Modeling Ebola

Tachikawa infectious boot camp, 2019
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`https://github.com/dushoff/Generation_talks`

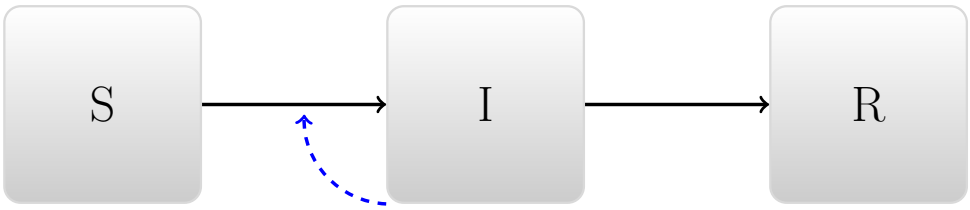
1 Dynamic modeling of infectious diseases

Models

- A model is a simplified view of the world
- Allows linking between assumptions and outcomes

Dynamic models

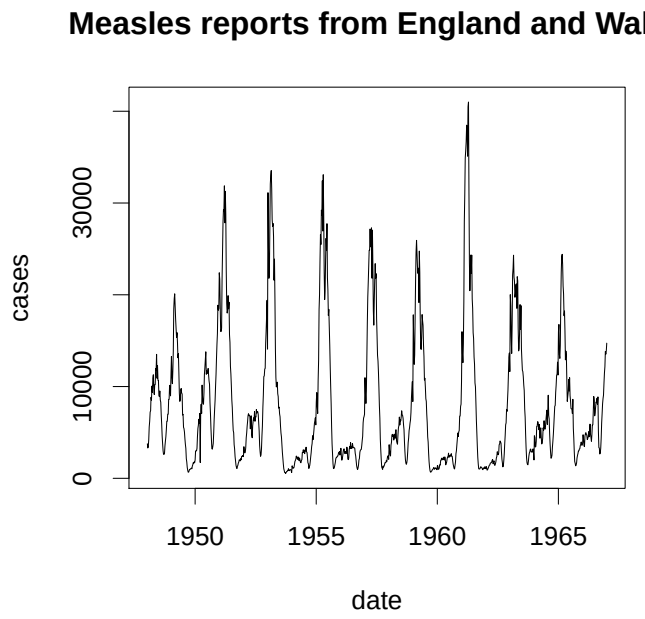
Connect scales



Small-scale events ⇔ Large-scale patterns and outcomes

Measles

Dynamic modeling connects scales



Ebola

Dynamic modeling connects scales

Statistics and theory

- Dynamical models are required to bridge scales
- Statistical frameworks are required to interpret noisy data
- We need tools that can incorporate dynamical mechanisms into frameworks that allow statistical inference
- Simple dynamical theories allow clearer interpretation and inspire better techniques

Questions

- Your model is not reality
- But it may help you answer a specific research question
- The model you use should be tailored to your question
  - What are the relevant details?

2 Early Ebola models

2.1 Process error and observation error

- **Observation error**: we don't observe the world perfectly
- **Process error**: we think our dynamical system has a fundamental random component
  - This is usually the only way to model processes where we treat individuals as individuals
- Doing both of these things is hard

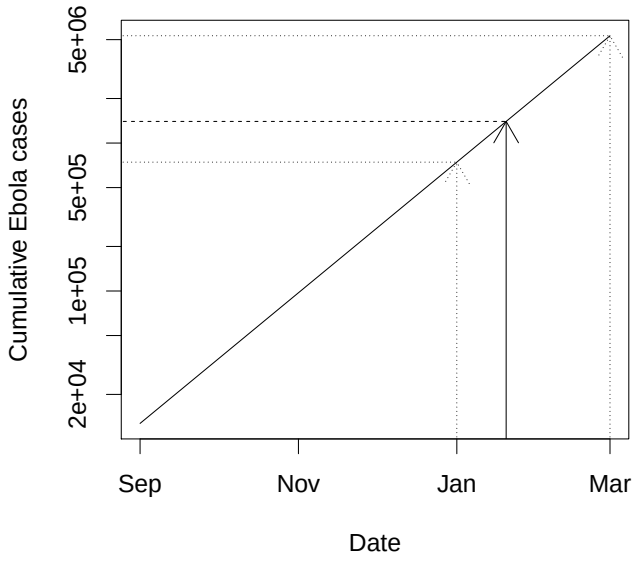
Lekone and Finkenstadt, 2006

- Modeled a small 1995 Ebola outbreak in DR Congo
- Used latent variables to consider both process error and observation error
- Result: More realistic model $\implies$ more uncertainty
- *DOI: 10.1111/j.1541-0420.2006.00609.x*

