Uncertainty Analysis & Communication

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Sensitivity analysis: deterministic epidemic models

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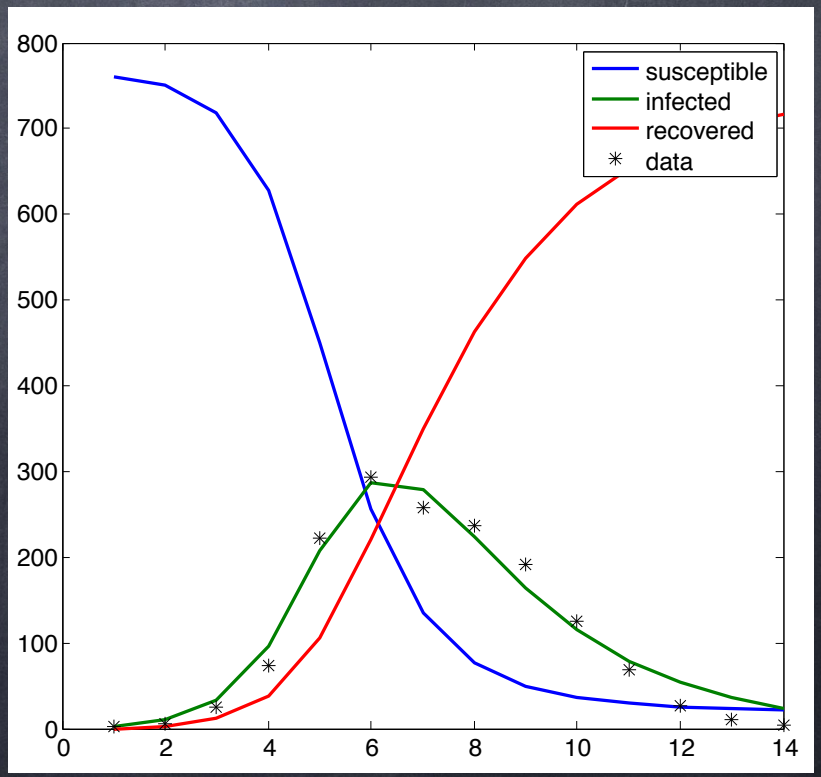
- Resorted to simple(ish) methods for inferring key quantities of interest



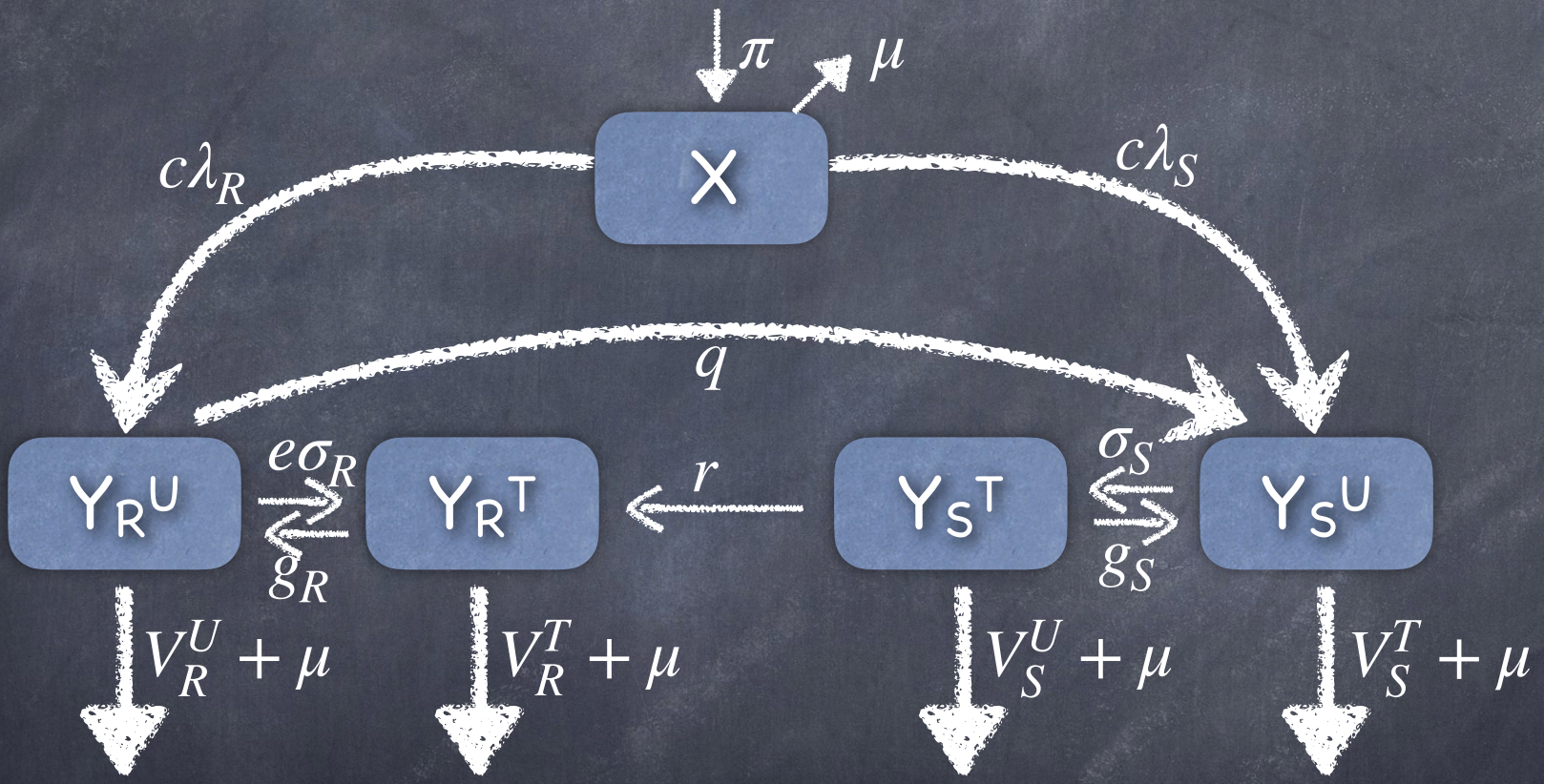
Sensitivity analysis: deterministic epidemic models

- So far, have dealt with reasonably simple models
- Few state variables and, critically, few parameters
- Resorted to simple(ish) methods for inferring key quantities of interest
- Complex models have many parameters about which we may have little information

Motivation

- In 2000, ~30% of gay men in San Francisco were infected with HIV, 50% of whom were taking combination antiretroviral therapy (ART)
- ART effective at reducing AIDS death rate in San Francisco, but does not completely eliminate infectivity
  - unclear whether net effect of increased distribution of ART would be to increase or decrease incidence of HIV
- Blower et al. introduced following model (Blower et al. 2000. A tale of two futures: HIV and antiretroviral therapy in San Francisco.Science 287:650-654.)

Blower et al. (2000) model



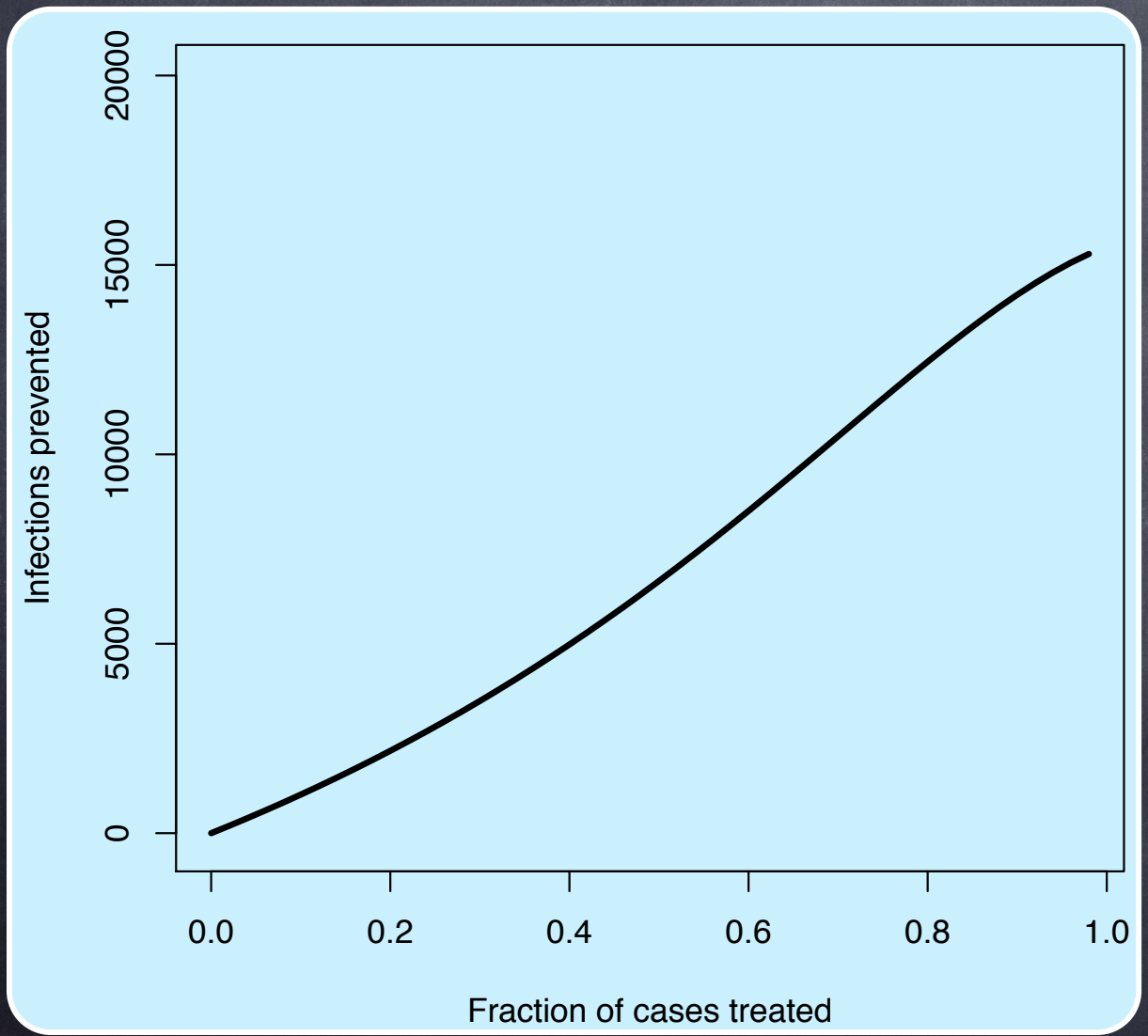
X -- susceptible

Y_R^U -- untreated, infected with drug-resistant strain etc

Lots of model parameters

- π -- rate at which gay men join sexually active community
- $1/\mu$ -- average time during which new partners are acquired
- c -- average number of new sex partners per year
- p -- probability of a drug-resistant case (relative to a drug-sensitive case) transmitting drug-sensitive viruses
- 1/q -- average time for an untreated drug-resistant infection to revert to a drug-sensitive infection
- σ -- per capita effective treatment rate
- e -- relative efficacy of ART in treating drug-resistant infections
- r -- rate of emergence of resistance due to acquired resistance
- g -- proportion of cases that give up ART per year
- ν -- average disease progression rate

