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Mathematical epidemiology Some background and modern directions that may help TB research

LIV-TB seminar
23 March 2017
2pm CTID Boardroom

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Background

- Mathematical epidemiology is at its centenary
- The very early models (Ross, 1915; Kermack and McKendrick, 1927; Reed and Frost, 1920s) tended to be concerned with exploring hypotheses
- E.g. K & K showed that an epidemic could end due to acquisition of immunity rather than the attenuation of the pathogen as had been previously suggested

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History (a bit subjective)

- 1950s-70s: Focus on simple models, often including randomness and mathematical analysis thereof
- 1980s-90s: Differential-equation based models (no randomness) stratified by age primarily for childhood infections
- 2000s: Random computationally intensive models aiming for high ‘realism’
- Current directions: Much more focus on models that can be fitted to data – randomness but computationally ‘cheap’

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Talk outline

- I will present short outlines of several different project / papers
- None of these is specifically about TB, but the modelling / statistical methodology should carry over
- The equations behind this are complex (and mainly not included) but the concepts are natural!

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Statistical framework

- ‘somewhat Bayesian’
- Put distributions on parameters
- Sample from these using MCMC
- Propagate this uncertainty forward in a transmission-dynamic model
- **Pros:** Unified conceptual framework; copes well with ‘small data’;
- **Cons:** Subjectivity; algorithmic difficulty

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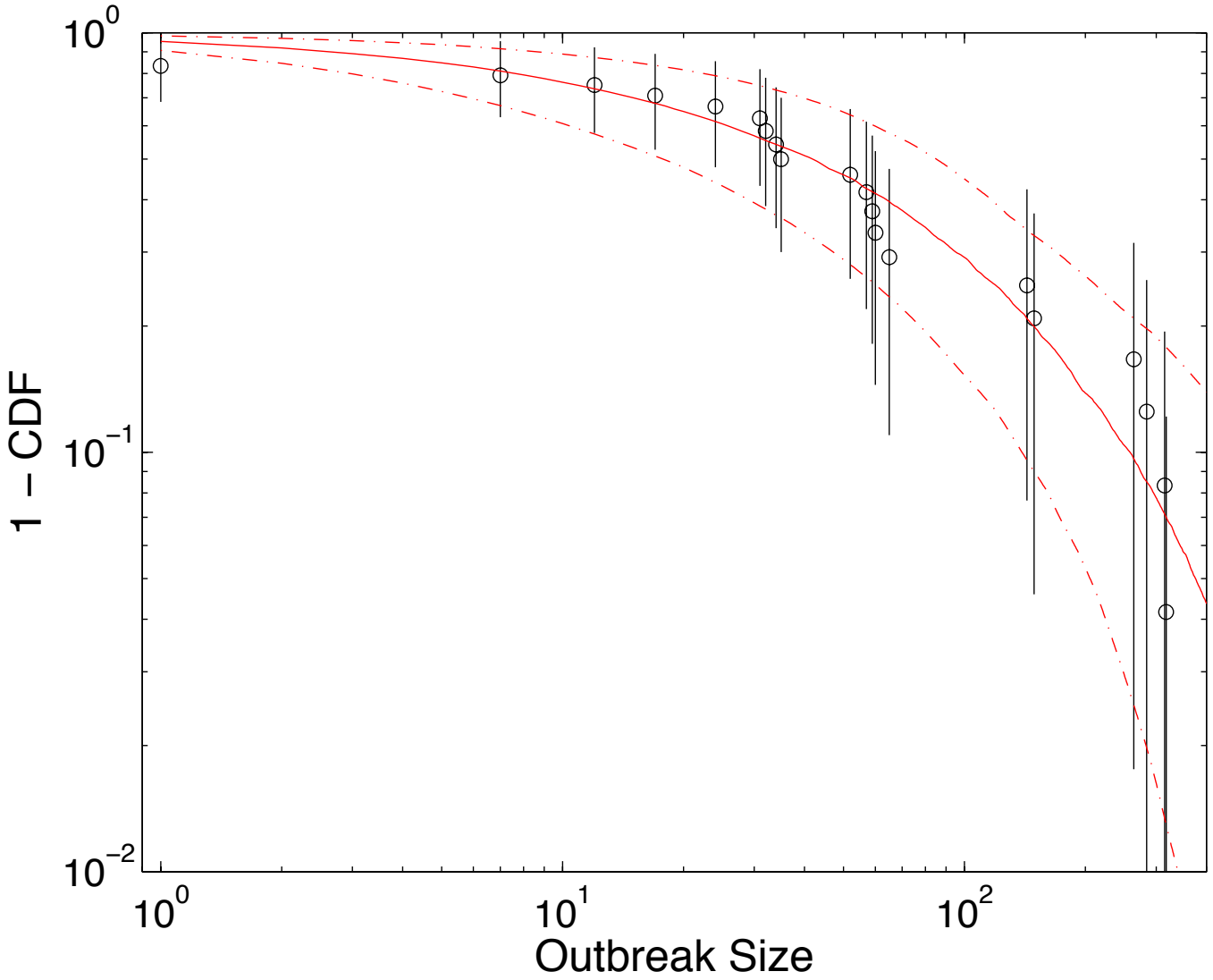
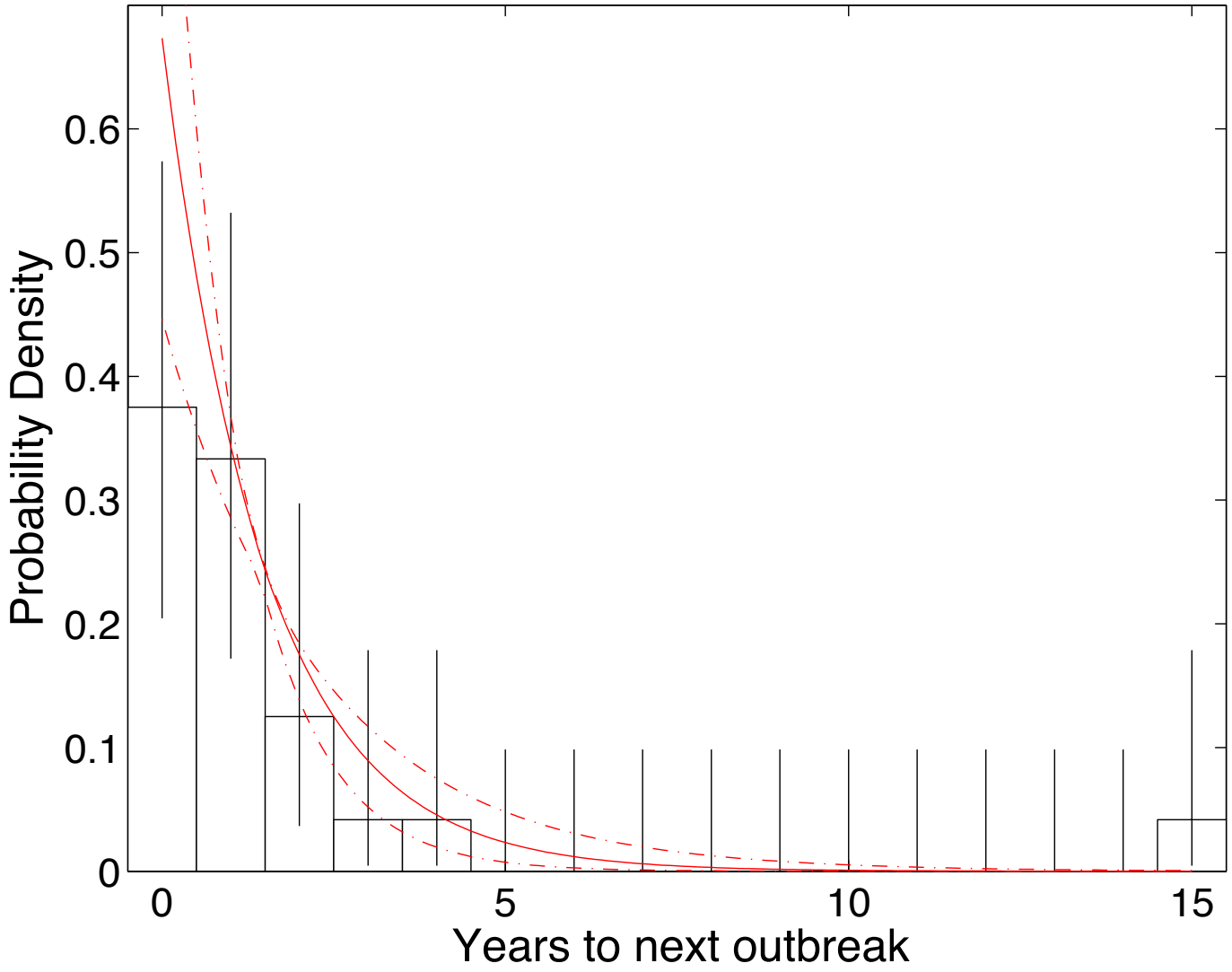
Ebola – historic outbreaks