2.2 Projection models

The CDC projection

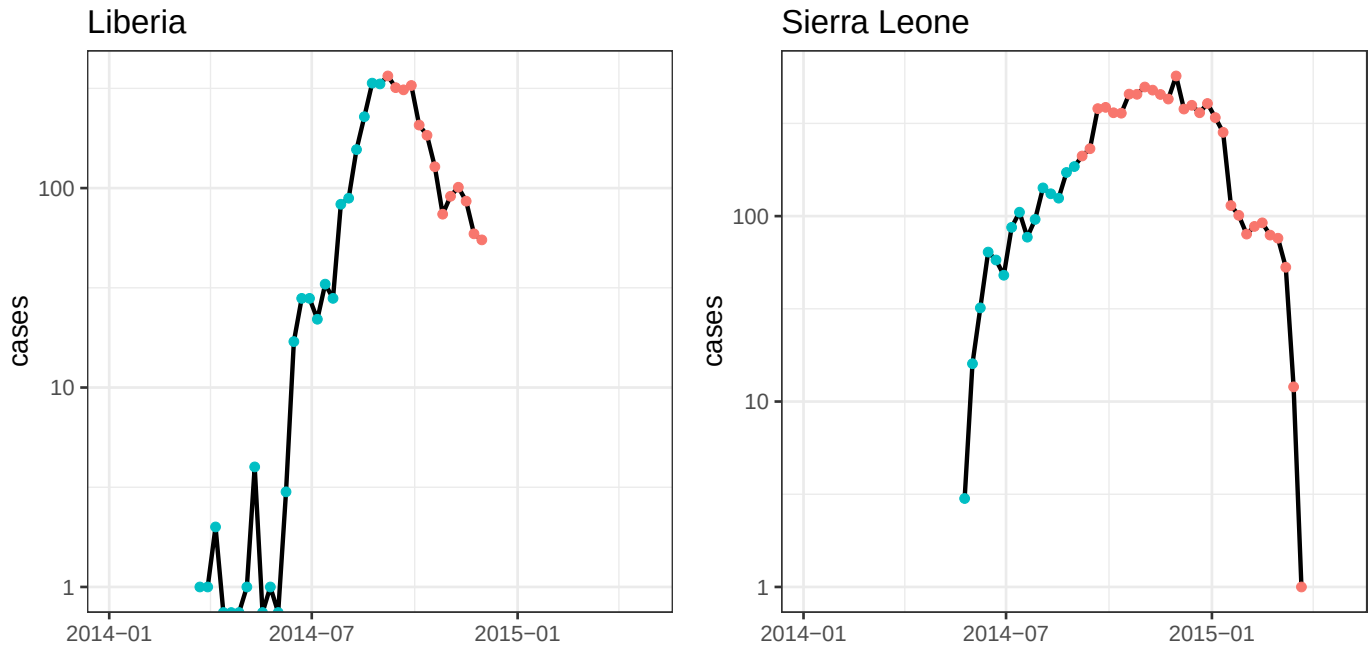
- Meltzer 2014 estimated > 1 million cases by "Jan 20, 2015" unless effective action was taken
- Model contained contained many compartments for infected people
  - disease stage, linkage to treatment
- Very crude handling of contact patterns, susceptibles



Projection models

- Wrong level of detail
- But they did address a question:
  - Does the West Africa Ebola epidemic have the potential to be a global crisis?

The epidemic

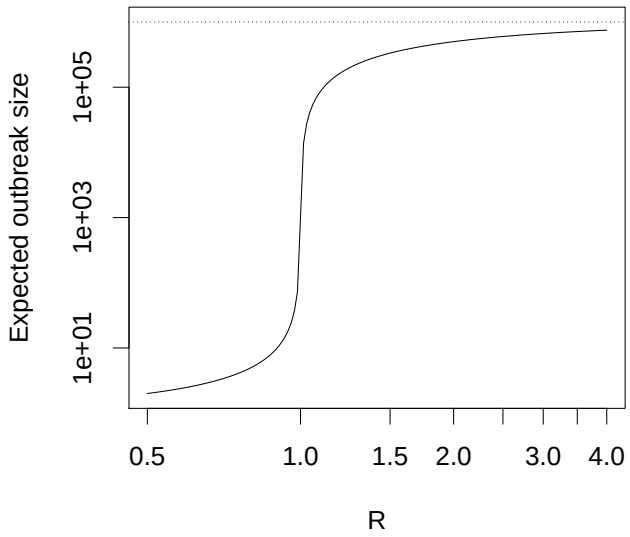


Ebola outbreaks

- Before 2014, most Ebola outbreaks were either
  - very small, or
  - pretty large (compared to some estimate of population at risk in a remote village)
- More or less consistent with simple picture

Predicted outbreak size

- Simple models argue that outbreaks should (almost always) be:
  - Very small (sub-critical), or
  - Very large (at the scale of the population)