Model predictions



- ART could prevent ~15,000 cases of 20 years
- How reliable is this?
- Model has 20 parameters
- Few (if any) known exactly

Sensitivity analysis: deterministic epidemic models

- To know robustness of model predictions, require a way of exploring output of a family of parameterized models
- If number of unknown parameters is bigger than, say, 2-4 then systematic grid search would be computationally intractable
- Qualitatively investigate variability in model output that is generated from uncertainty in parameter inputs
- Perform multiple model evaluations using randomly chosen values for parameters

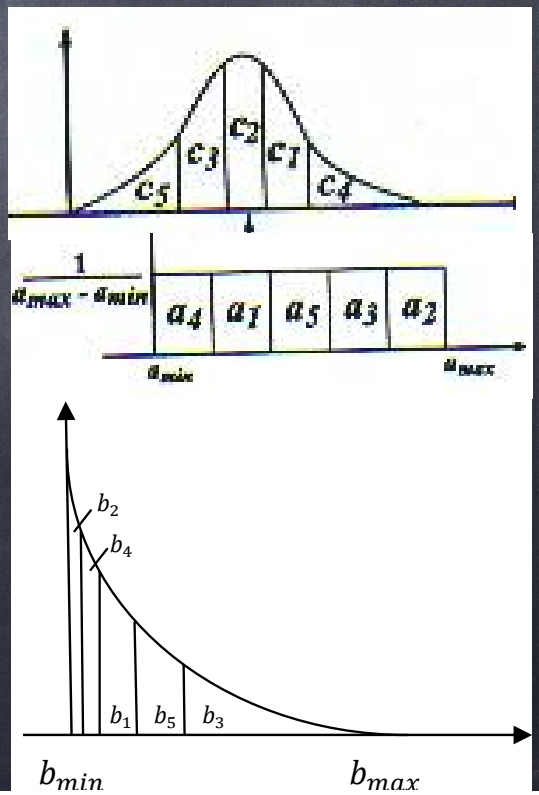
Monte Carlo analysis

- Assume parameters described by specific distribution and split parameter space into equal width intervals
- Then choose one from each interval

$0 < \beta < 10$ Normal distribution

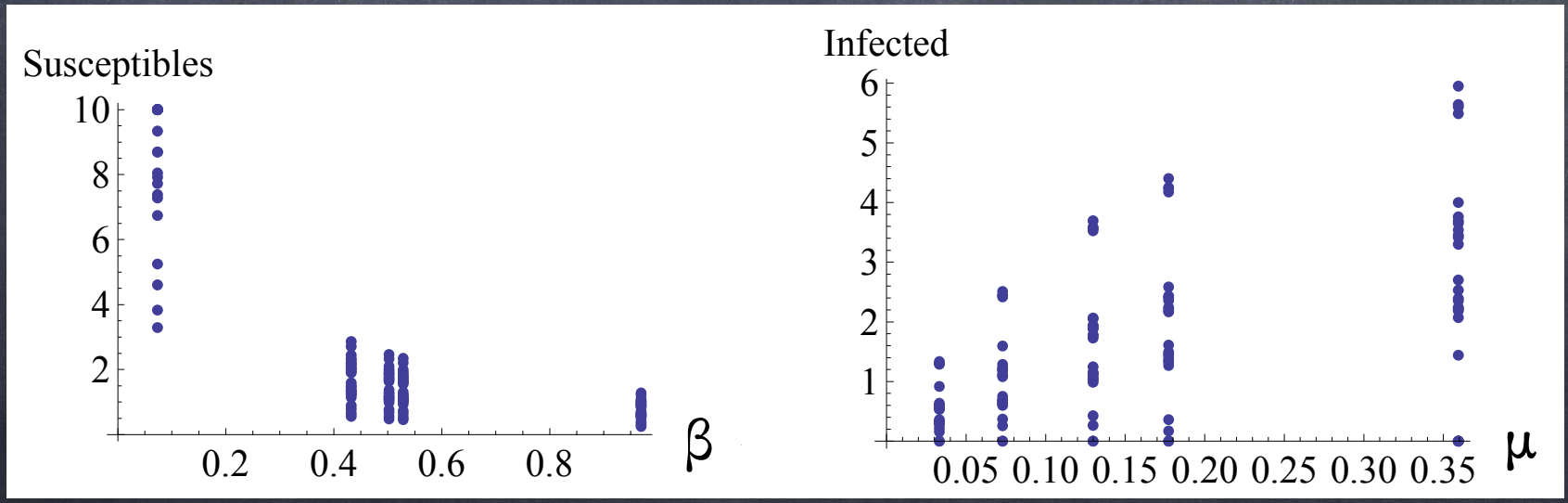
$1/7 < \gamma < 1$ Uniform distribution

$0 < \mu < 1/2$ Beta distribution



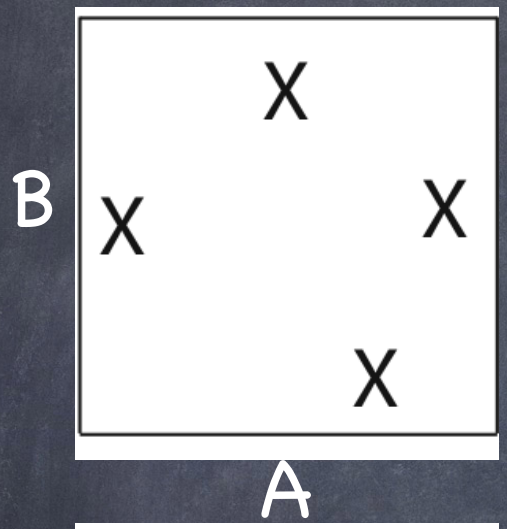
Monte Carlo analysis

- Using parameter combinations determined by Monte Carlo simulation, examine scatter plots of output against each parameter



- Problem: for SIR model, if we choose 5 random values for each parameter, need to perform 5^3 computations

Assume 2 unknown parameters



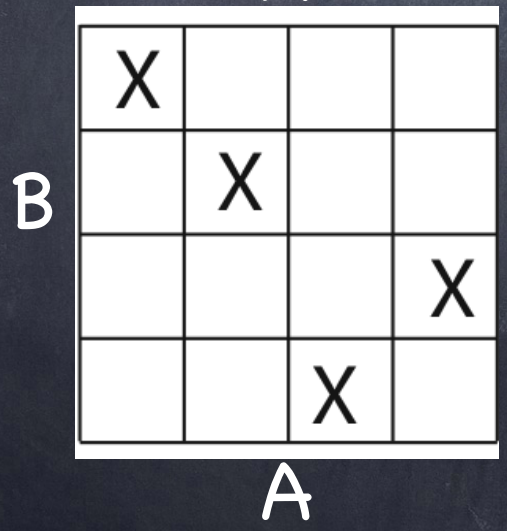
In **random sampling**, new sample points are generated without taking into account previously generated sample points

eg, for i=1:10

$A(i) = rand*(A_{max} - A_{min}) + A_{min};$

$B(i) = rand*(B_{max} - B_{min}) + B_{min};$

end



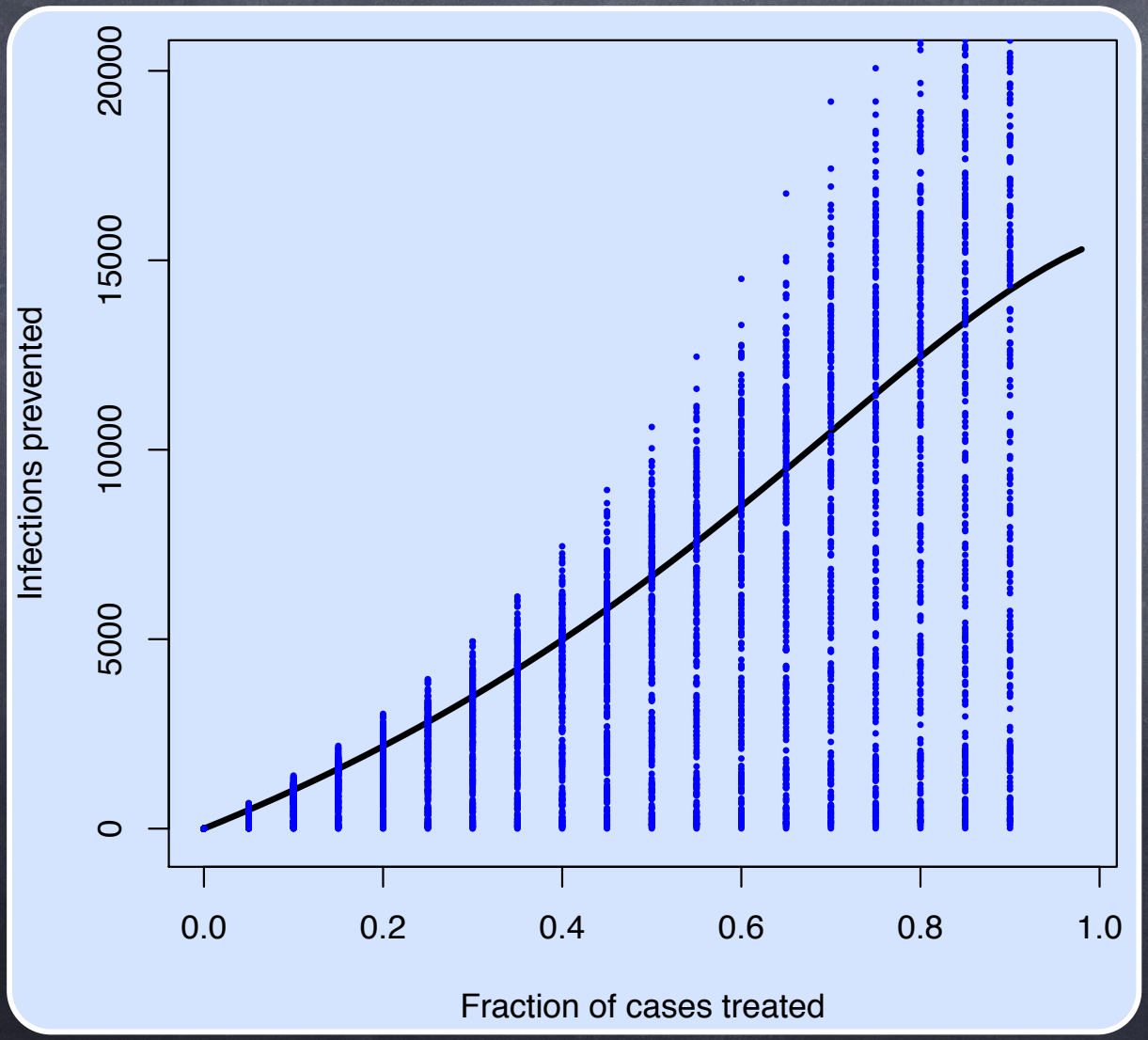
In **Latin Hypercube sampling** one must first decide how many sample points to use and for each sample point remember in which row and column sample point was taken