- Ebola outbreaks are highly variable
- Rather than try to use differential equations, I considered a branching-process model
- Also, waiting times between outbreaks and the variability in case fatality rates is variable and inferable from historic data



Ebola outbreaks pre-2014

Together with fitted model based on a branching process



Ebola outbreaks pre-2014

Waiting times between outbreaks versus a ‘memoryless’ distribution

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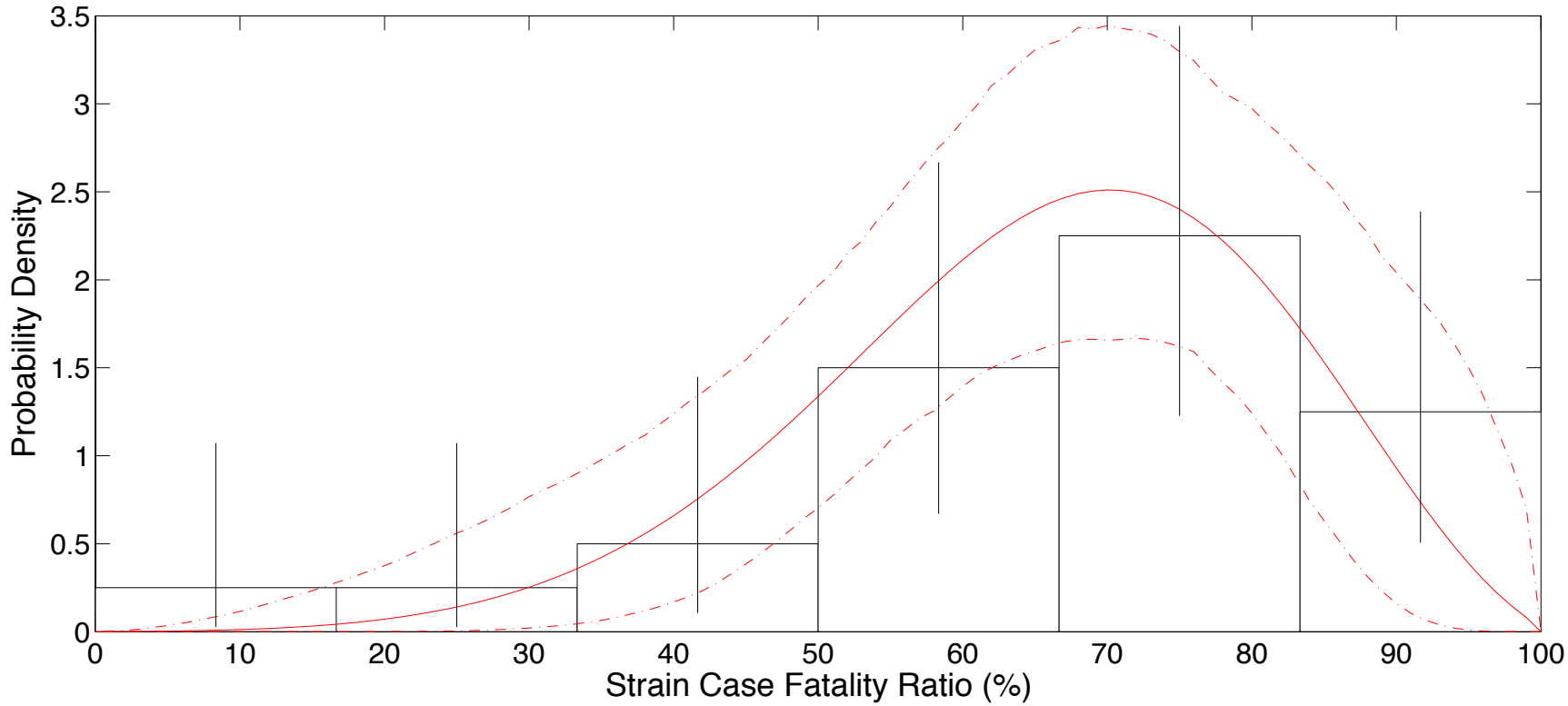

Ebola outbreaks pre-2014

Case fatality rates

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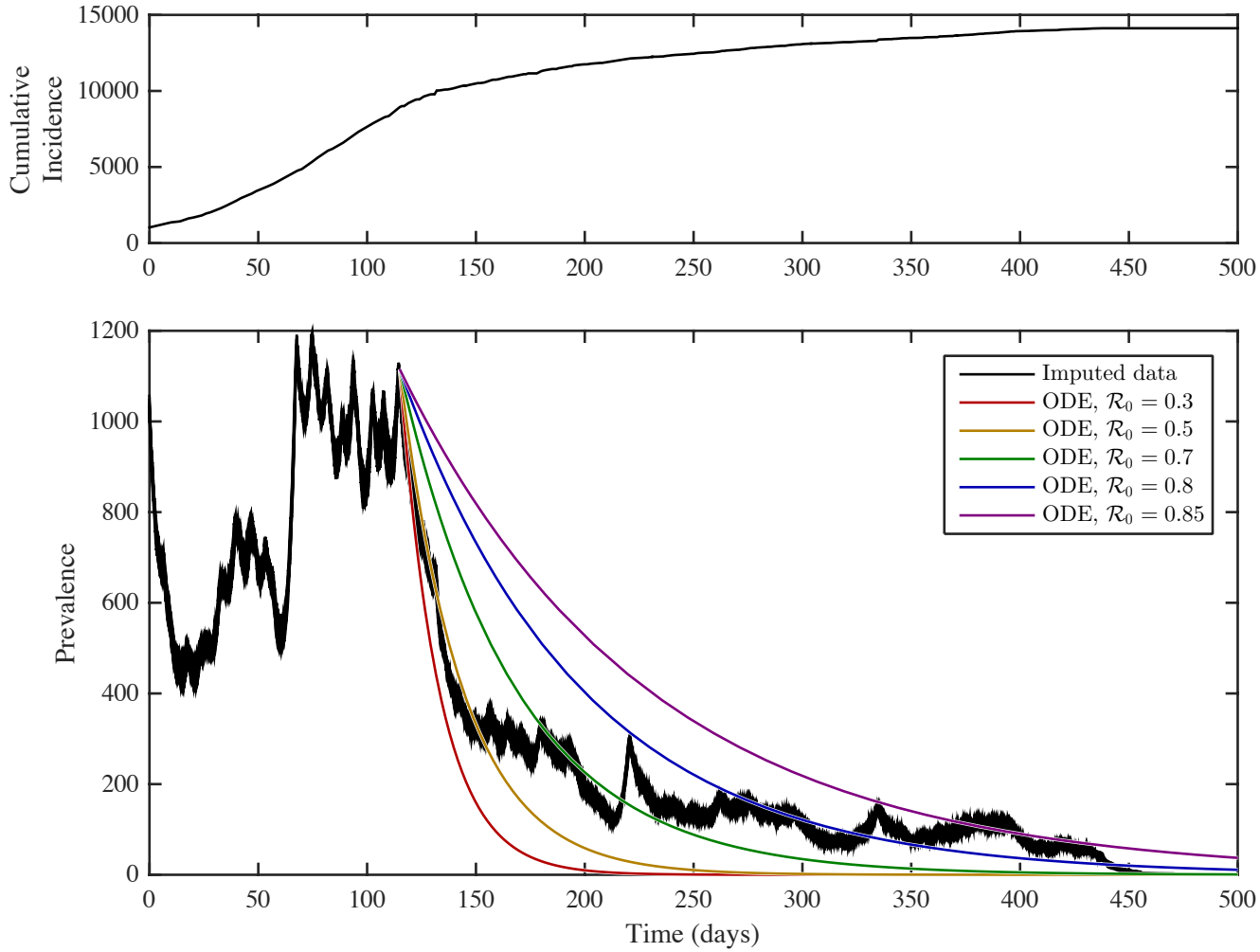
Weak transmission

- Near criticality ($R_0 \approx 1$) epidemics behave differently from far from it
- TB in some contexts may be close to criticality
- Joint work with Malwina Luczak, Graham Brightwell, Svarte Janson.