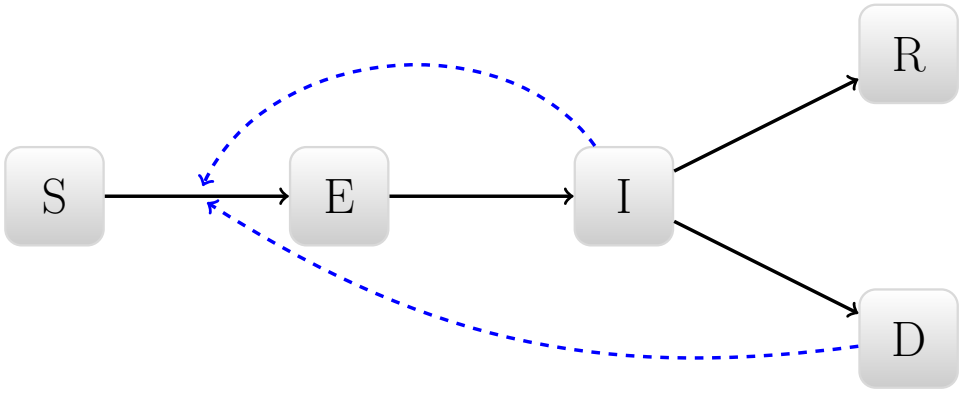
3 Some simple models

3.1 Burial transmission

Post-death transmission and safe burial

- What proportion of Ebola spread occurs before vs. after death?
- Highly context dependent
  - Funeral practices, disease knowledge
- What if it's more than we think?
  - Disease spreads slower?
- *Weitz and Dushoff* Scientific Reports *5:8751.*

Disease model including post-death transmission



Ebola burial example

- Burial transmission increases the mean generation interval
  - *Increases* estimate of $\mathcal{R}$
- . . . increases variation
  - *Decreases* estimate of $\mathcal{R}$
- So what's the result?
  - It feels like it should increase
  - The filtered mean approach tells us: shifting transmission later must increase the estimate

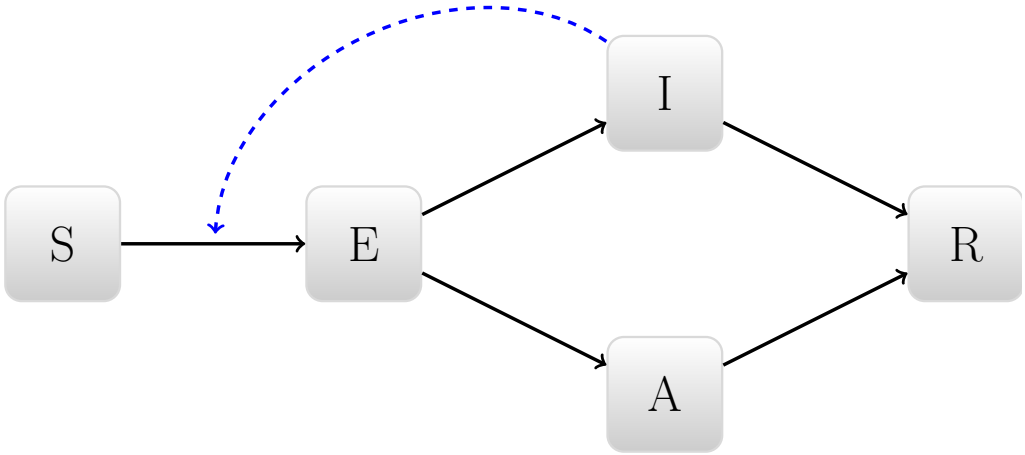
Summary

- Different parameters can produce indistinguishable early dynamics
- More after-death transmission implies
  - Higher $\mathcal{R}_0$
  - Larger epidemics
  - Larger importance of safe burials
- $r =$ strength something $\times$ generation speed something

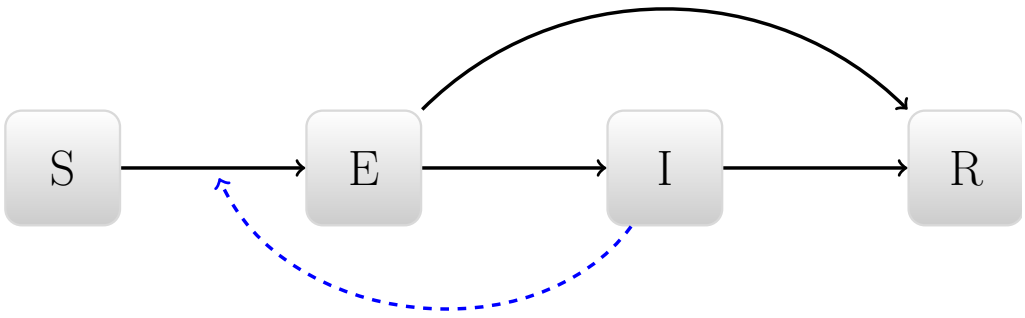
3.2 Dynamic effects of sub-clinical infections

- People with no history of clinical Ebola illness have Ebola-specific antibodies:
  - In forests where animals carry Ebola
  - In places where past Ebola outbreaks have occurred
- What if $\approx 50\%$ of infected people have *sub-clinical* infection?
- *Bellan et al.* Lancet *384:1499–1500, October 2014*