Packages available for use in R & Matlab

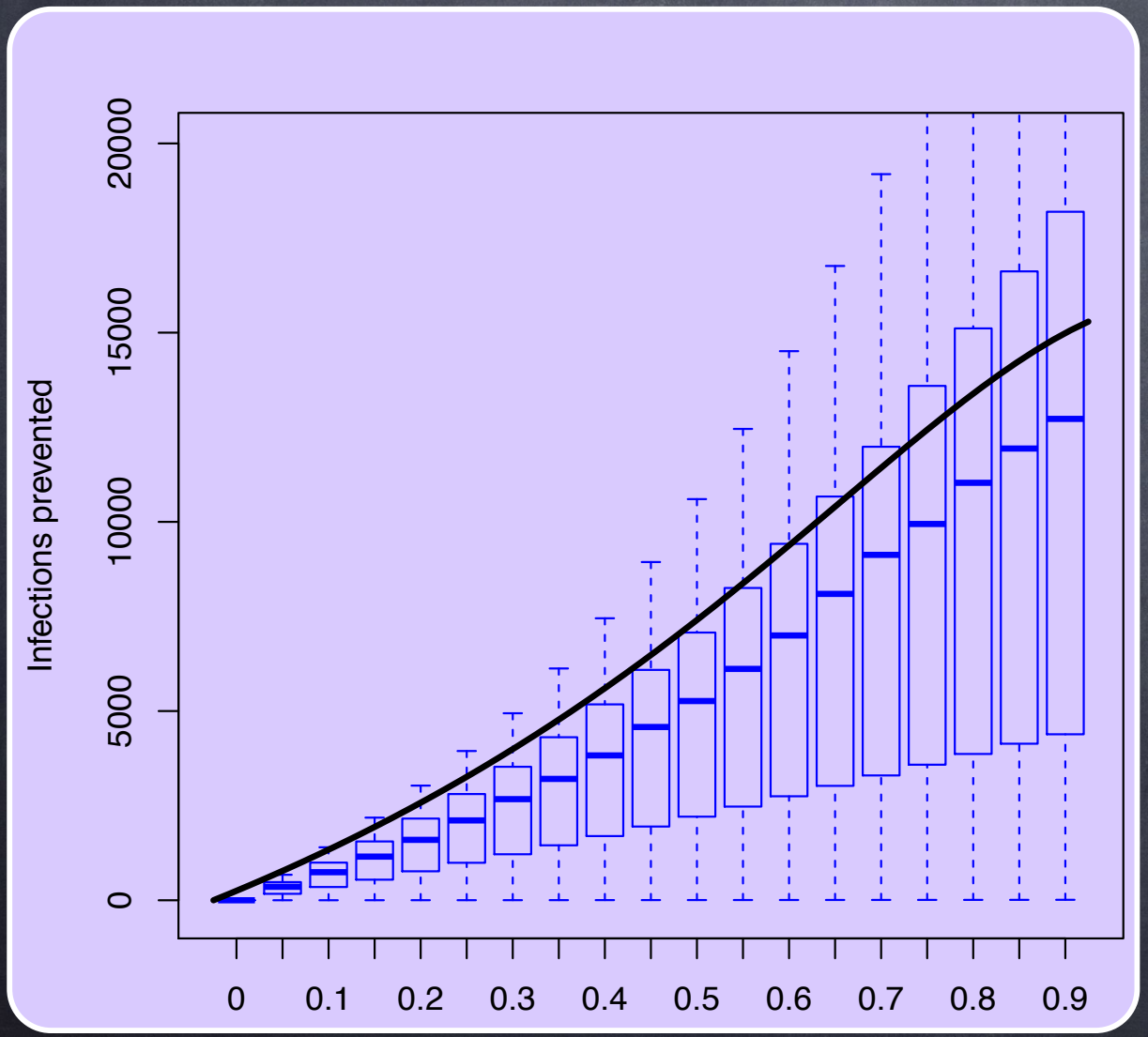
Typically, LHS random numbers in unit interval (0,1)

Need to 'stretch': $A = LHS\_rand*(A_{max}-A_{min})+A_{min}$

Results of LHS
Specified ranges of 18 parameters



Box-Whisker plot

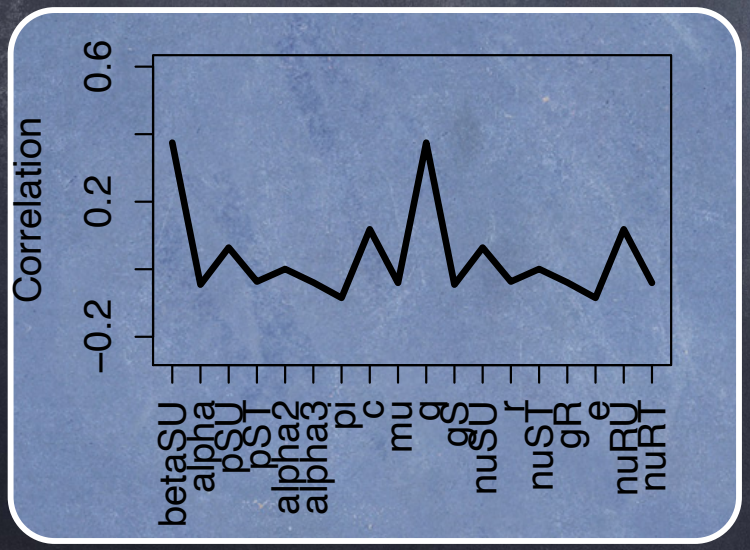


Evidently, our best guesses at parameter values are somewhat optimistic

At least ART is not found to be counter-productive in this respect → an open question at time of this study

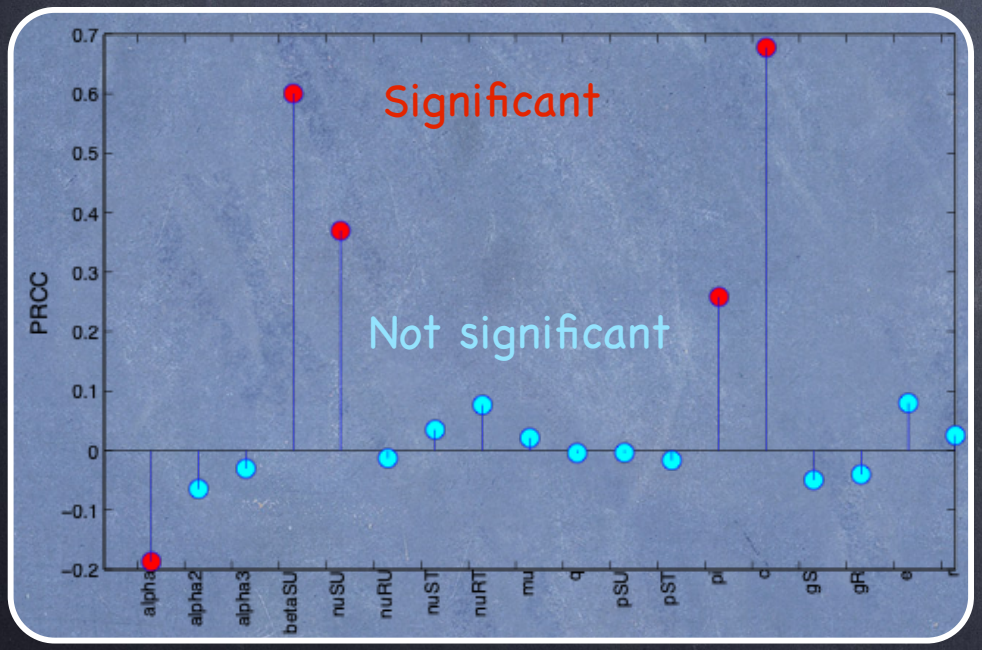
Which parameters important?

- Can explore correlation between vectors of parameters studied and outcome of interest (in this case, # cases prevented)



Which parameters important?

- BUT, linear correlation ignores fact that model output for each value of a parameter simultaneously includes changes in other parameters



Can use partial rank correlation to establish sensitivity of conclusions to specific parameters

So far, ...