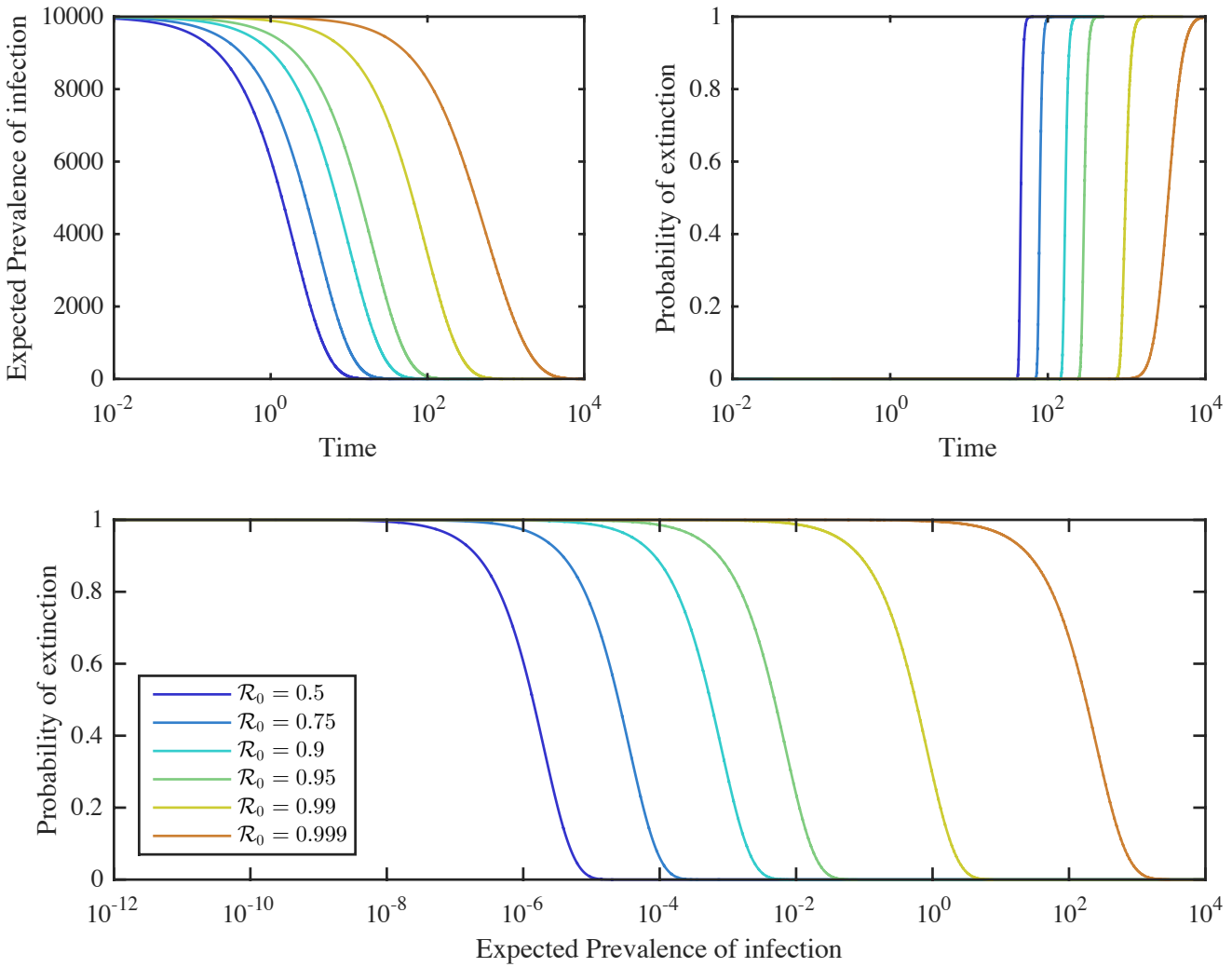


2014 Ebola in Sierra Leone

Compared to LSHTM model

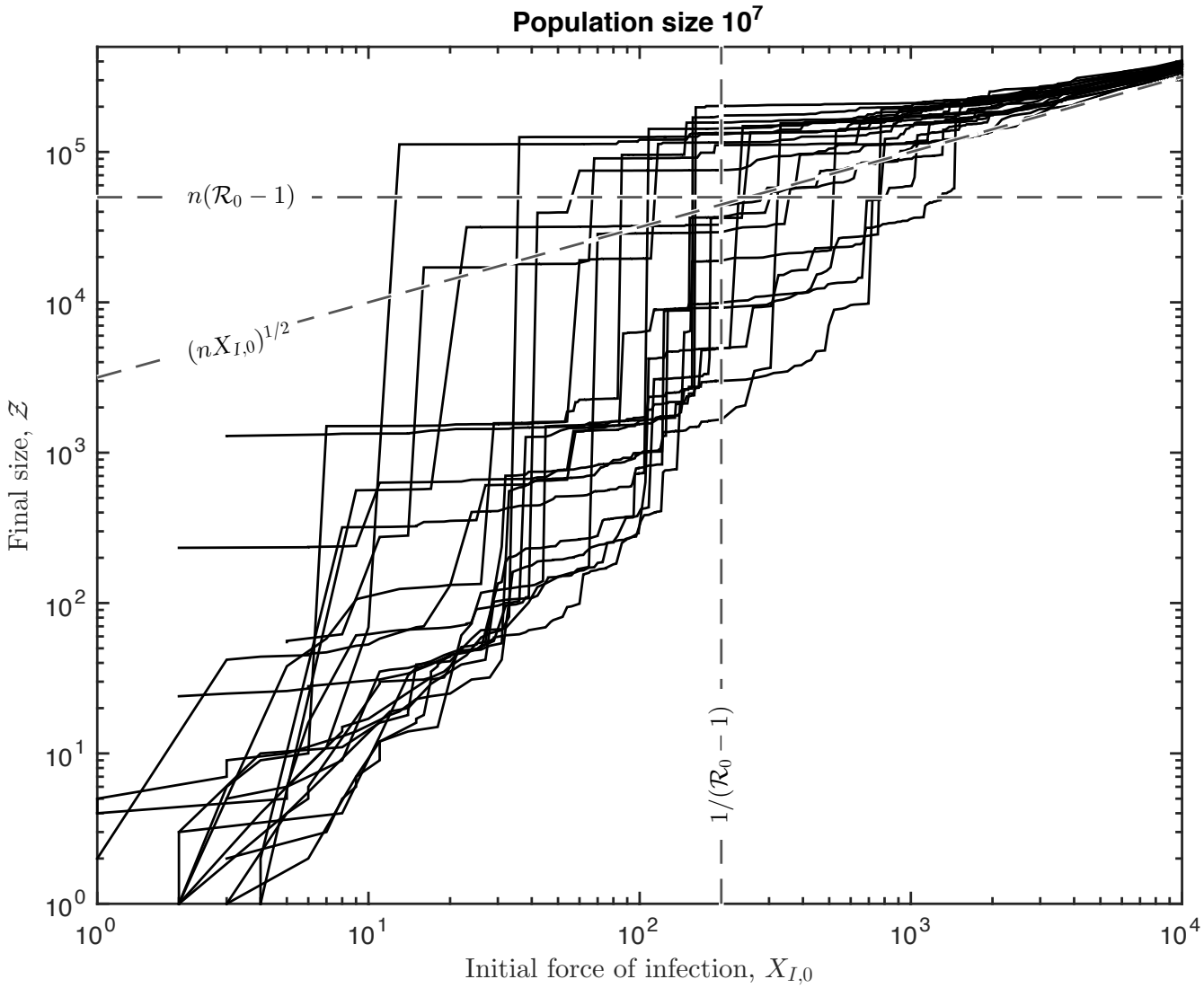
The post-control period exhibits fast decay but a long time to extinction

The standard explanation for this is varying R_0 – is there another possibility?