Add sub-clinical immunity



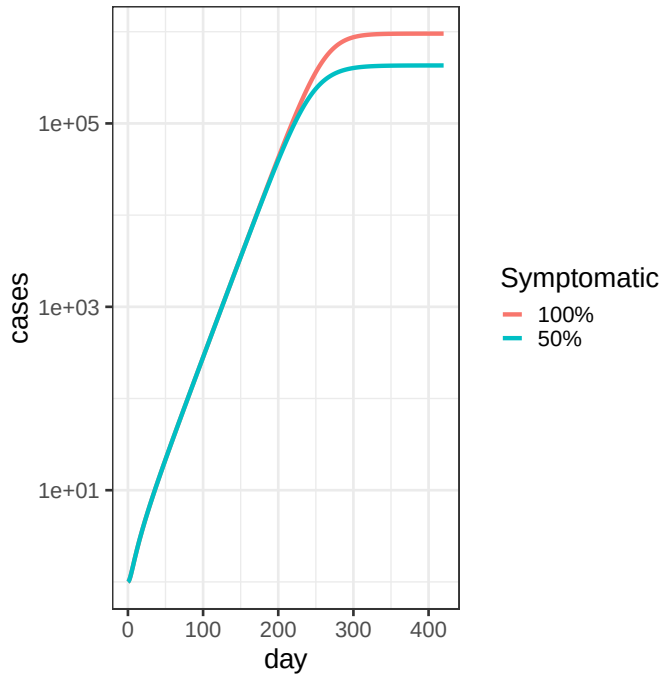
Simplify

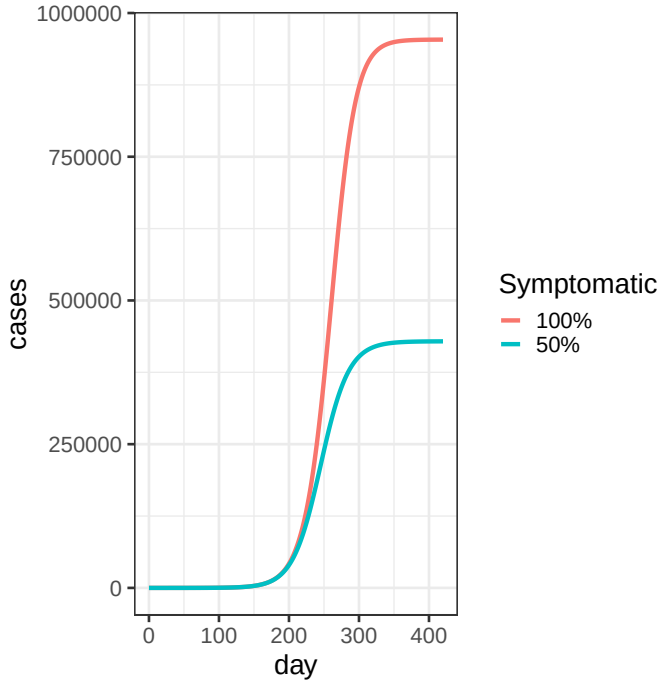


What is the effect of sub-clinical immunity?

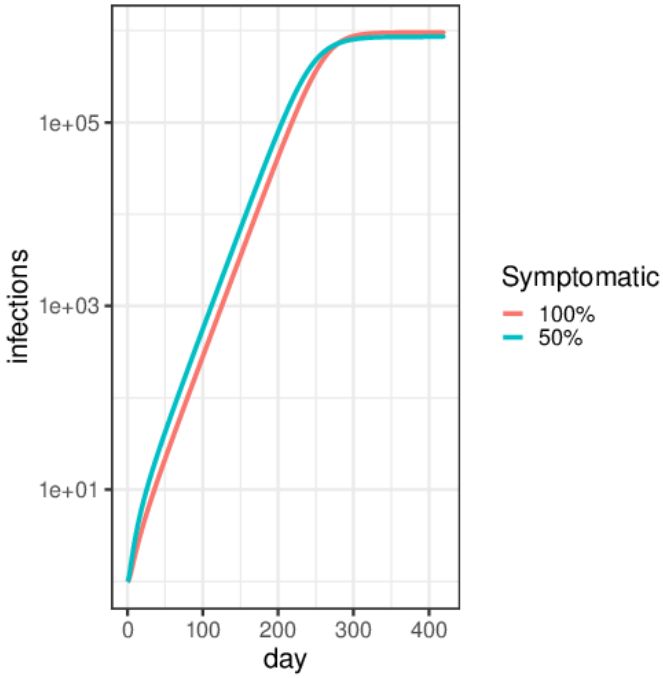
- What do we already know?
  - Parameters and starting conditions?
  - Incidence time series?