- Important to distinguish between two sources of error in model predictions

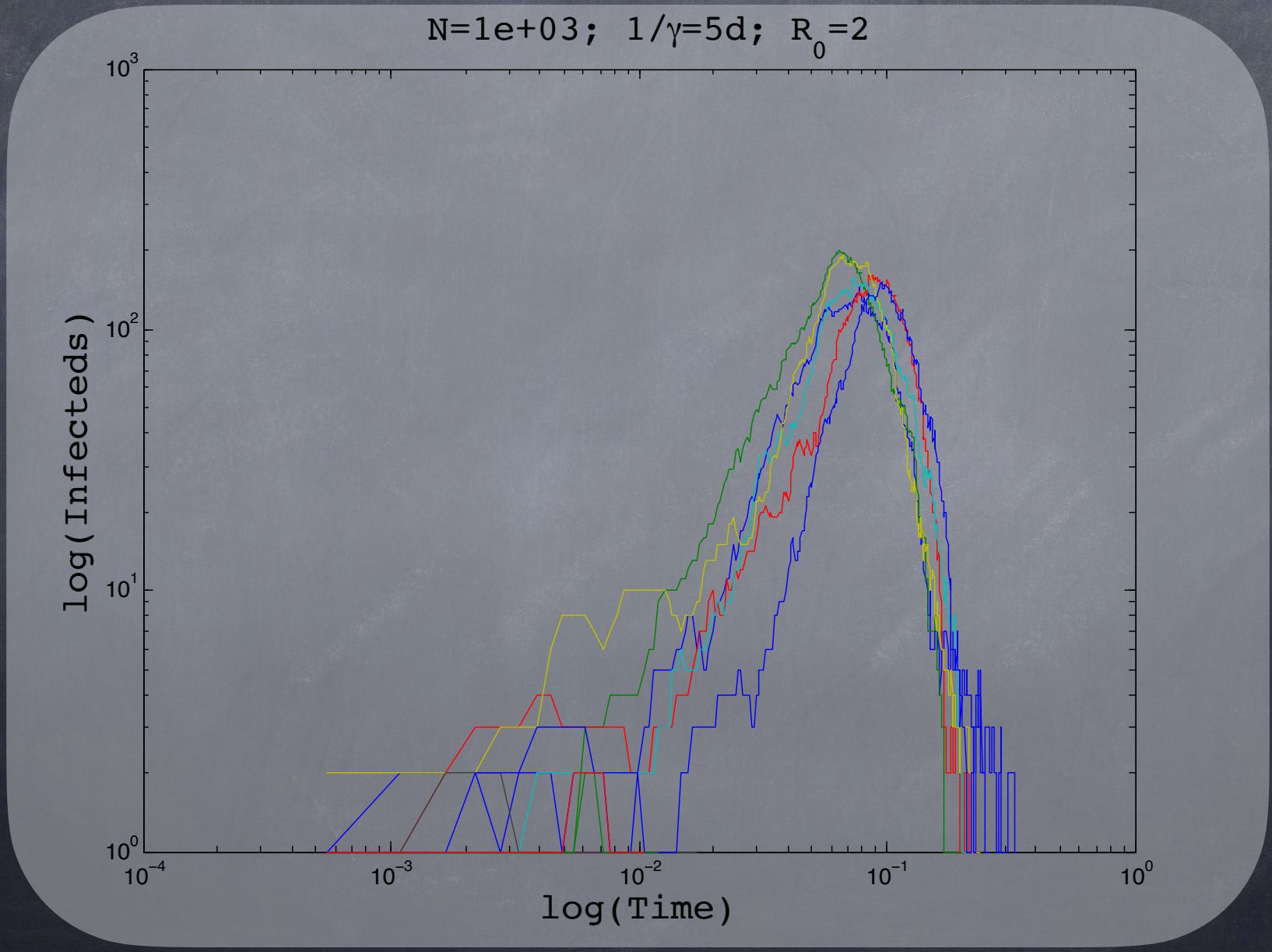
  I. Variability: arises from stochasticity in process and measurement

  - solution is to explore many model realizations

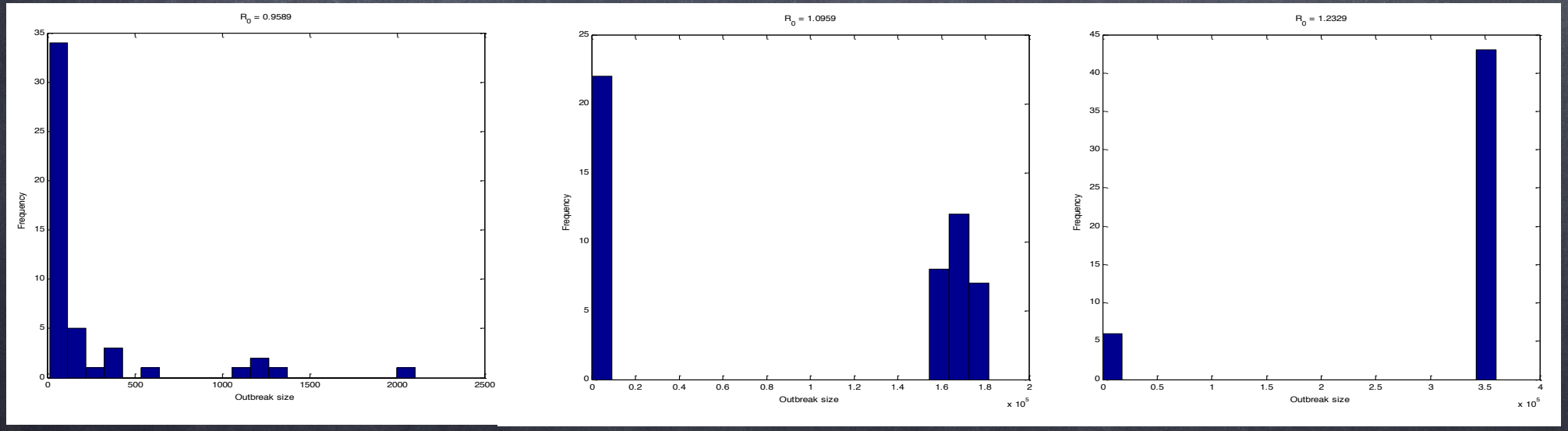
  II. Uncertainty: results from absence of information on parameters/processes