Theoretical results for the SIS model

These show a decoupling of expected prevalence and extinction probability



Theoretical results for SIR model

These show strong initial-condition dependence

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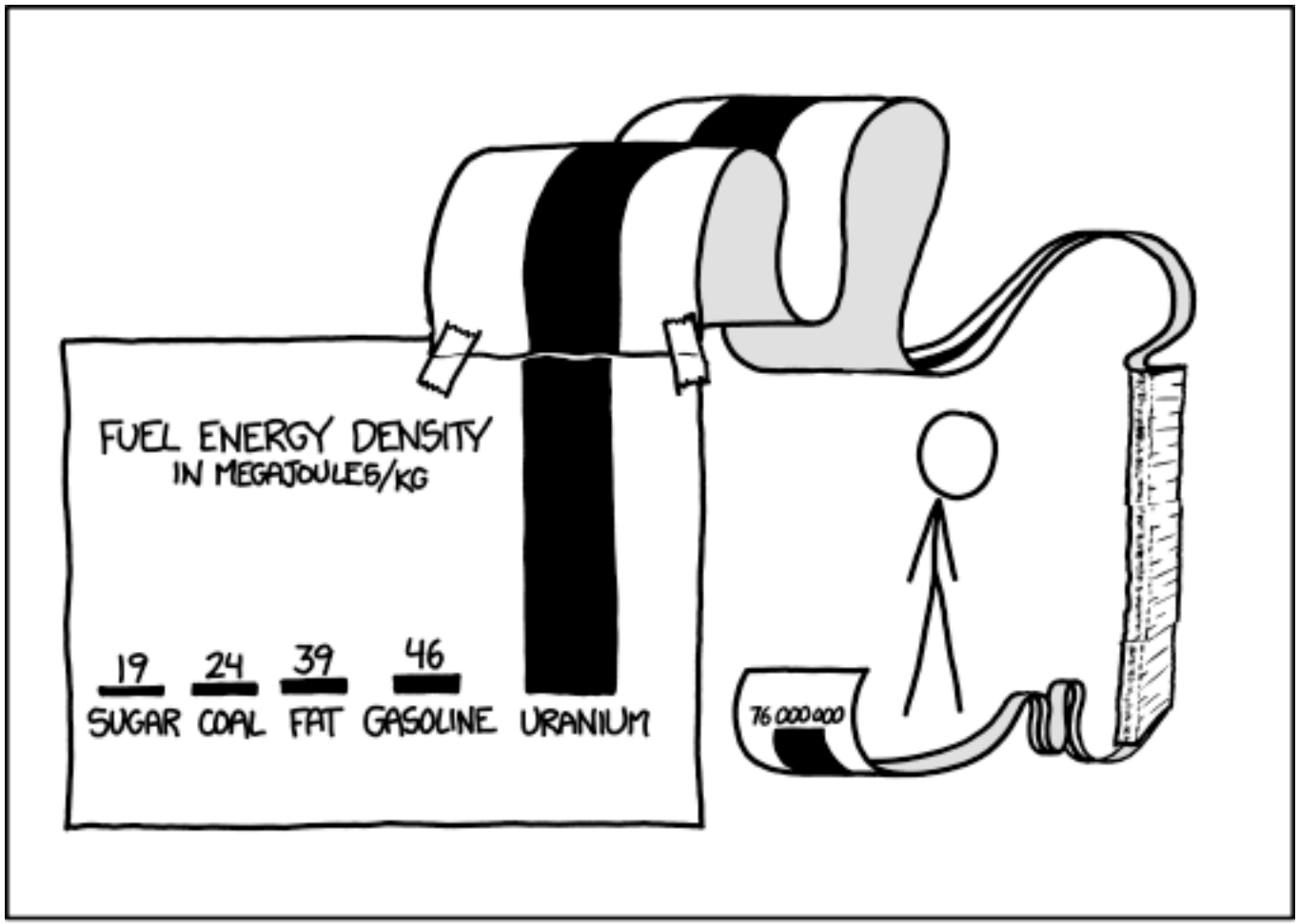

SCIENCE TIP: LOG SCALES ARE FOR QUITTERS WHO CAN'T FIND ENOUGH PAPER TO MAKE THEIR POINT *PROPERLY.*

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Emergence of influenza pandemics

- Ebola outbreaks exhibited the memoryless property
- Does pandemic influenza? We considered a Bayesian model selection problem
- Fit inter-pandemic times to either an exponential (memoryless) or Gamma (history-dependent) distribution and calculated the **probability** of each hypotheses – this is possible in Bayesian inference, not a misinterpretation of a p-value!
- Work with Ed Hill and Mike Tildesley

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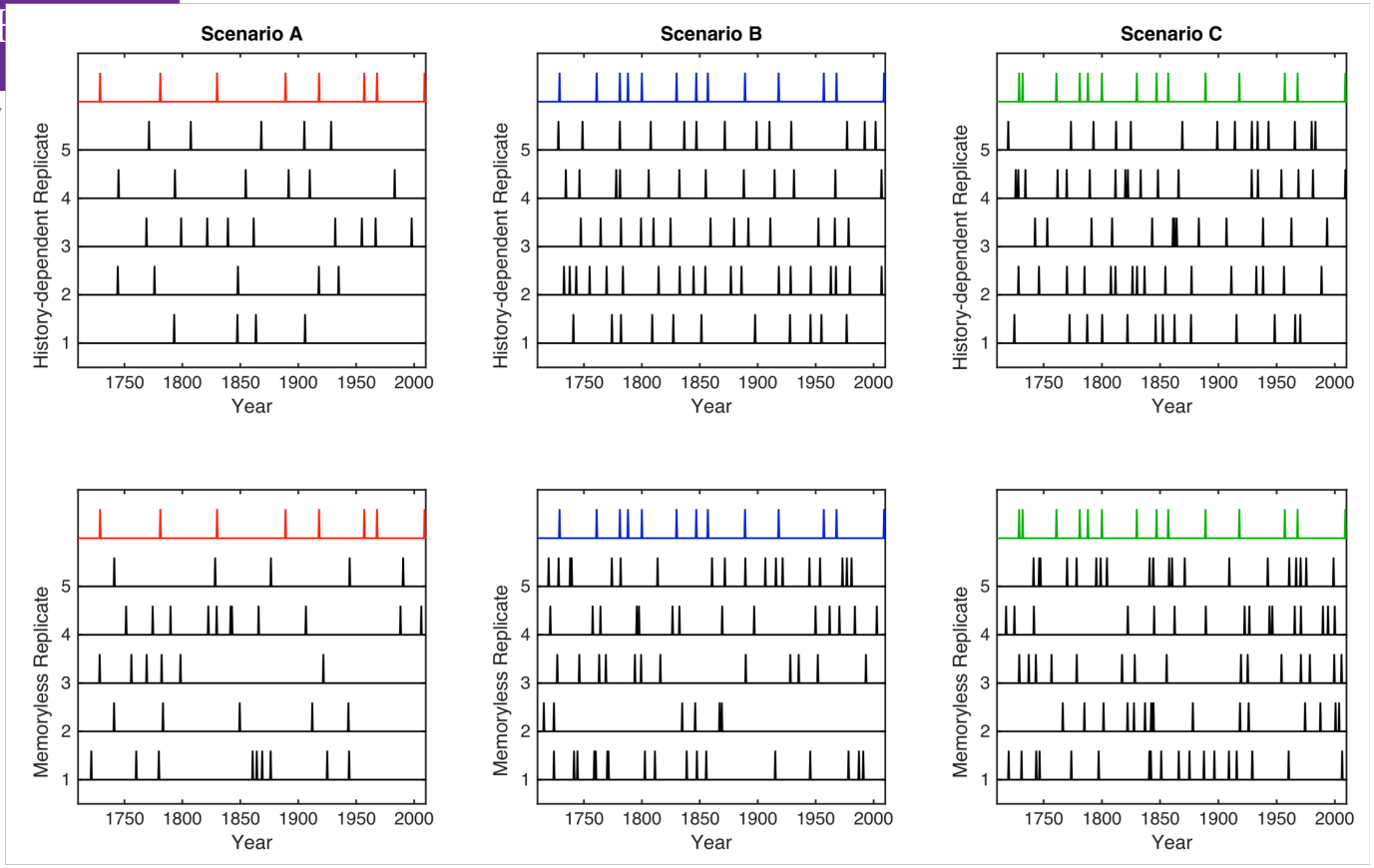

Historic influenza pandemics

Colour: real data; Black: simulated; Top: history-dependent; Bottom: memoryless; Columns: different assumptions about the actual history of pandemic influenza.