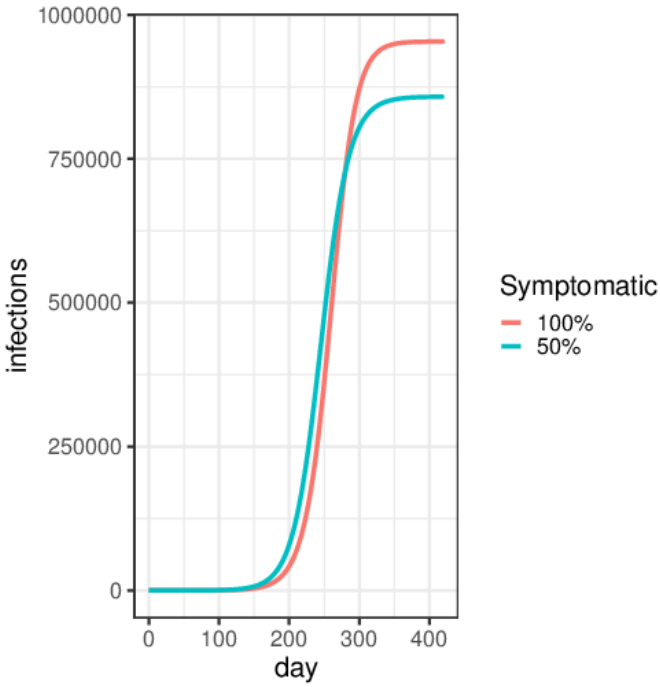
Ebola *cases*





Ebola *infections*



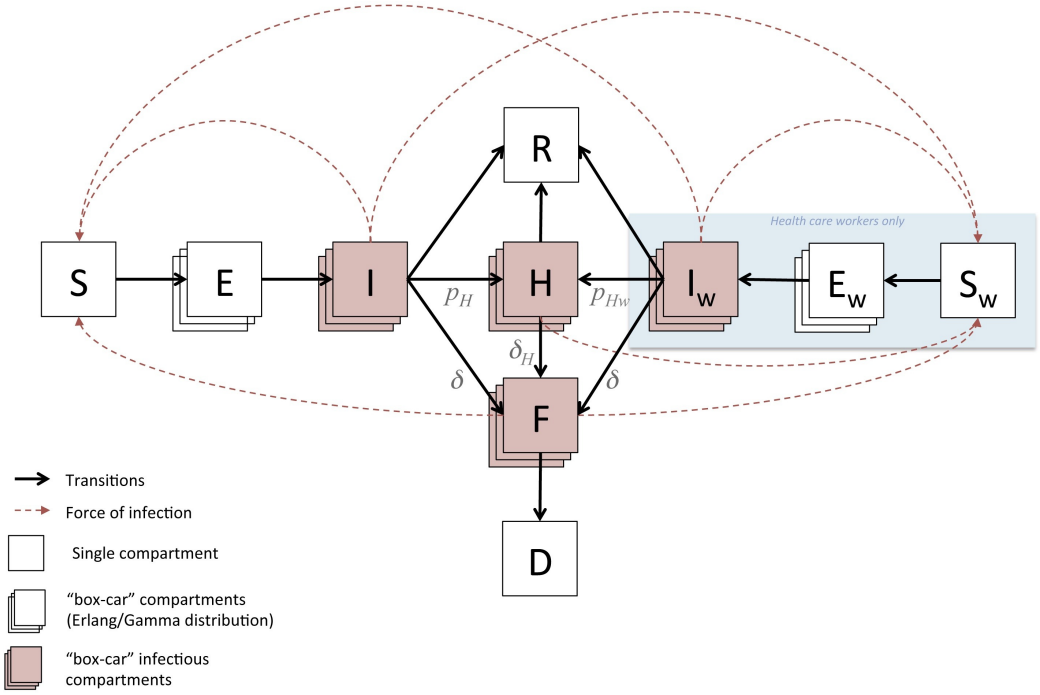


Estimation

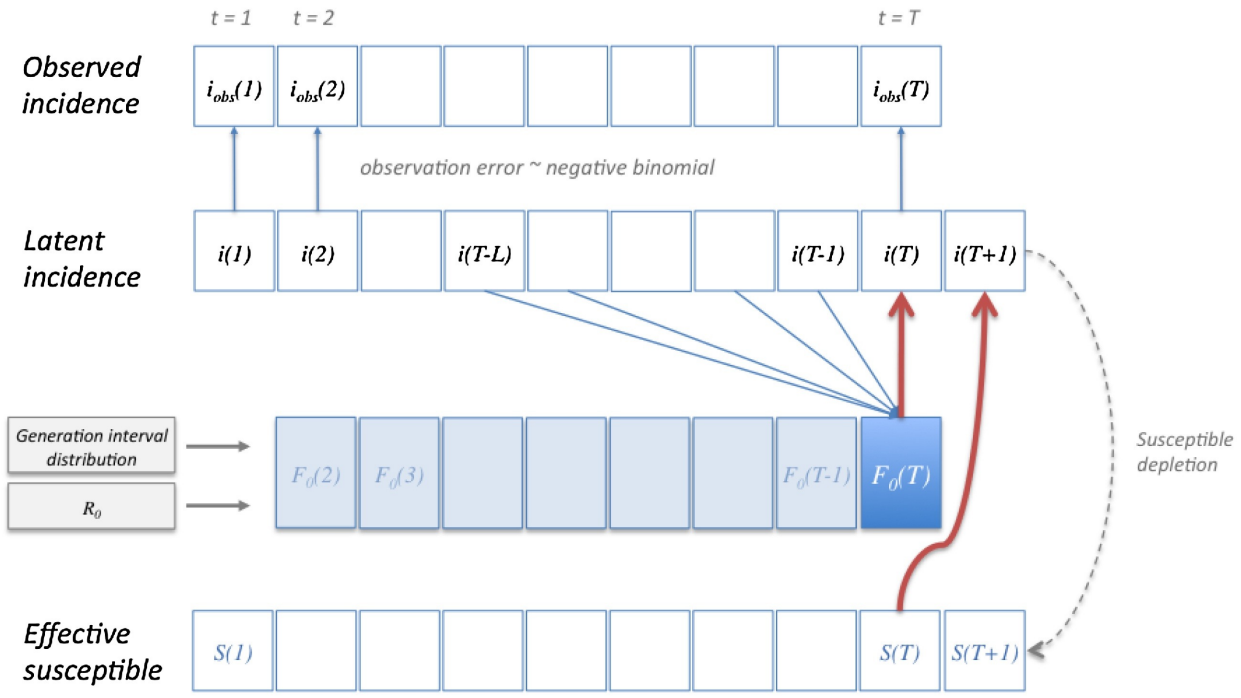
- Indirect evidence
  - Not enough information, and too many complications
    - Population structure, changes through time
- Direct evidence
  - Easy: how common is sub-clinical infection?
    - More evidence is available now
    - . . . but not as much as we expected.
  - Hard: how protected are people who recover from it?

4 Forecasting

Compartment model approaches



Discrete-time renewal equation

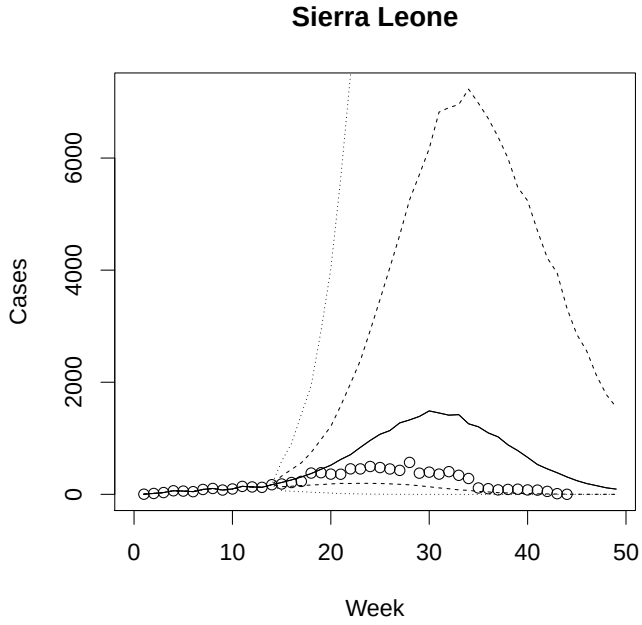


https://doi.org/10.1016/j.epidem.2017.02.011

Relevant detail

- The things we are good at estimating and modeling may not be sufficient to forecast Ebola spread
- We don't know enough about:
  - contact structures
  - beliefs and behaviours

What we don't know!



5 Ethics

- History of abuse → strong rules
- In general, you can't put public good ahead of participant interests
- It's hard to achieve clinical equipoise – would *you* want to be in the control arm?
- *Bellan et al.,* BMJ *2014;349:g7518*

Vaccine trials

- What are the *ethics* of controlled trials in the middle of a deadly epidemic?
- What are the *logistics* of controlled trials on the down-slope of an epidemic?