  - solution is (efficient) sensitivity analysis

Stochastic Epidemics

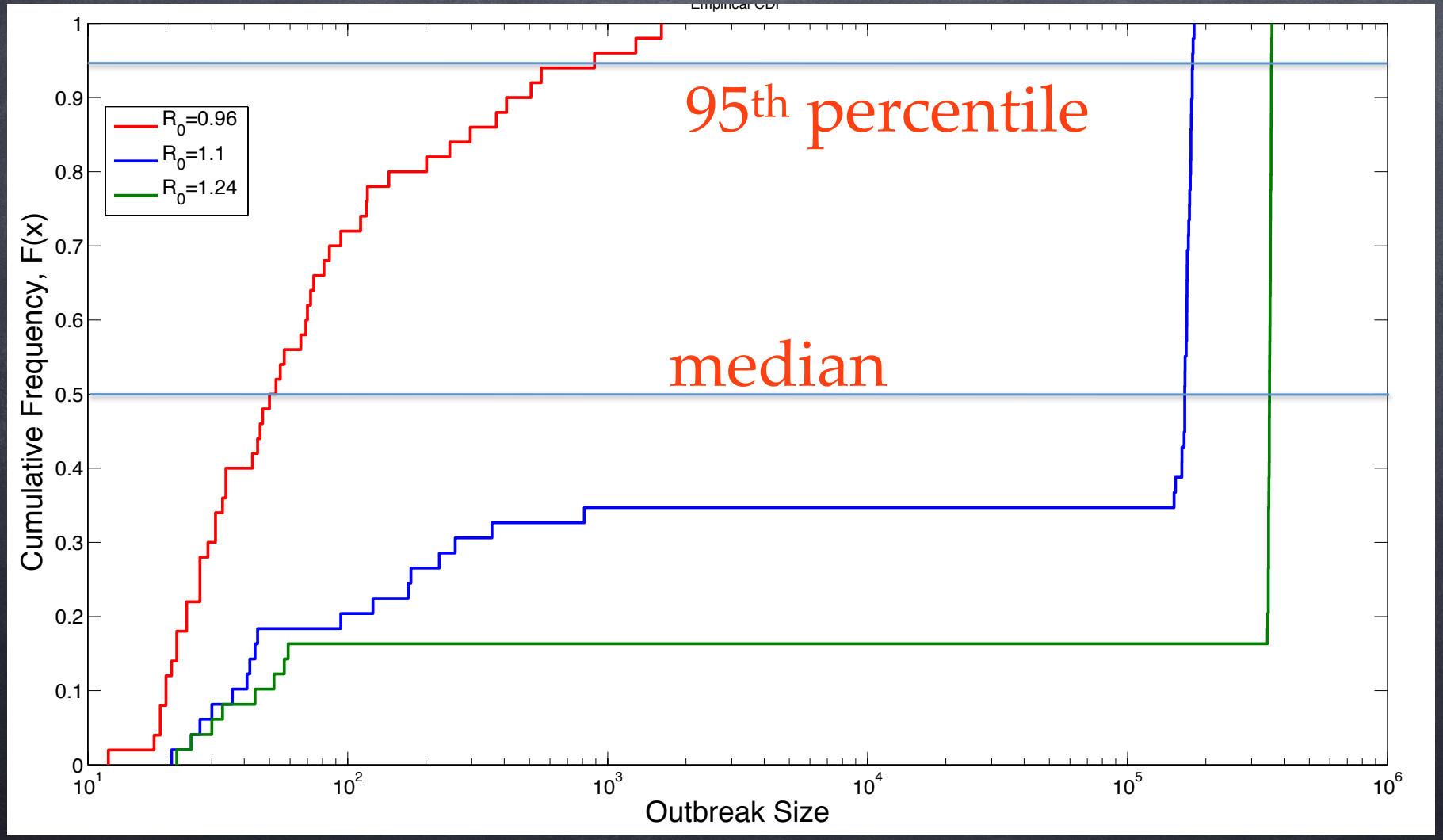


Characterising variability

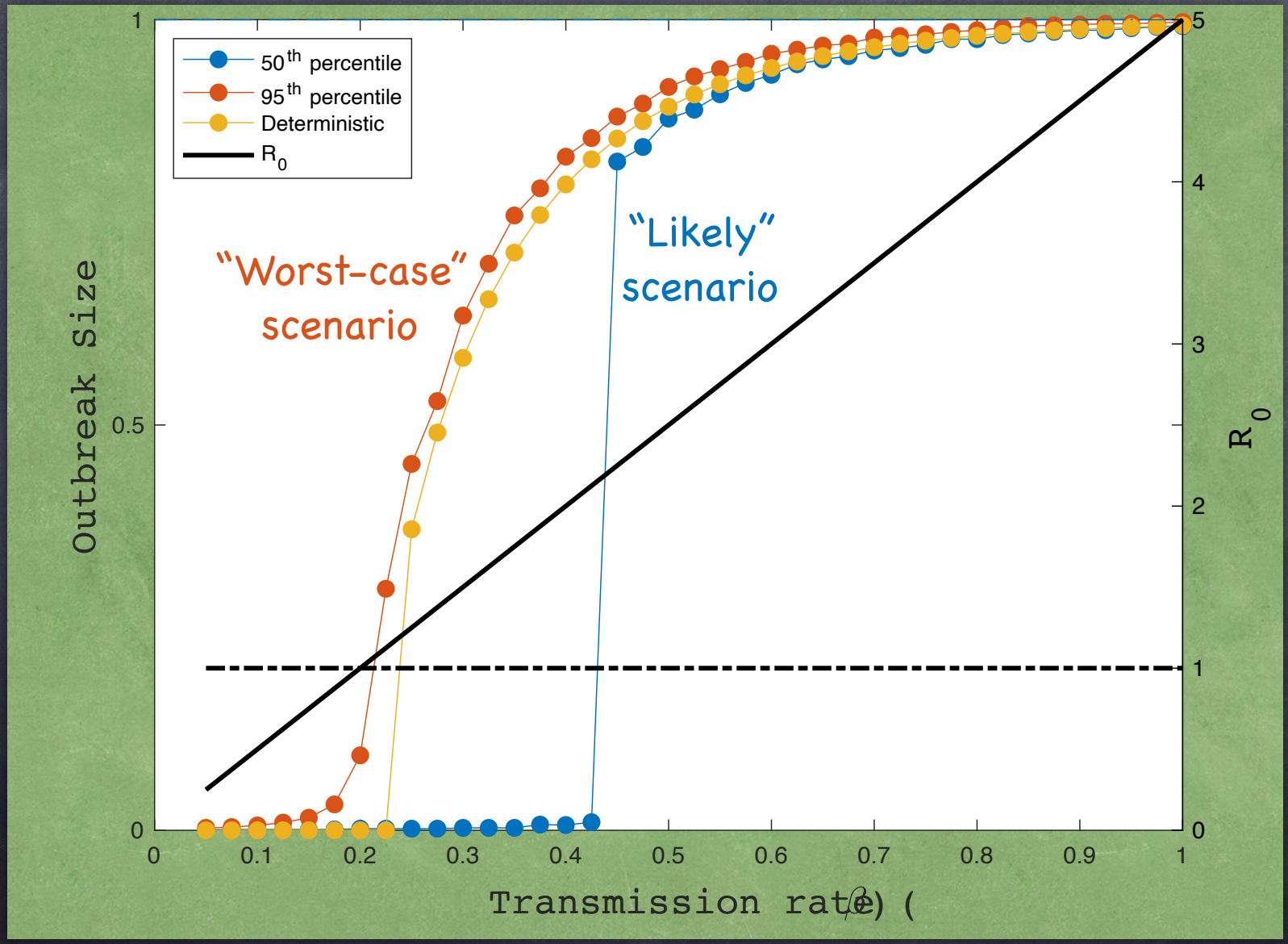


This is referred to as the J-to-U transition

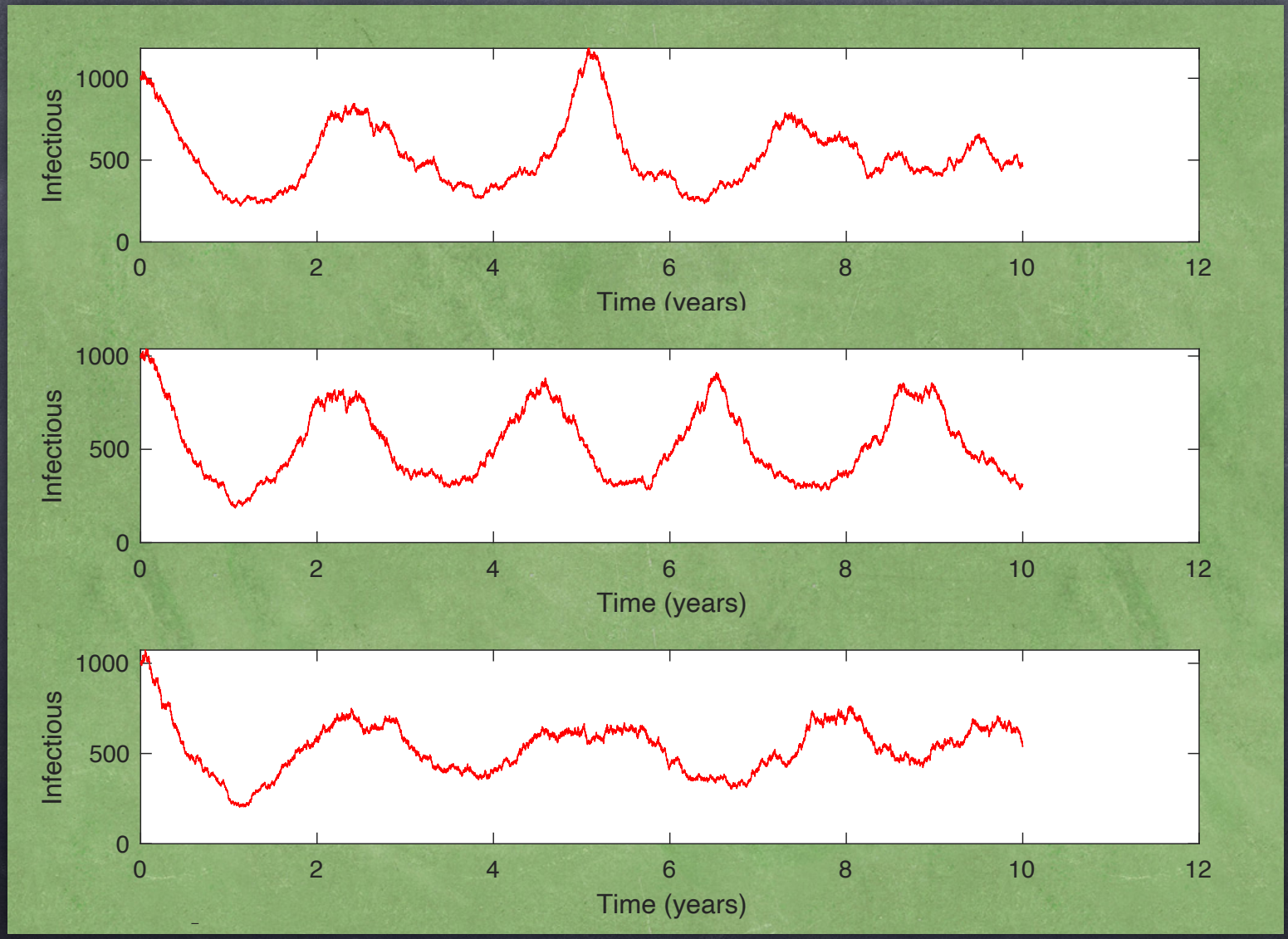
Quantifying distribution



Remember this?



Variability Vs Uncertainty



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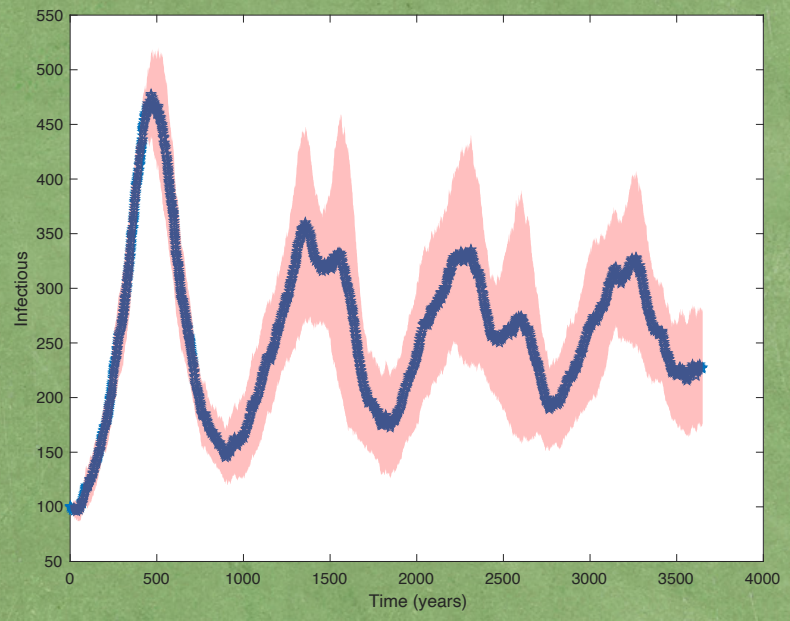
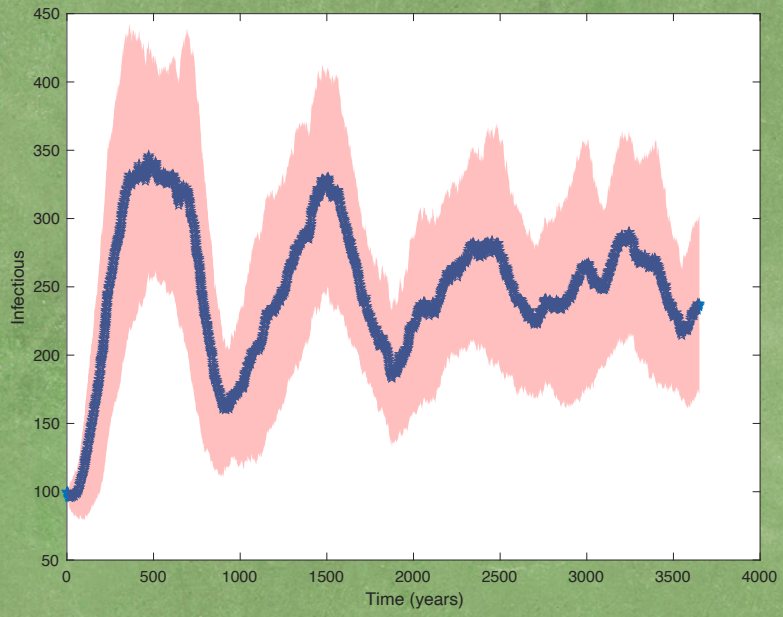


