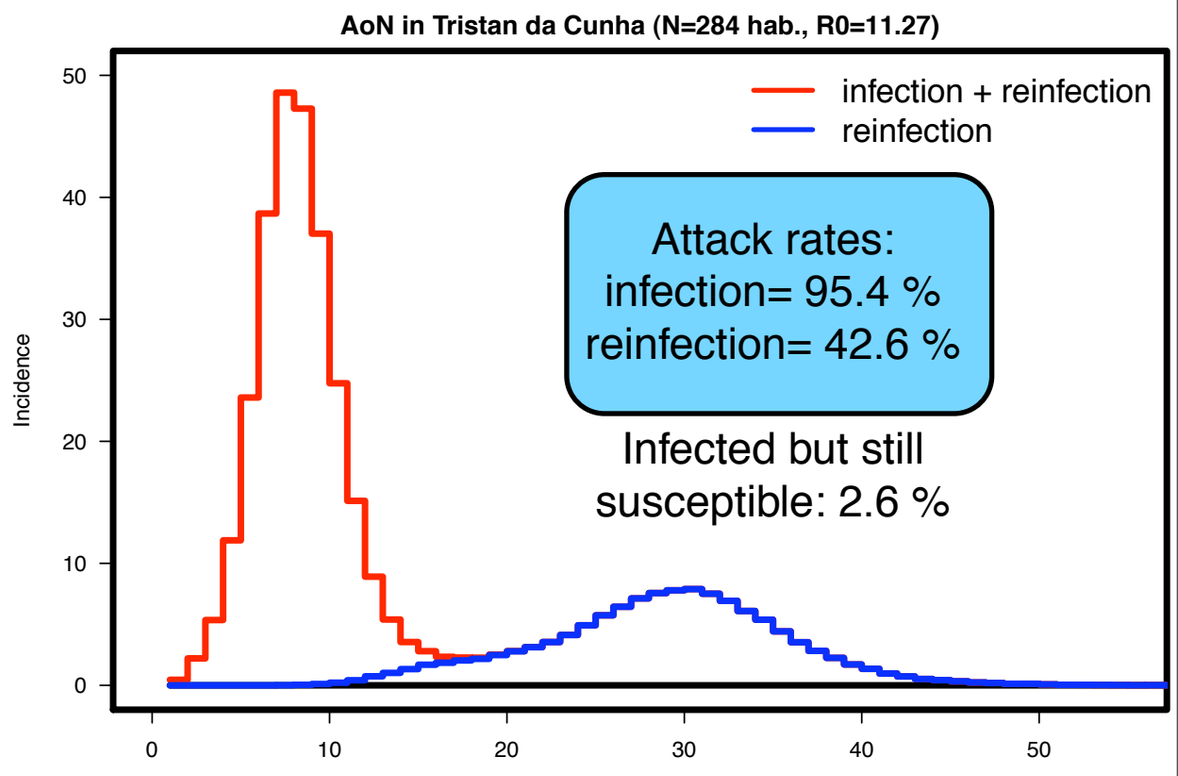

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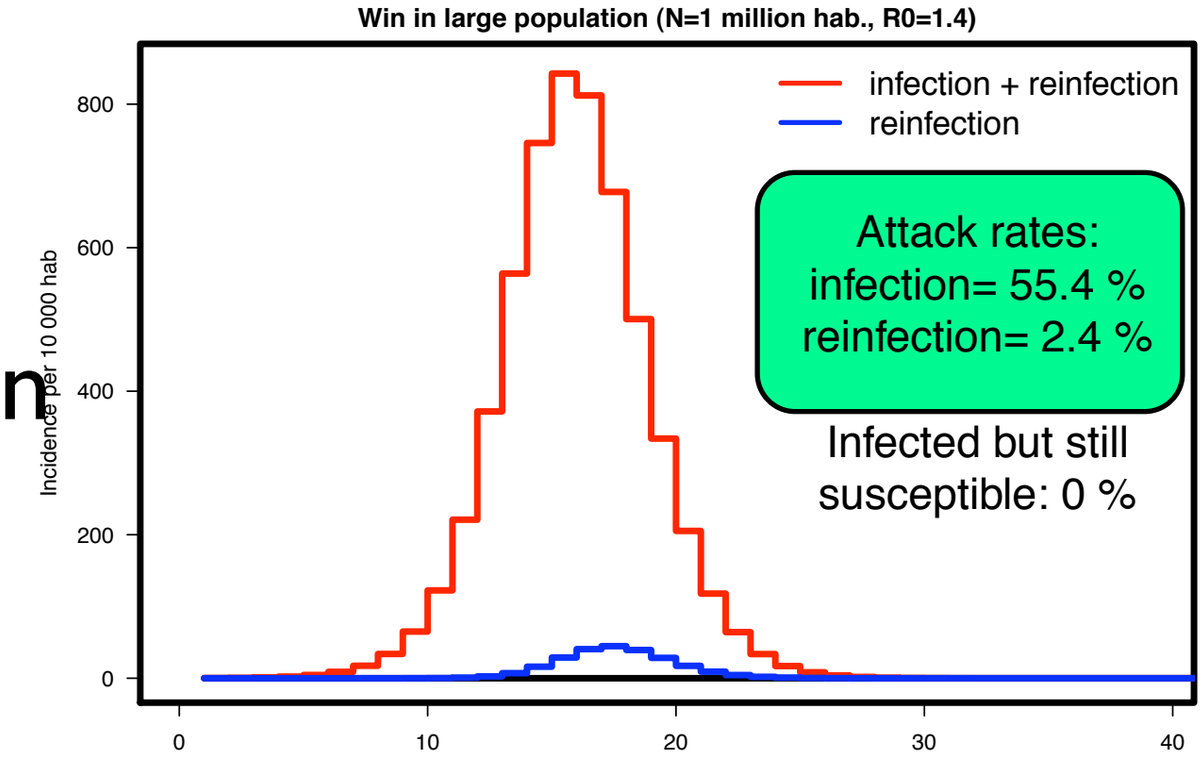

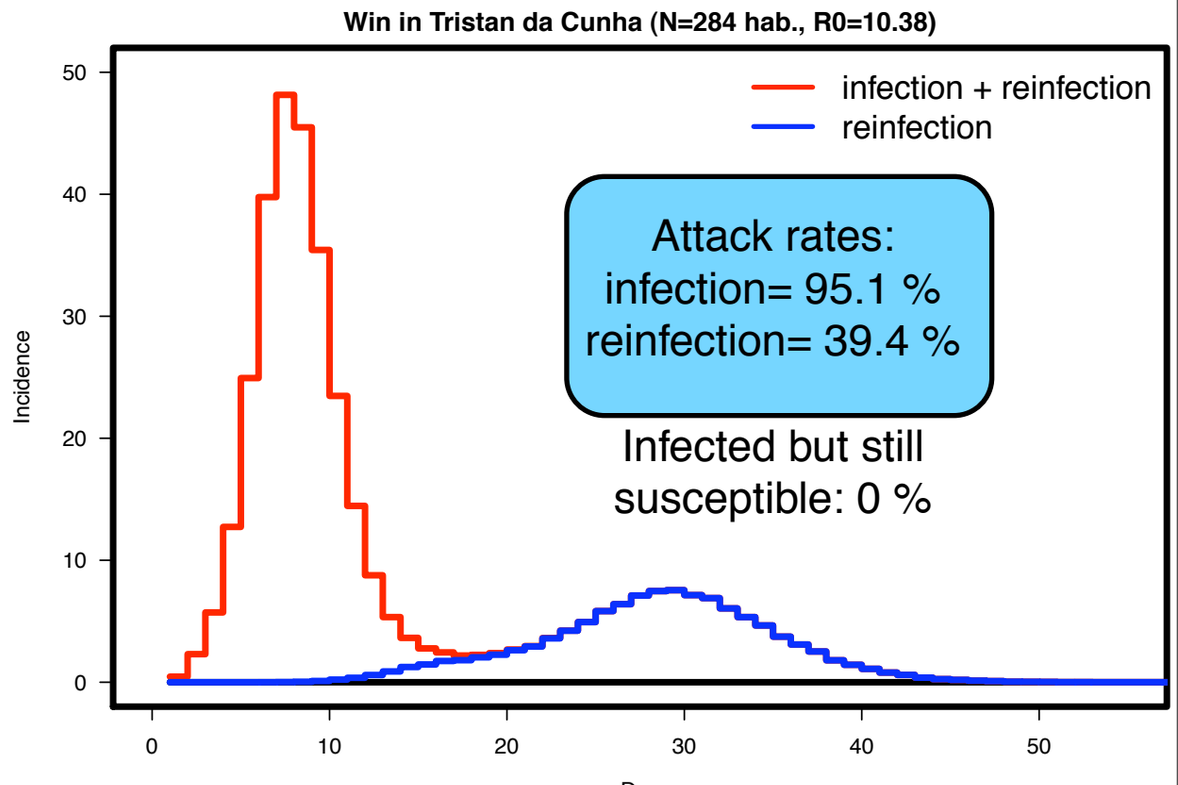

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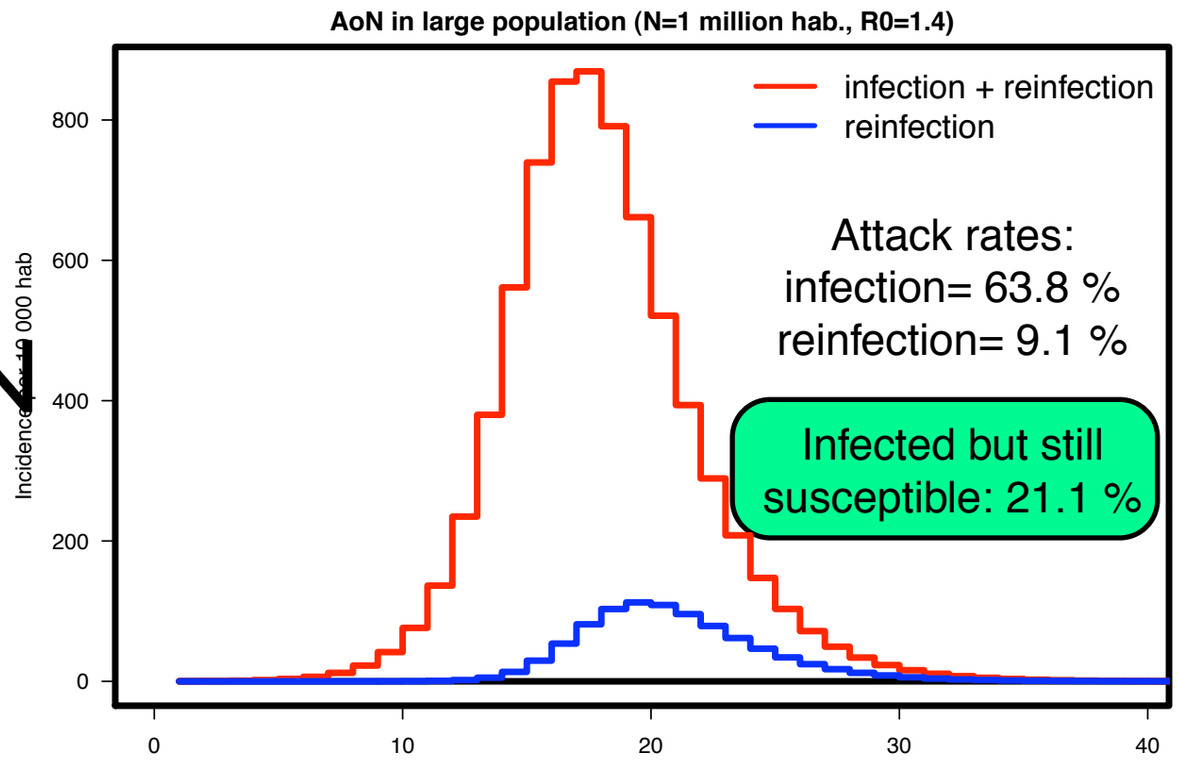