5.1 The statistical power and validity of Ebola vaccine trials

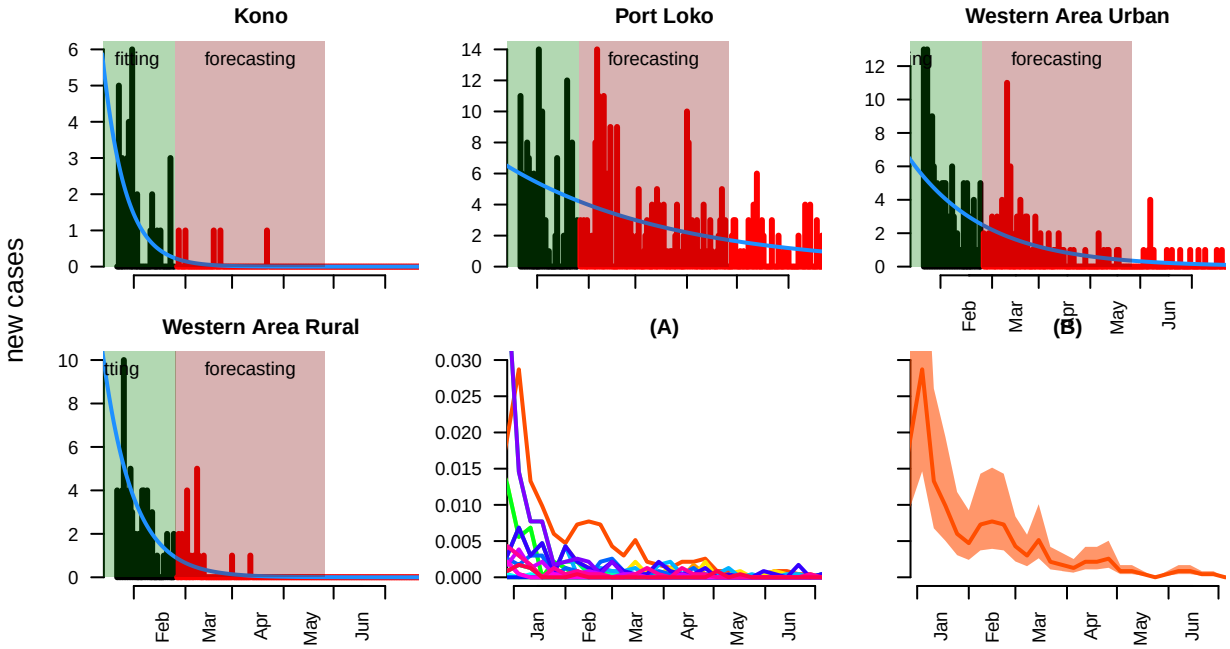
Randomized controlled trials

- The gold standard of medical evidence
- A plan is made, and then participants are individually and randomly assigned to **treatment** and **control** groups
- Control groups sometimes get something that is meant to be good for their health, too
  - E.g., a meningococcal vaccine

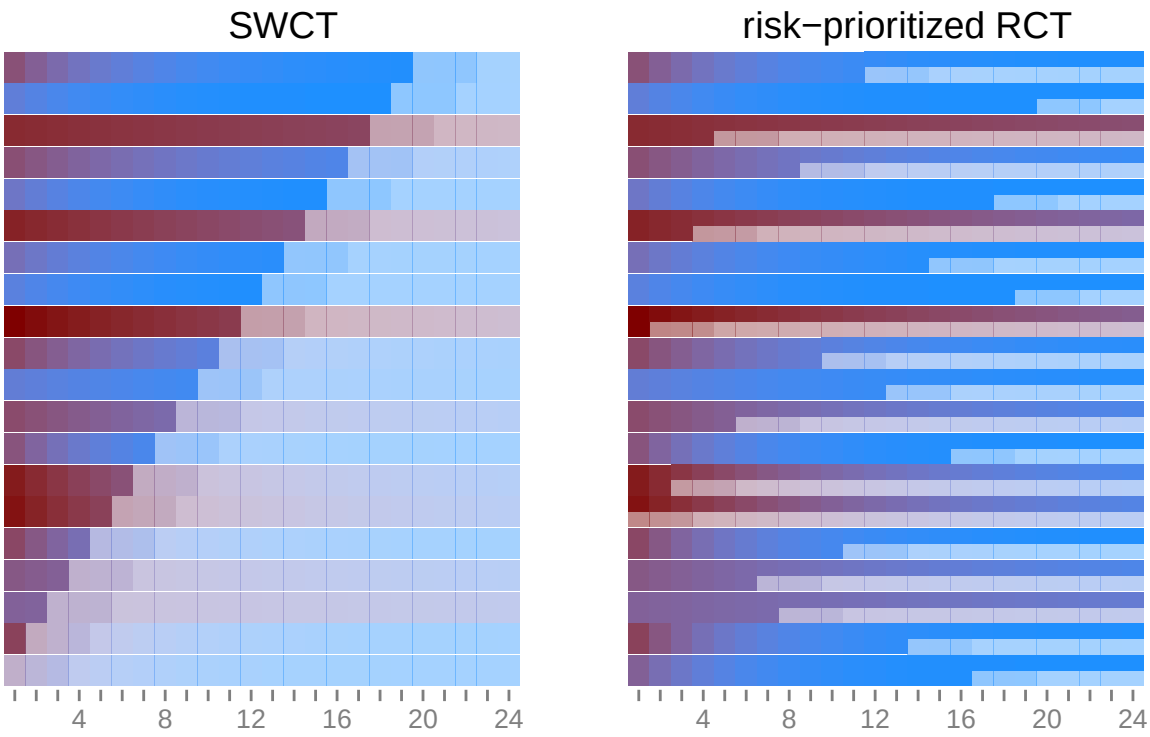
Stepped-wedge controlled trials (SWCT)