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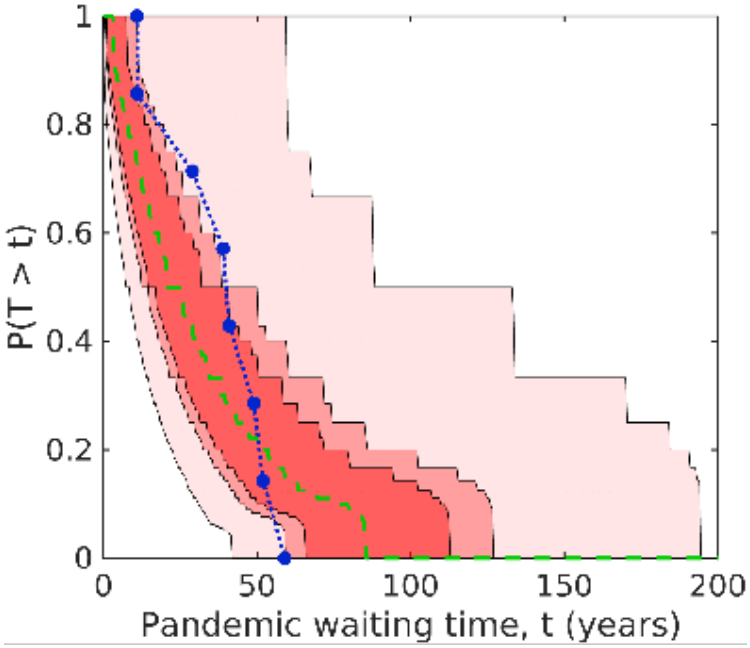
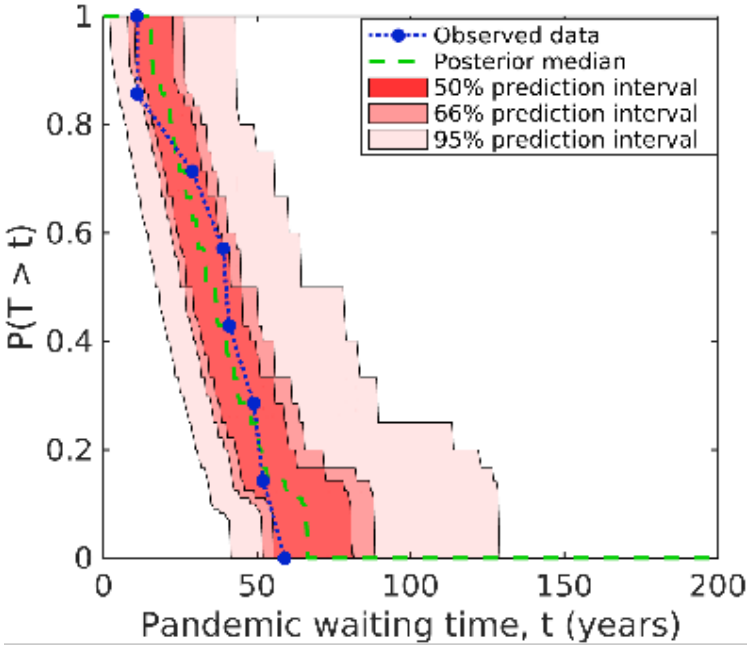
The model fits well (scenario C strong prior)

Memoryless



History-dependent



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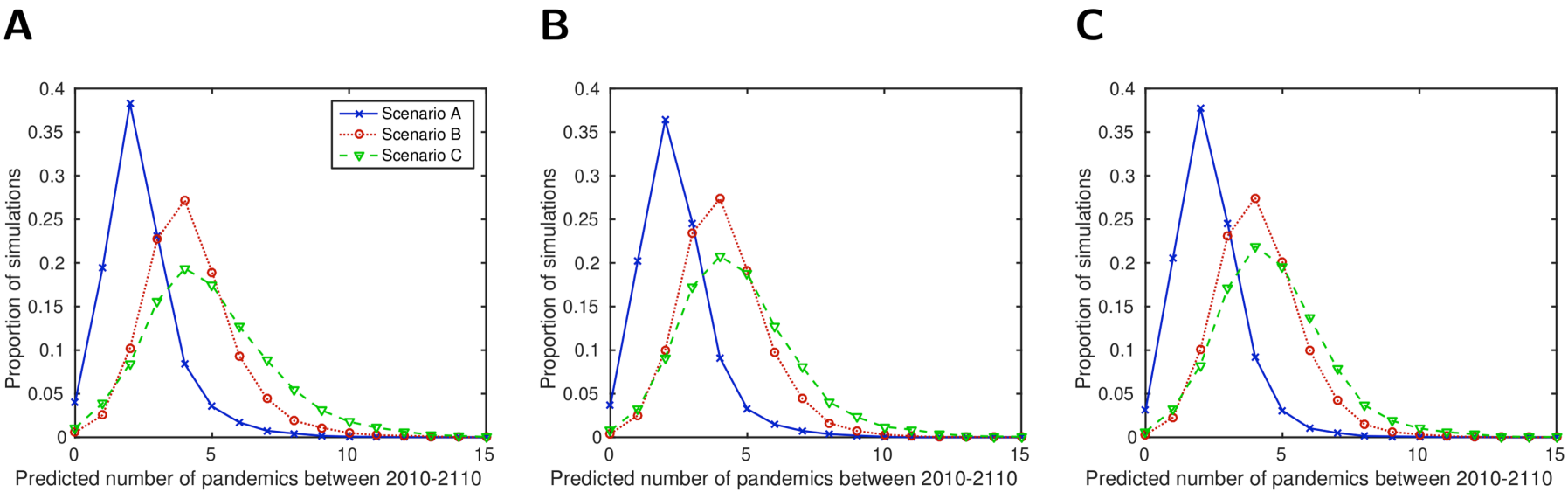

Prediction

We can use these to predict next century's pandemics

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Households

- Many populations are split into easily identifiable, well connected small sub-units
- In mathematical work, these are customarily called **households**, but the methodology is general
- Here, the idea is to calculate all outcome probabilities by brute force
- Work with Tim Kinyanjui, Josh Ross, Stefan Guettel, Jackie Cassell, Jo Middleton

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Scabies in care homes

Sarcoptes scabiei is an ectoparasite that infests human skin, where it burrows and lays eggs causing intense itching and scratching. We capture its dynamics in a residential care home of size $N = S + E + I$ using the stochastic SEI model:

$$\begin{aligned} (S, E, I) &\to (S-1, E+1, I) \text{ at rate } \lambda SI \,, \\ (S, E, I) &\to (S, E-1, I+1) \text{ at rate } \gamma E \,. \end{aligned} \tag{8}$$

We make the modelling choice

$$\lambda = \frac{\beta}{(N-1)^{\alpha}} \,, \tag{9}$$

leaving us with paramters

$$\boldsymbol{\theta} = (\alpha, \beta, \gamma) \,. \tag{10}$$

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Scabies in care homes

The data† takes the form $\mathbf{y} = (N_a, C_a, T_a)_{a=1}^{n}$, representing care home size, number of cases at treatment and time between first infection and treatment.

N	57	18	57	29	35	26	92
C	4	5	9	3	4	15	2
T (days)	61	172	161	368	123	123	4

Then the likelihood takes the form

$$L(\mathbf{y}|\boldsymbol{\theta}) = \prod_a \mathbf{v}_{C_a}^{\top} \mathrm{e}^{T_a \boldsymbol{Q}(N_a, \boldsymbol{\theta})} \mathbf{u}_{\text{init}} \,.$$

† Hewitt, K A, Nalabanda, A and Cassell, J A (2014) Scabies outbreaks in residential care homes: factors associated with late recognition, burden and impact. A mixed methods study in England. Epidemiology and Infection. ISSN 0950-2688

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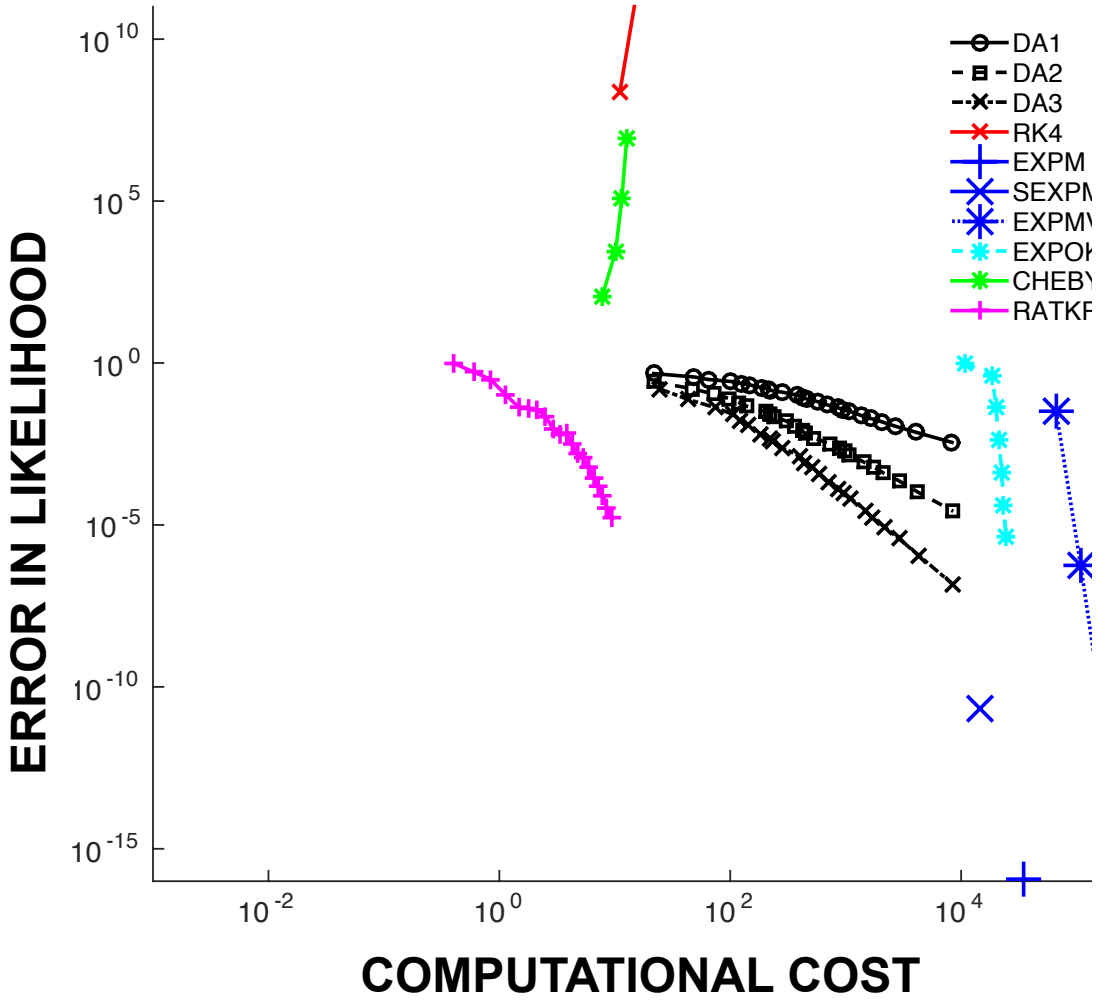
Mathematical content – numerics matter!