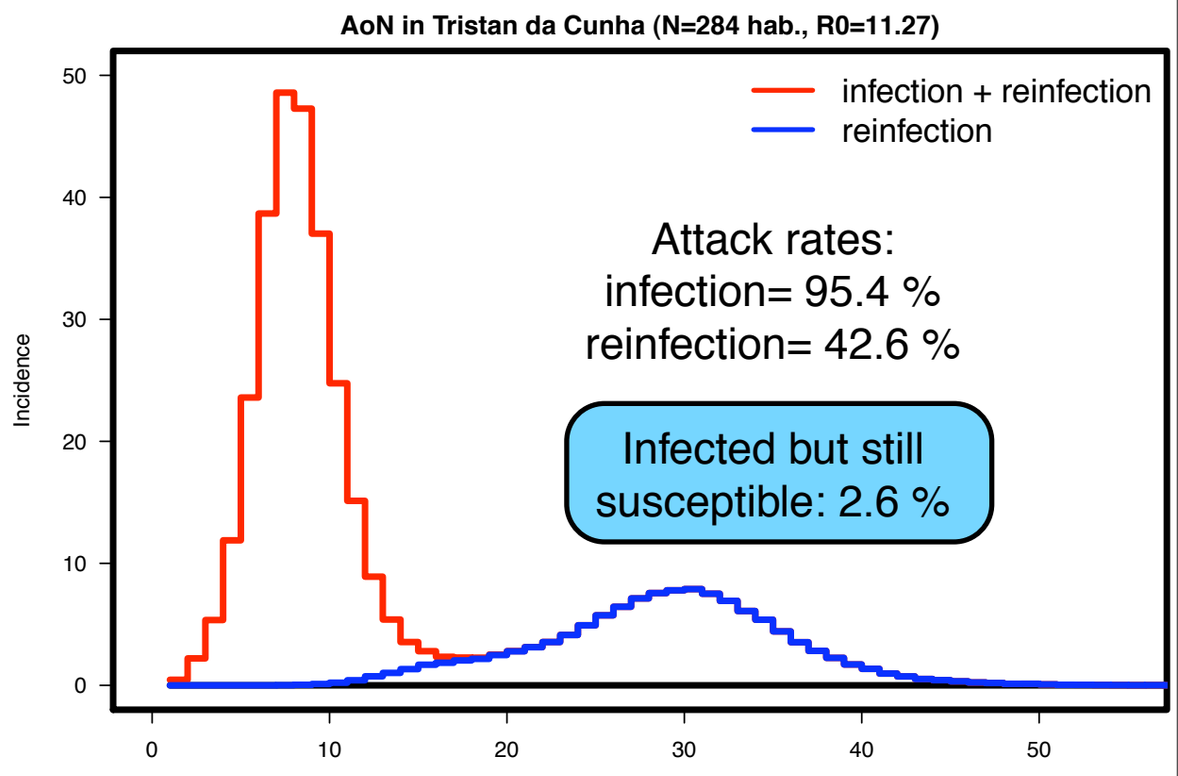

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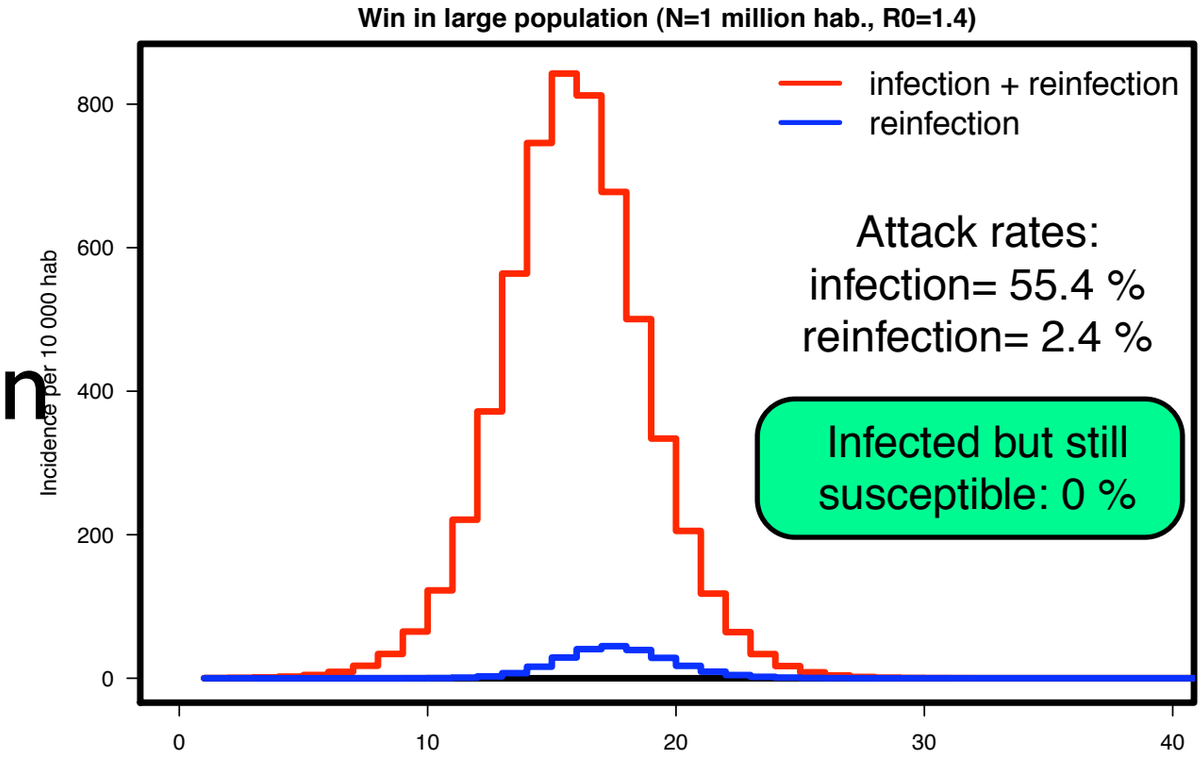

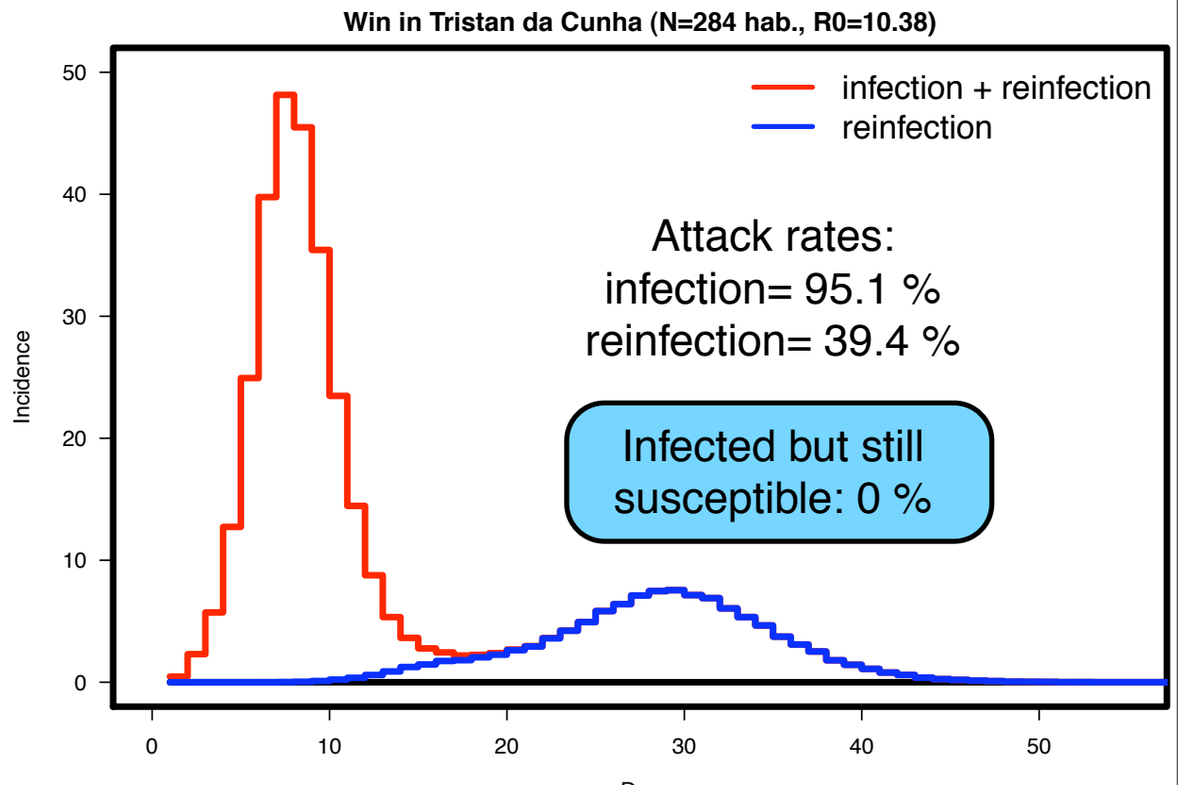

Conclusion

- Maximum likelihood via Iterated Filtering (MIF, Ionides *et al.* 2006) is a rigorous statistical framework for parameter inference and selection based on AIC for non-linear stochastic models.
- Identifiability analysis and 95% CI via log-likelihood profile
- Rapid influenza reinfection is likely due to a combination of ecological and immunological factors:
  1. Window-of-reinfection (Win) + high exposure
  2. Lack of antibody response (AoN) + re-exposure
- During a pandemic, the lack of antibody response has a greater impact than the window-of-reinfection (break of herd immunity)
- Experimental validation and accurate predictions with a more realistic large population model (heterogeneous mixing, seasonal forcing, external reintroduction, pre-existing immunity, etc.)