- Sometimes it's unethical to delay vaccination (or other treatment) to participants
- You still can't necessarily vaccinate everyone at once
- It may be possible to evaluate efficacy by randomizing the *order* in which people are vaccinated
  - A free lunch!
- This is a relatively *fragile* idea
  - Not as powerful as RCT
  - If RCT is not ethical, then it's also not ethical to make logistical concessions to study objectives

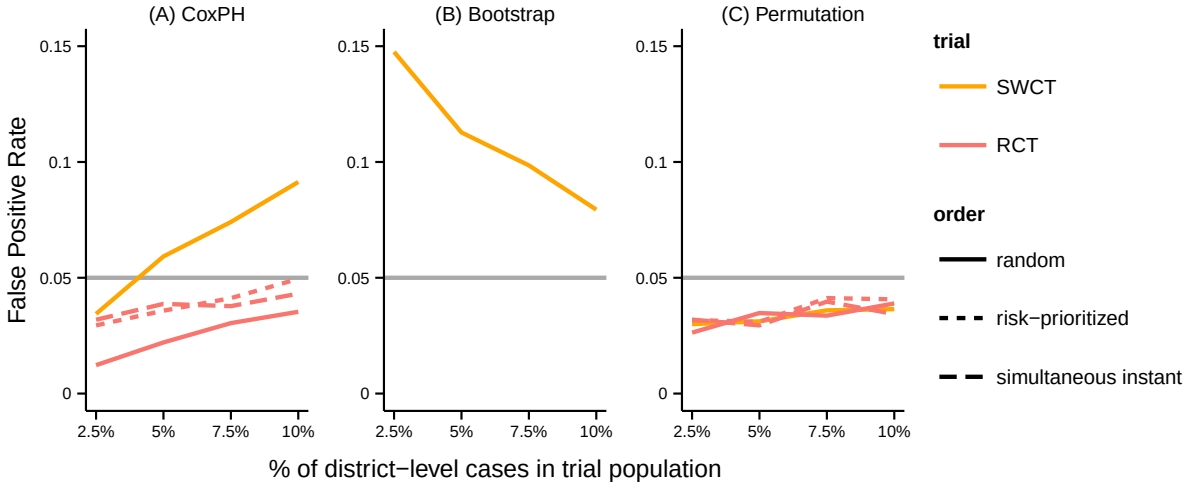
Simulated incidence



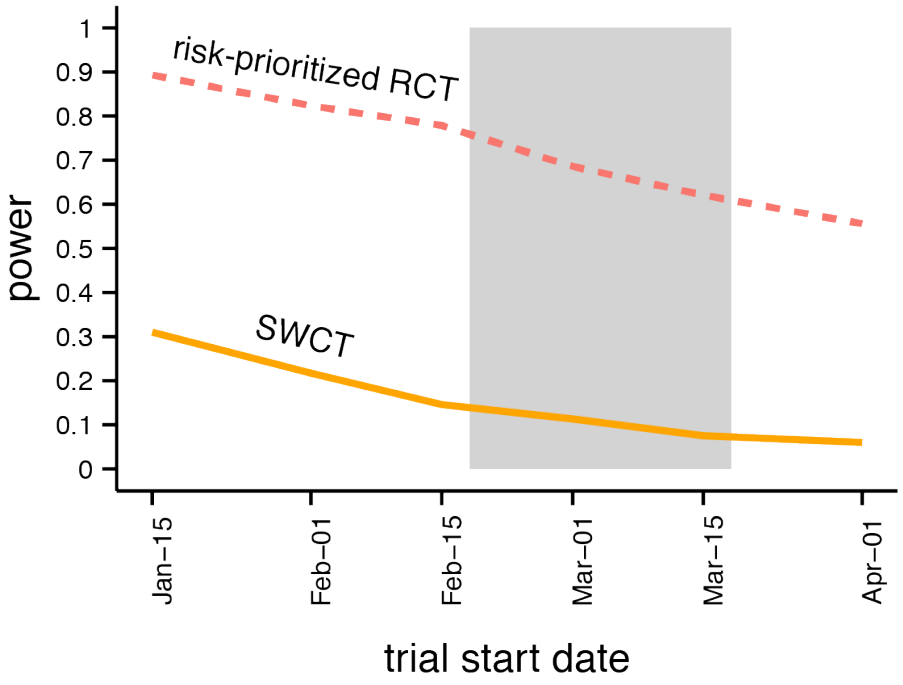
Vaccine rollout scenarios



Statistical validity



Statistical power



Summary

- Spatiotemporal variation undercuts SWCT
  - Reduces power
  - Reduces or eliminates ethical advantages
- RCTs surprisingly robust to all kinds of issues
  - Also allow prioritization
- Permutation tests can rescue statistical validity
- Changing landscapes
  - Hard to do an Ebola vaccine trial when incidence is very high or very low

6 Conclusions

- Dynamic models allow us to explore the meaning of *scientific* hypotheses
- They are most useful when they help us understand mechanisms in a scientific way
  - Don't trust mathematical results that you can't explain
- We need to recognize what we don't know
  - Use statistical methods
  - Recognize when your uncertainty is large