100 realizations, only demographic noise



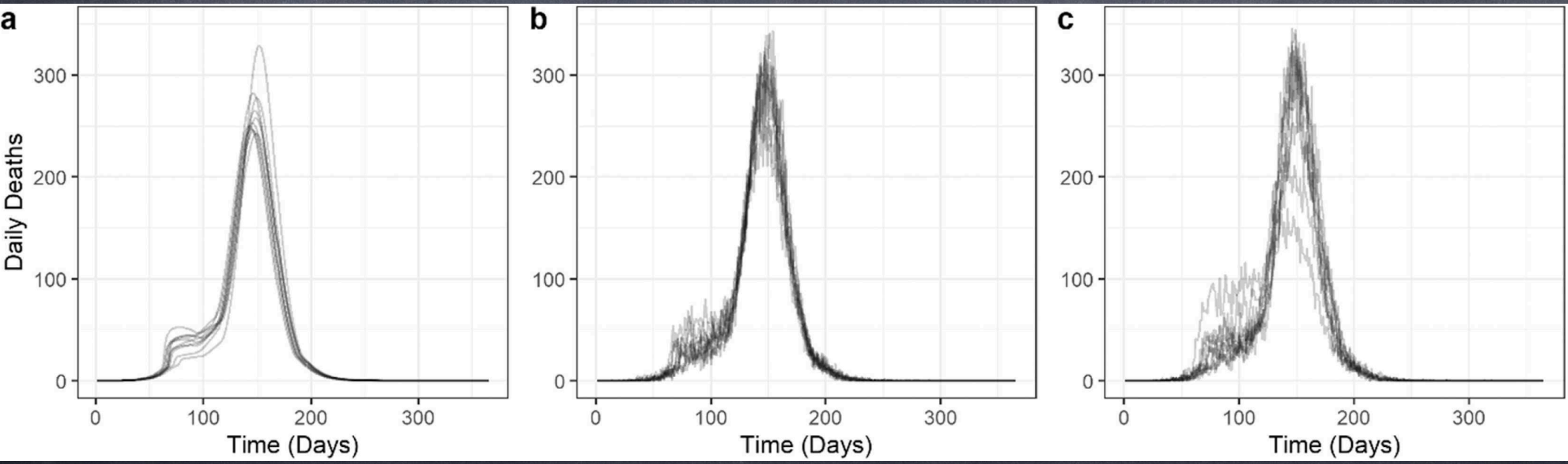
100 realizations, demographic noise + parametric uncertainty

COVID-19 example

Deterministic - uncertainty in parameters

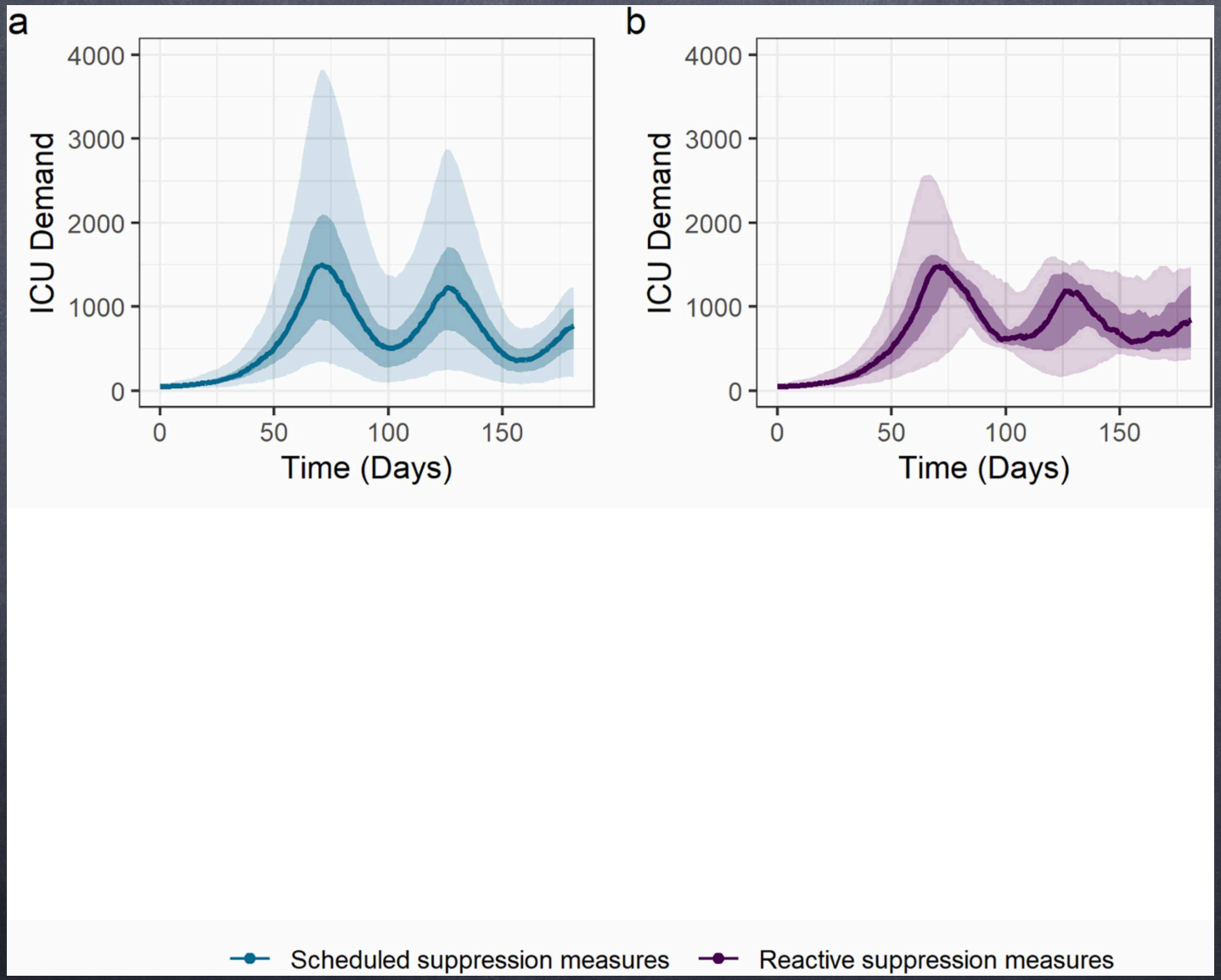
Stochastic - fixed parameters

Stochastic - uncertainty in parameters



McCabe et al. (2021; Epidemics)

COVID-19 example



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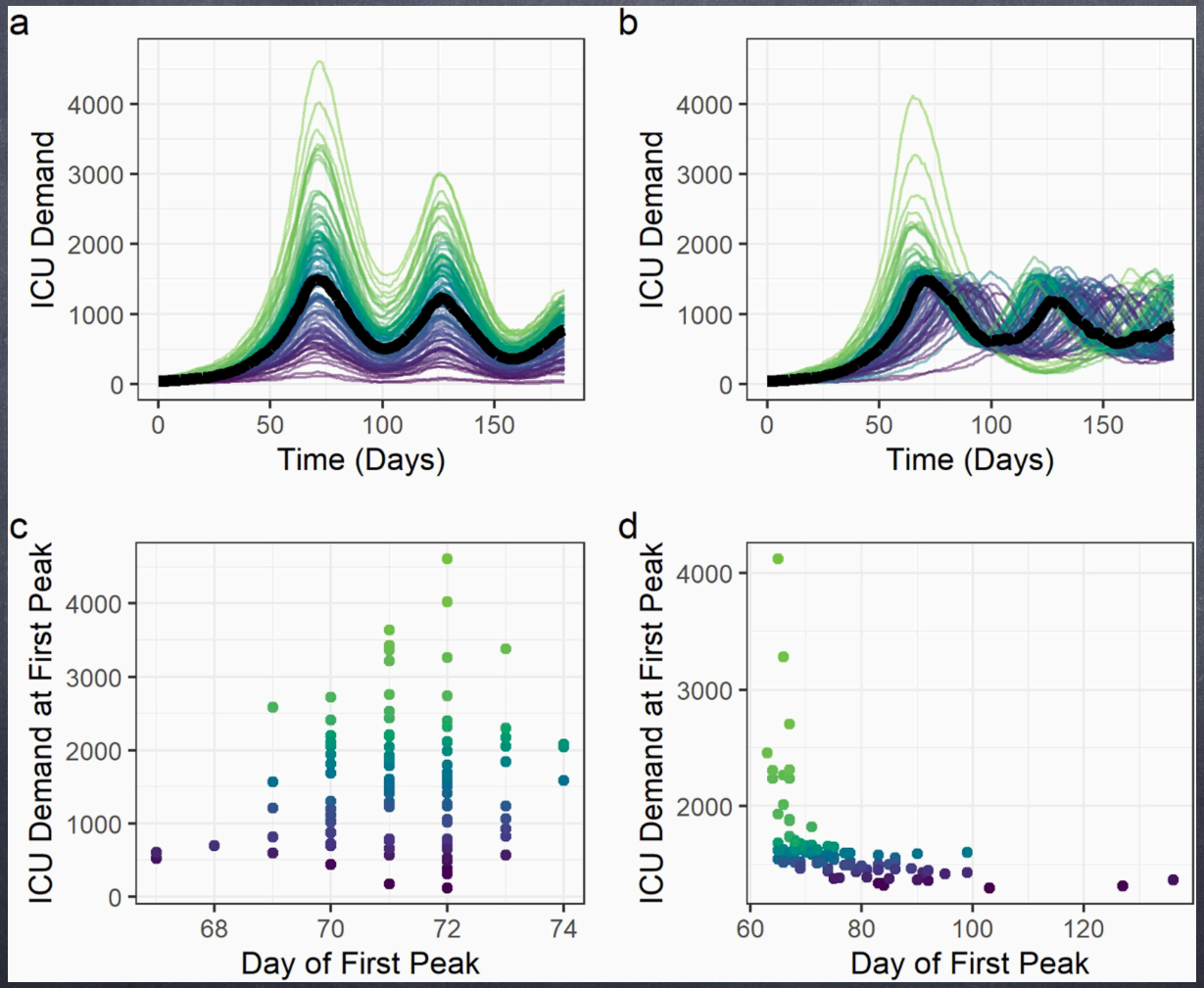