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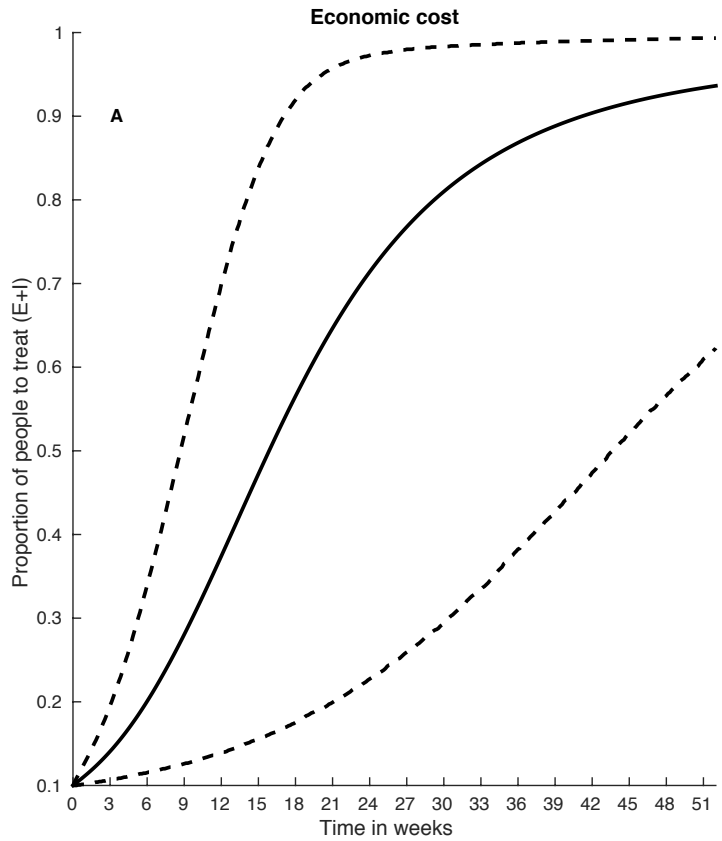
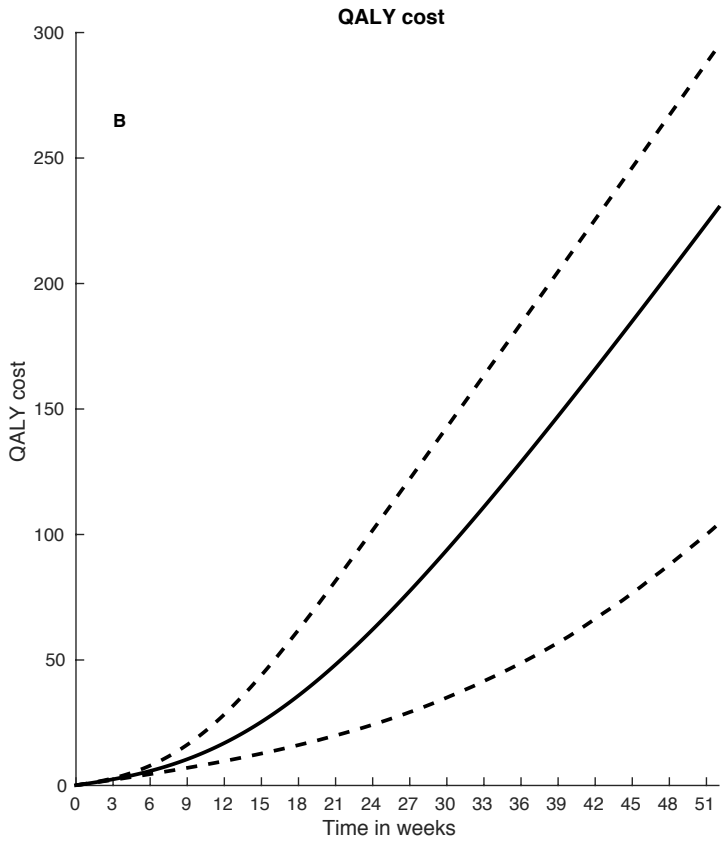
Use of transmission dynamic model to quantify costs of delay





4.2. *Safety of Ivermectin*

Barkwell and Shields [8] reported 172 deaths in a population of size 210 over a 36 month period, and 15 subsequent deaths over 6 months in a sub-population of 47 who had received ivermectin treatment, as well as 10 deaths in the remaining population of 163 over that 6 months period. They reported deaths for each month in the two sub-populations over the six months following ivermectin treatment. Barkwell and Shields performed two statistical tests on these data: chi-squared and Fisher's exact. Of these, Fisher's exact test is more accurate for small populations and answers the following question: if two groups, one of size 163 and one of size 47, are formed by picking individuals from the total population of 210 (with 25 deaths) uniformly at random, then what is the probability p of the pattern of deaths observed, or one with more deaths in the population of size 47. This test gives $p < 0.0001$ when applied to the data.

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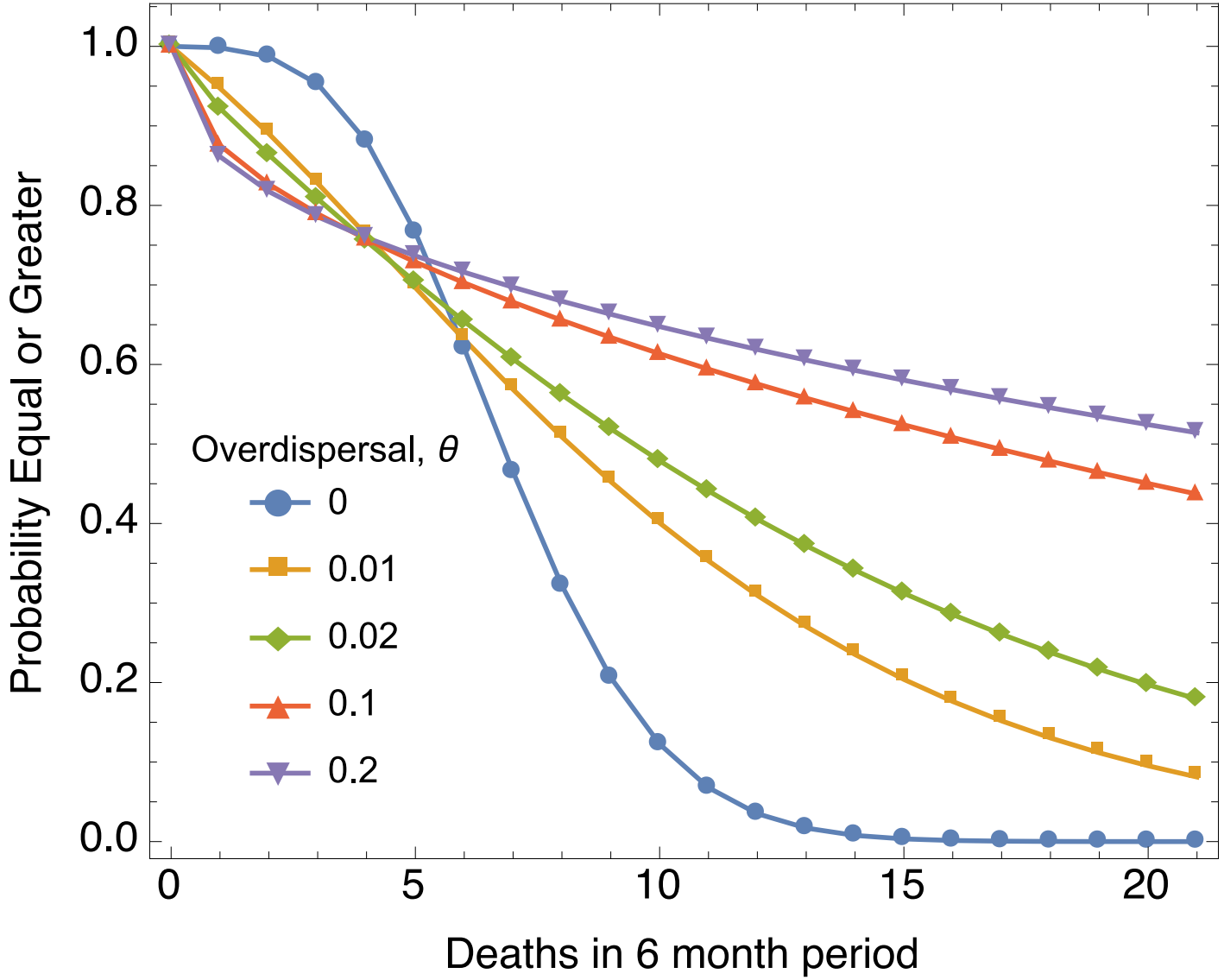
Assuming variability in death rates massively increases *p*