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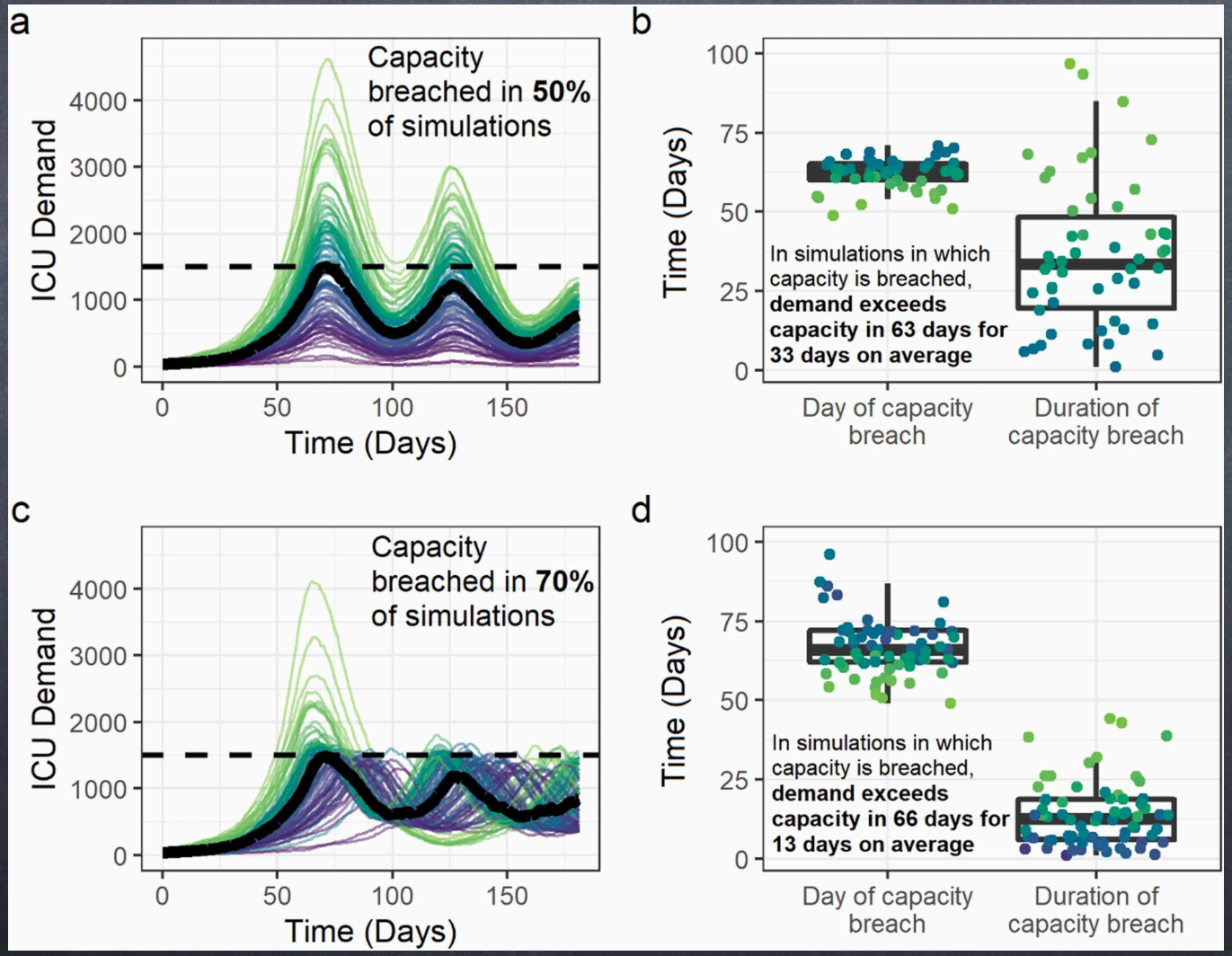


McCabe et al. (2021; Epidemics)

Uncertainty in model structure

- Multiple model comparisons
  - Brett et al. paper on early warning signals in models of differing complexity/dimension
  - Prediction of vaccine impacts (Pitzer et al. 2012)
  - Forecasting

Pitzer et al. (2012; PLoS ONE)

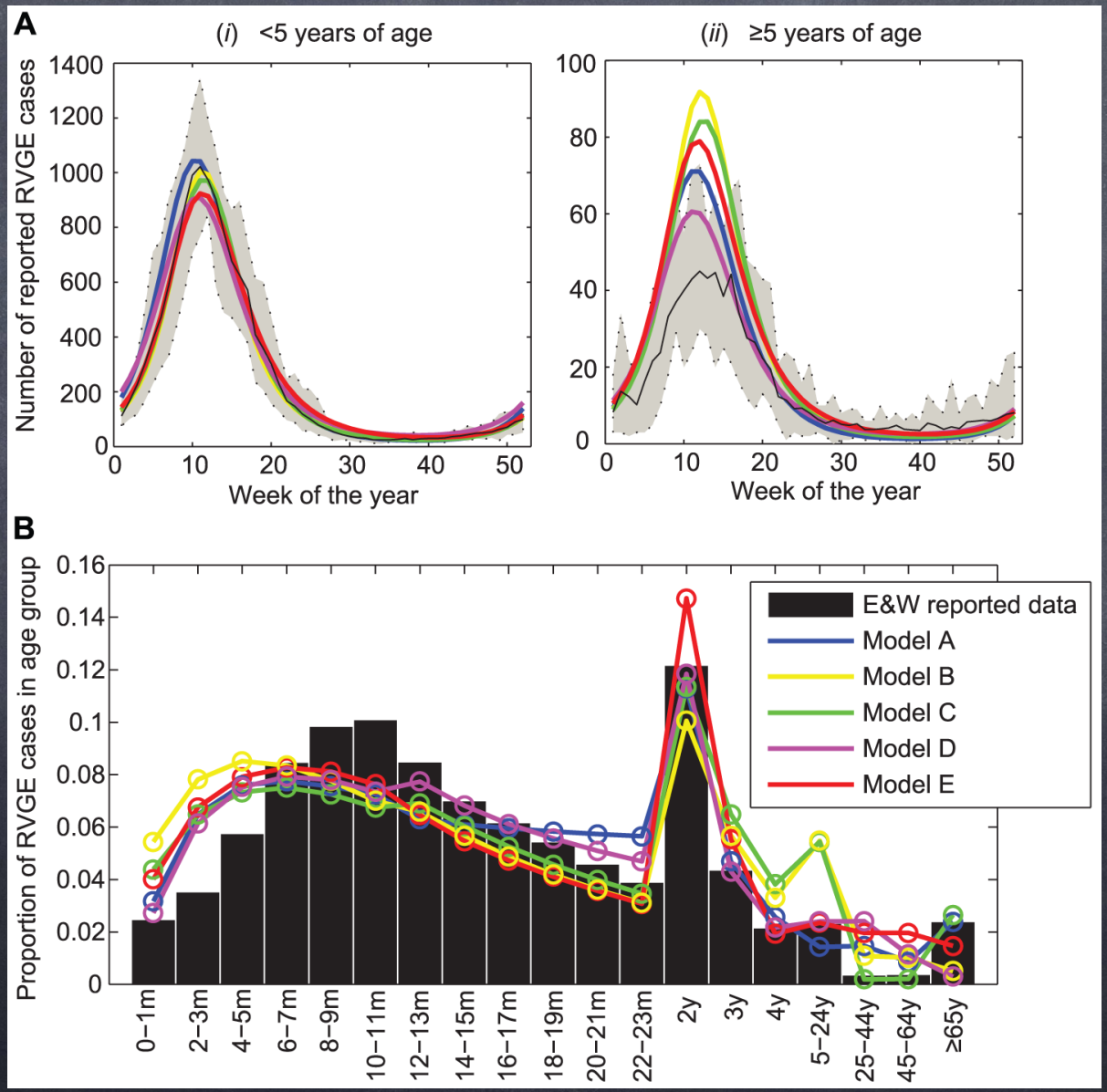
- Multiple models of rotavirus transmission dynamics

Multi-model comparison

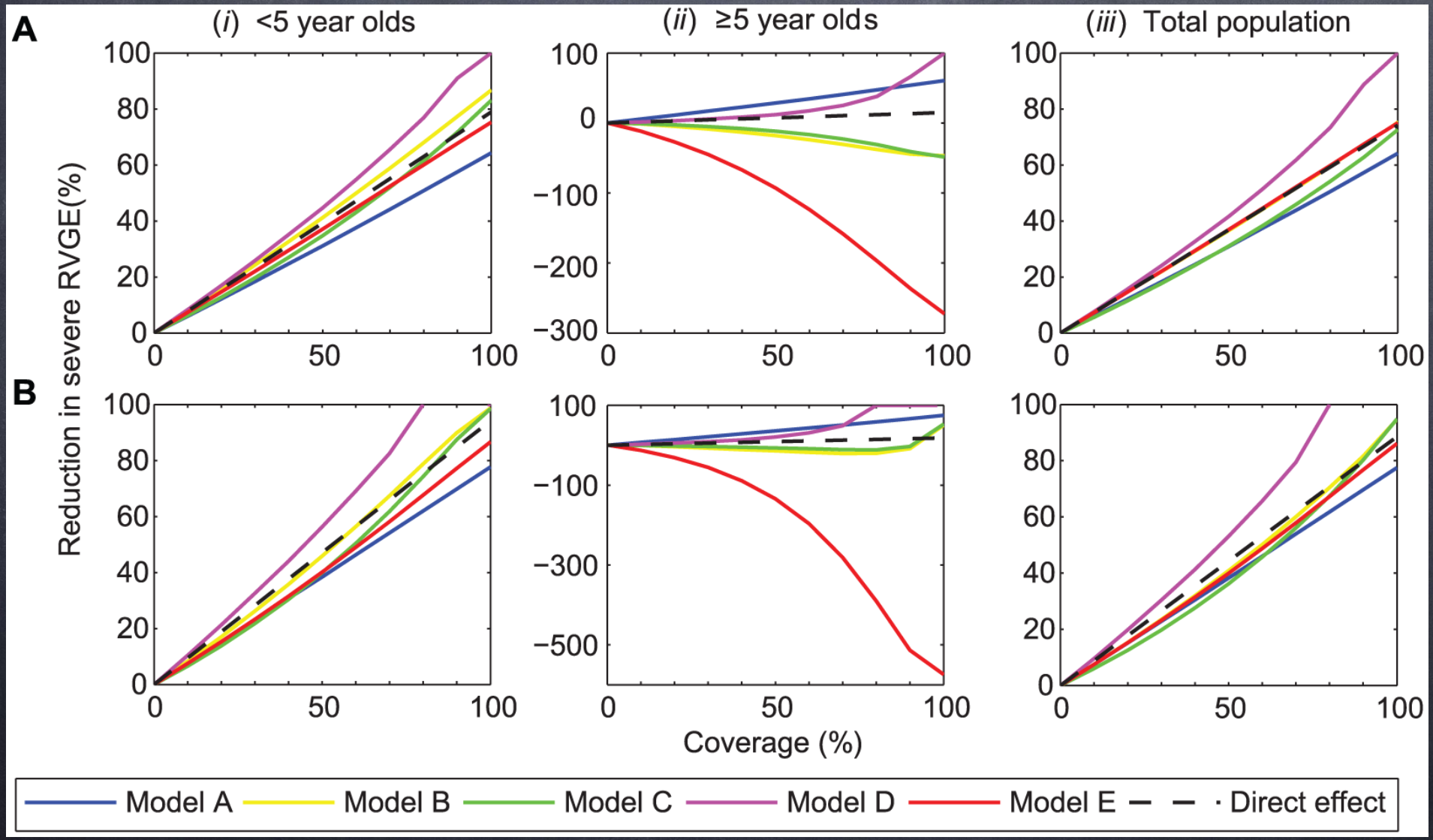
Model A	Model B	Model C	Model D	Model E
Risk of infection and severity of RVGE depend on age	Risk of infection and severity depend on the number of previous infections	Risk of infection and severity depends on age and the number of previous infections; short delay between infection and onset of infectiousness	Risk of infection and severity depends on the number of previous infections	Following infection, individuals develop full immunity or become susceptible again
Temporary immunity following infection	Temporary immunity following infection	Temporary immunity following infection	No period of full immunity following infection	Probability of developing full immunity depends on the number of previous infections
Severe and mild RVGE are tracked separately and vary in infectiousness; asymptomatic infections do not transmit	After 2 infections, subsequent infections are less infectious and not reported	After 2 infections, subsequent infections are less infectious and not reported	After 4 infections, all individuals develop full immunity (that may wane)	After 4 infections, all individuals develop full immunity (that may wane); asymptomatic infections do not transmit
Only severe RVGE cases are reported	Only severe RVGE cases are reported	Only severe RVGE cases are reported	Mild and severe RVGE cases are reported; reporting rate depends on age (<5 or ≥ 5 years old)	Mild and severe RVGE cases are reported

doi:10.1371/journal.pone.0042320.t001

Multi-model comparison

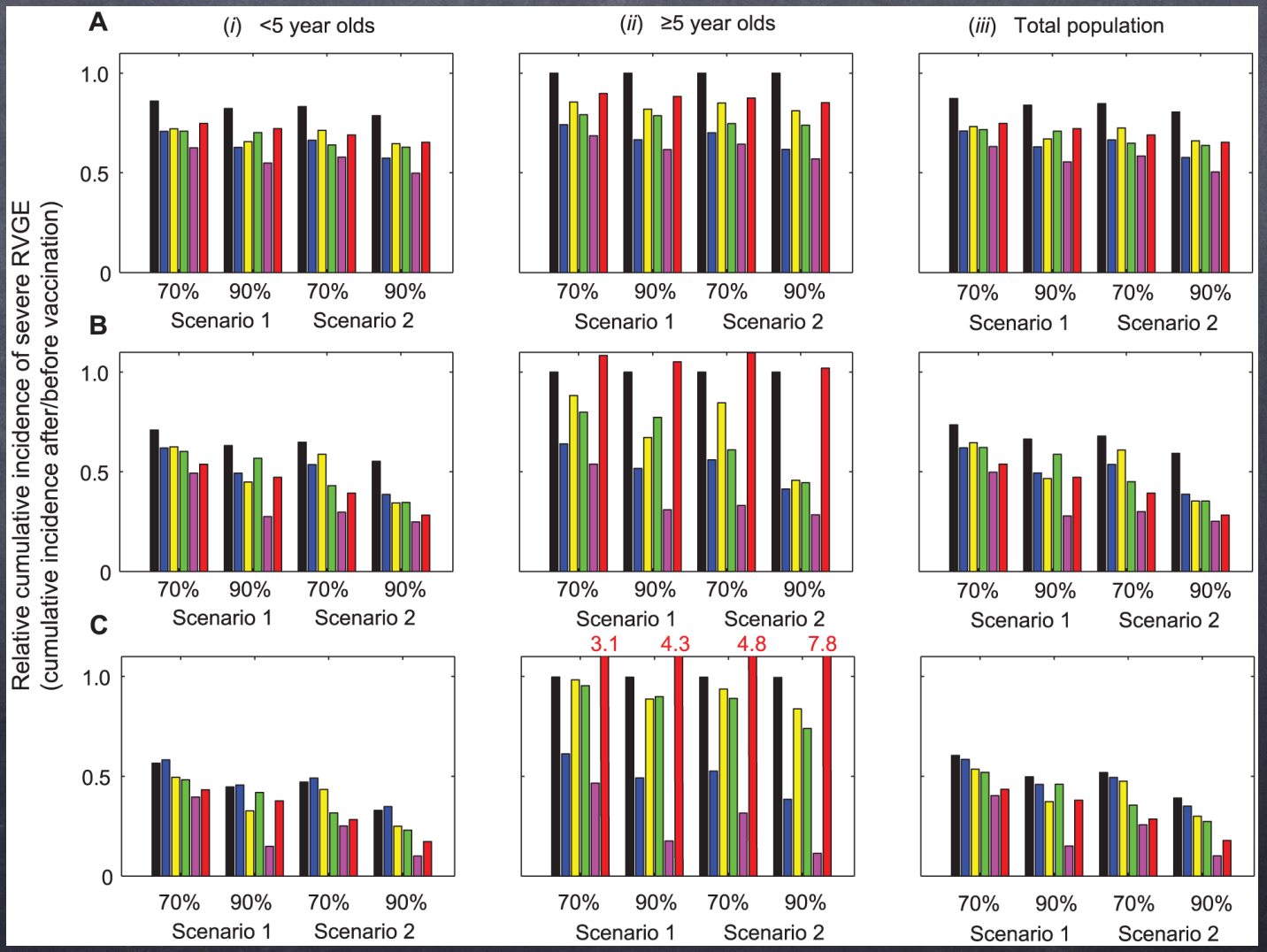


Multi-model comparison

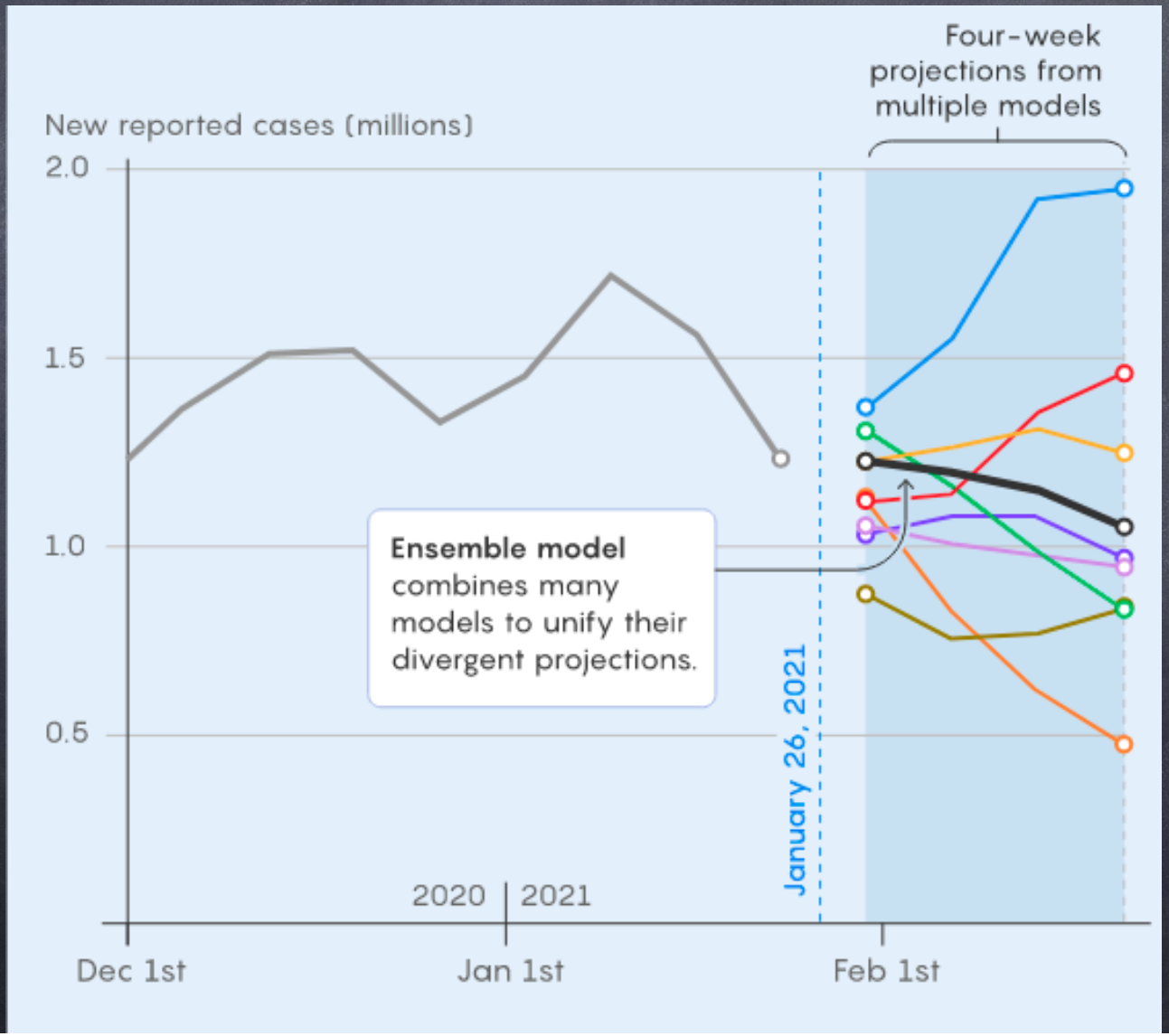


Multi-model comparison

- Variation in model predictions of vaccination impact
- Reflect key differences in model explanation for <5 rota incidence
- Which is "right"?



Uncertainty in model structure



Summary

- Important distinction between variability (due to nonlinearity & noise) and uncertainty (unknown model structure/parameters)
- Need careful thought when presenting to policy makers
  - Discretize outcomes
  - Sensitivity analyses
  - Multi-model comparisons