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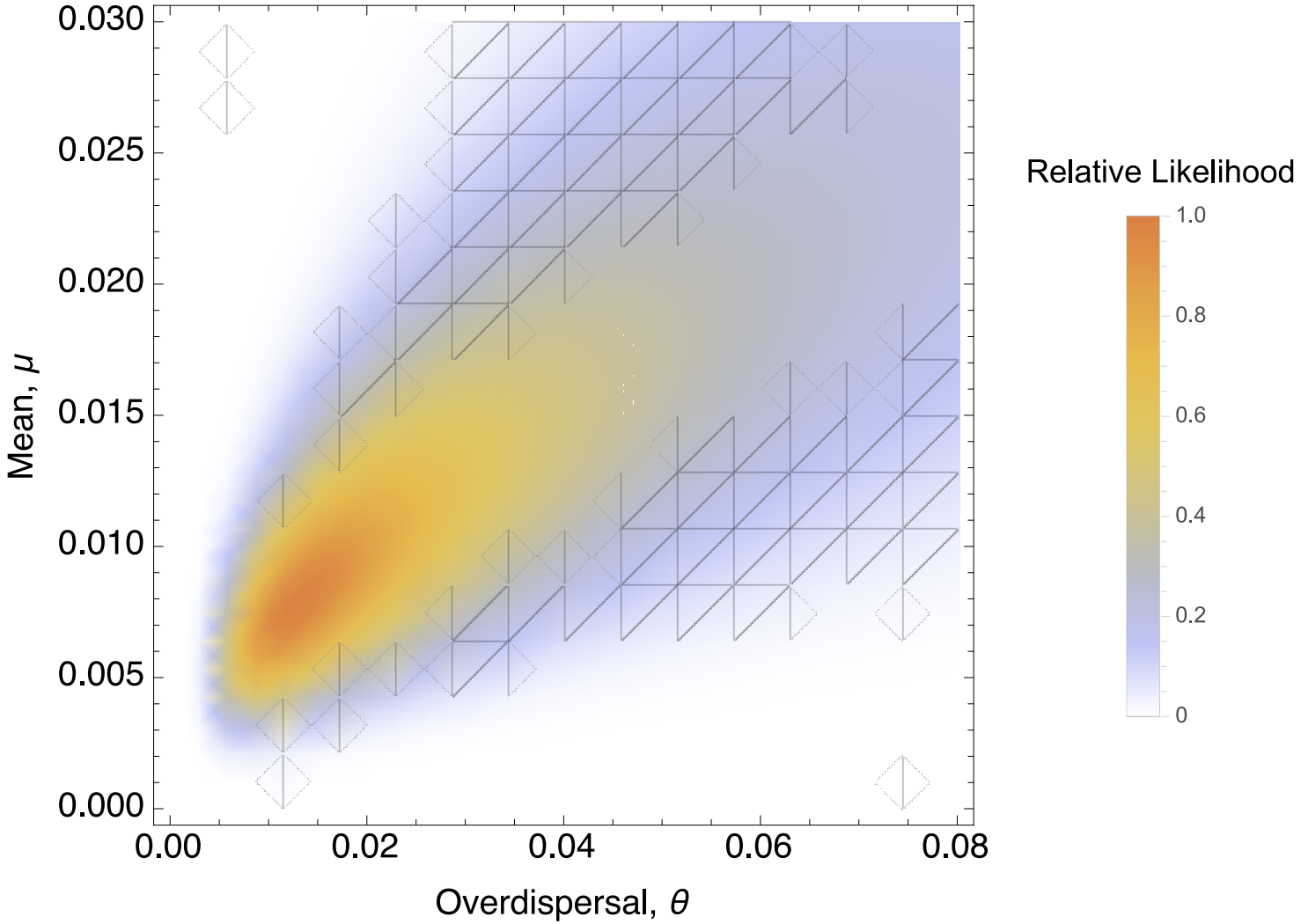
Plausible levels of heterogeneity in B&S data:



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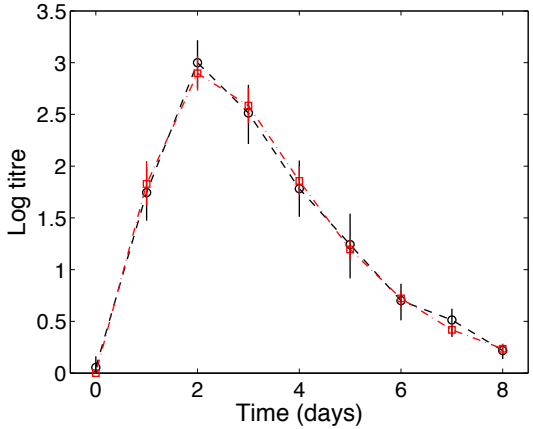
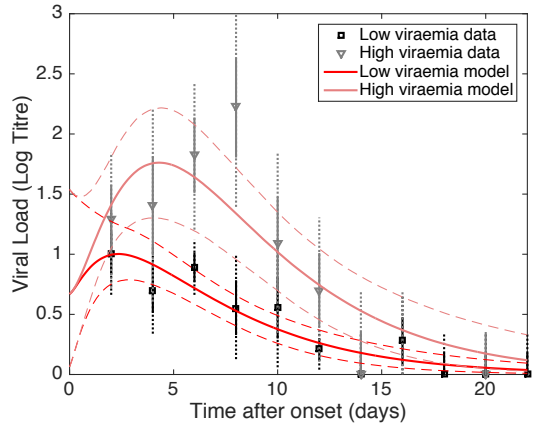
Conclusion ...

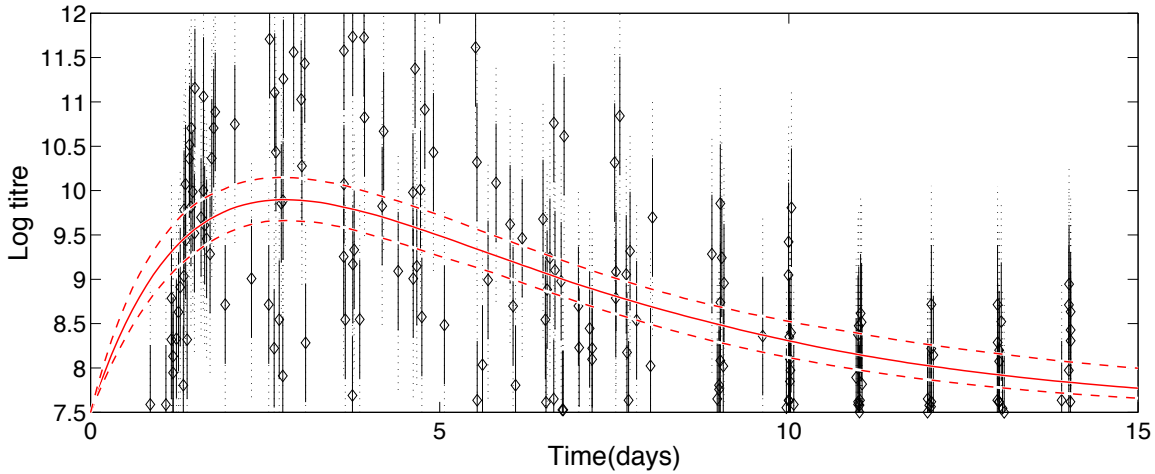
IVERMECTIN MAY WELL BE SAFE

Real shedding data

For influenza, Ebola and norovirus:

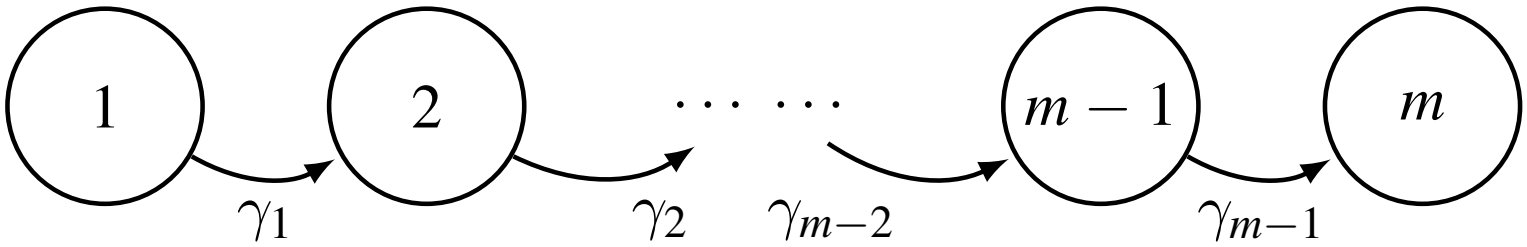






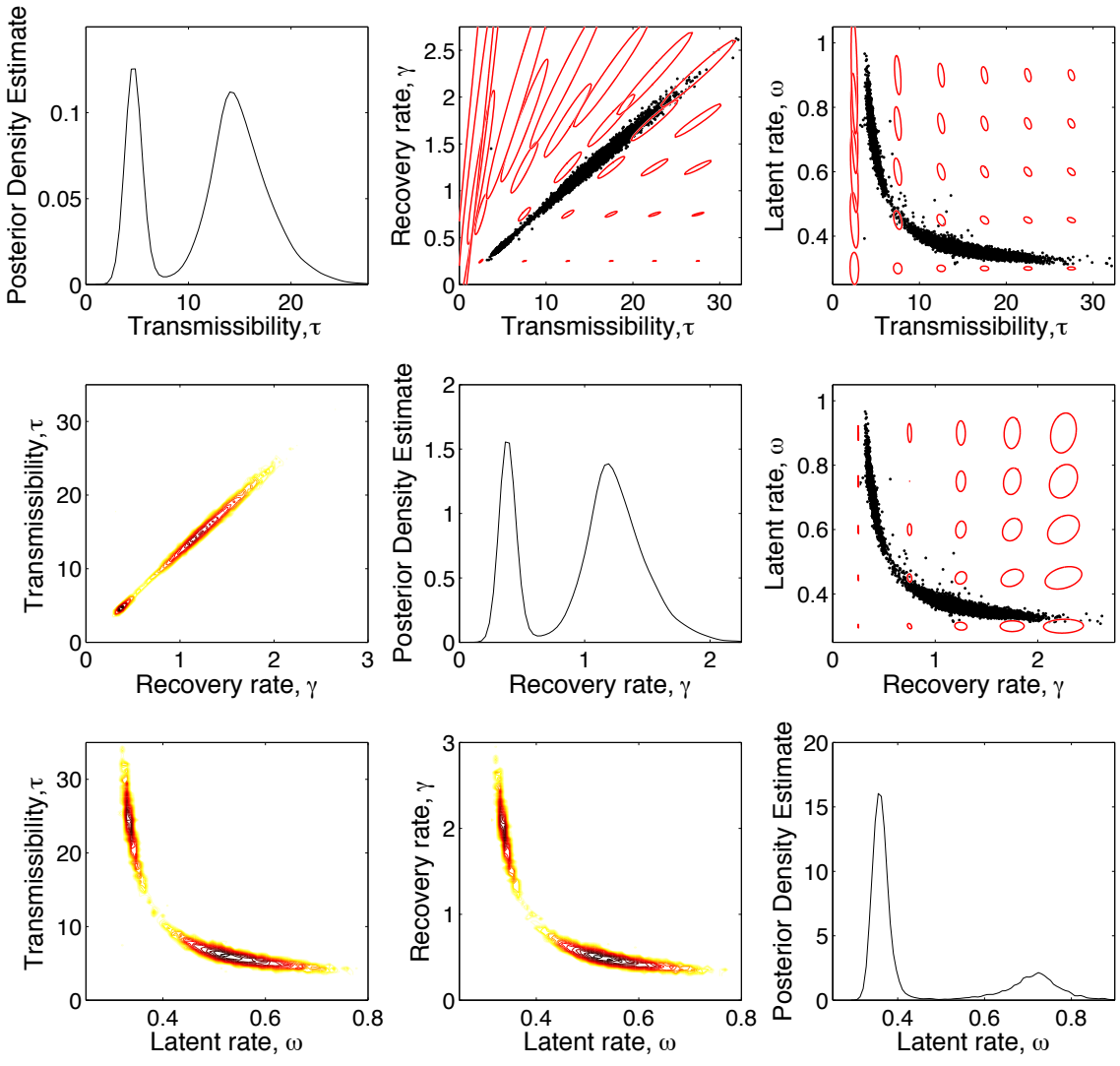
Compartmental model

State-space models where an individual is in a state $X(t)$ at time t are common in epidemiology:



The 'shedding' data comes from experimentally infected individuals. We suppose that the measured log titre (amount of live virus) is proportional to the expected infectiousness in the linear model above, $\mathbb{E}[\lambda(X(t))]$. We can solve the Markov chain to get derivatives with respect to parameters so these are available as well as the likelihood.

Influenza posterior

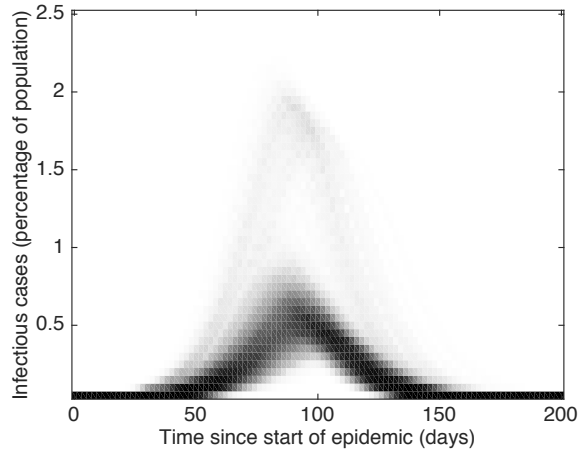


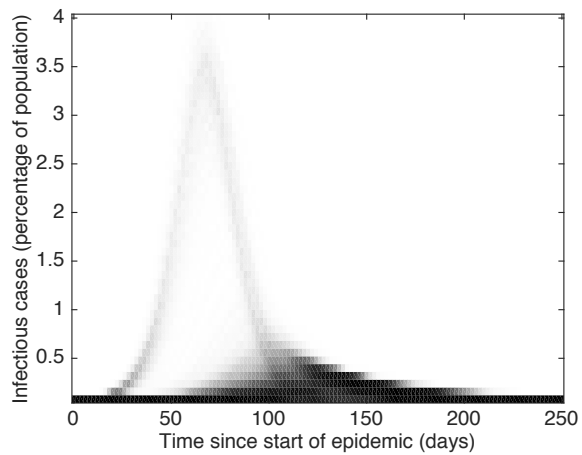
Influenza uncertainty quantitification

This allows us to propagate uncertainty forward for population-level predictions

Consider a DDE model for delayed interventions; if $\epsilon = 1$ these always work (top plot) and if $\epsilon = 0$ they only work before the infectious period (bottom plot):

$$
\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= -\frac{\beta}{N} S(t) I(t)\,, \\
\frac{\mathrm{d}E_1}{\mathrm{d}t} &= \frac{\beta}{N} S(t) I(t) - 2\omega E_1(t) - \pi_1(d) \frac{\beta}{N} S(t-d) I(t-d)\,, \\
\frac{\mathrm{d}E_2}{\mathrm{d}t} &= 2\omega (E_1(t) - E_2(t)) - \pi_2(d) \frac{\beta}{N} S(t-d) I(t-d)\,, \\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= 2(\omega E_1(t) - \gamma I_1(t)) - \epsilon \pi_3(d) \frac{\beta}{N} S(t-d) I(t-d)\,, \\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= 2\gamma (I_1(t) - I_2(t)) - \epsilon \pi_4(d) \frac{\beta}{N} S(t-d) I(t-d)\,,
\end{aligned}
$$





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THANKS FOR YOUR TIME!

Papers, collaborators, contact details etc:

http://personalpages.manchester.ac.uk/staff/thomas.house/