Mathematical modeling reveals the potential consequences of the worldwide emergence of the H58 haplotype of *Salmonella* Typhi

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What is mathematical modeling?

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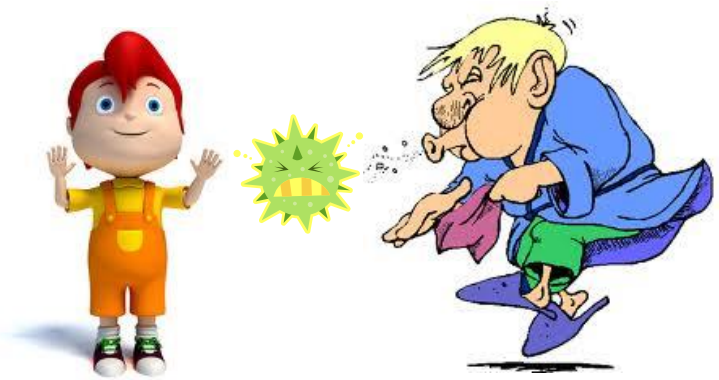
- Description of a system using mathematical concepts and equations
- Differs from traditional statistical modeling methods which assume independent observations
- Takes into account NON-LINEAR effects that result from the interaction of infectious and susceptible individuals



Why model?

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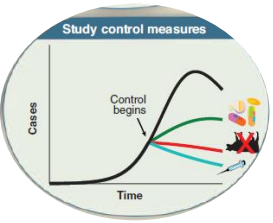
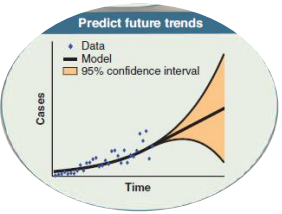
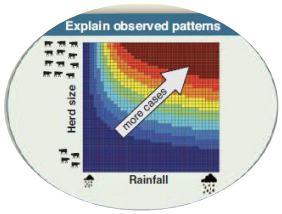


- Study control measures
  - What level of indirect protection can be expected from different vaccination strategies?



- Predict future trends
  - Will vaccination eliminate typhoid, or can we expect incidence to rebound?



- Explain observed patterns in data
  - Why is typhoid incidence increasing in different parts of the world?
  - HYPOTHESIS: Patterns can be explained by the emergence of H58 haplotype at different times in setting with different baseline incidence

Lloyd-Smith et al, Science (2009)

Emergence of the H58 haplotype

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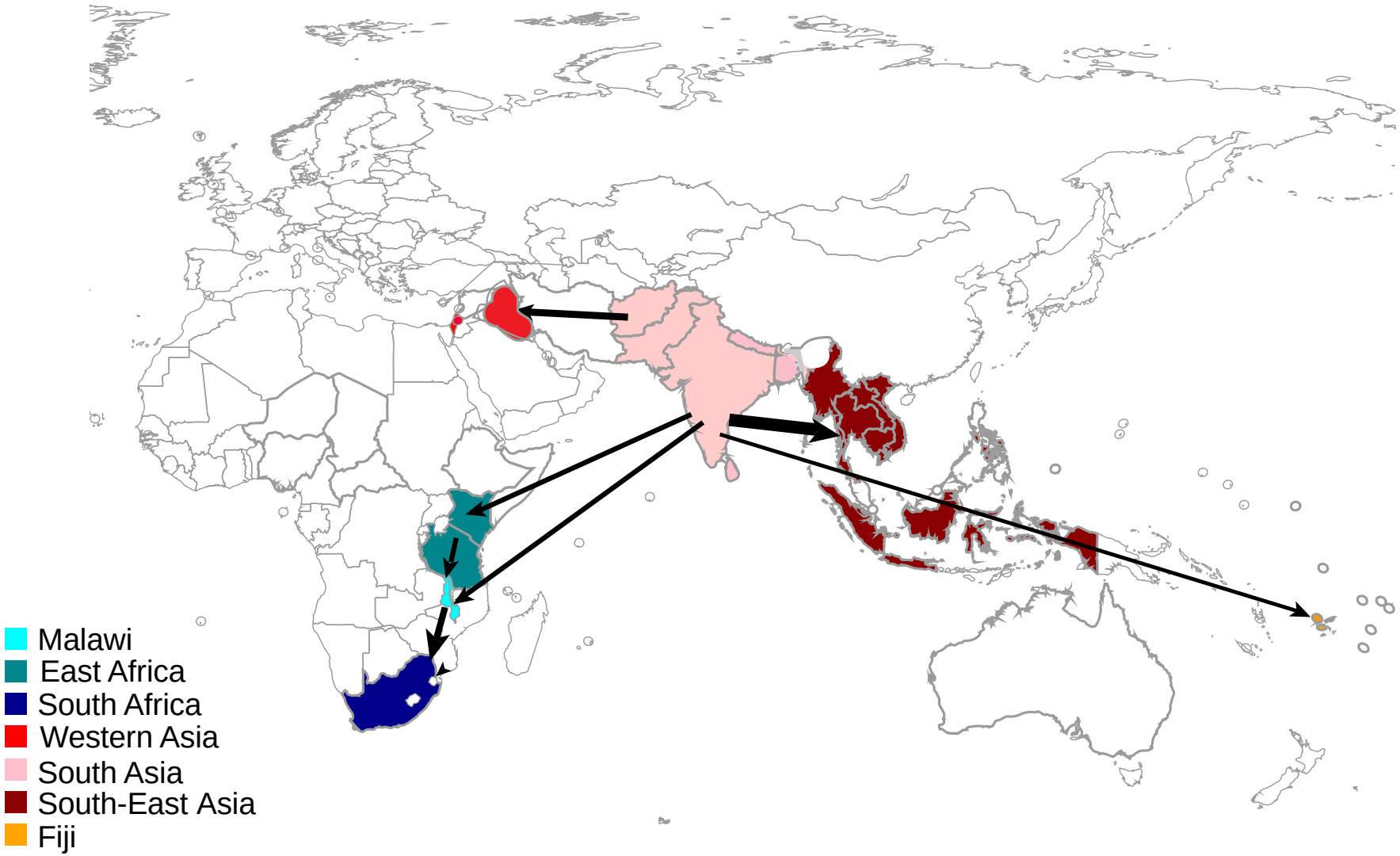
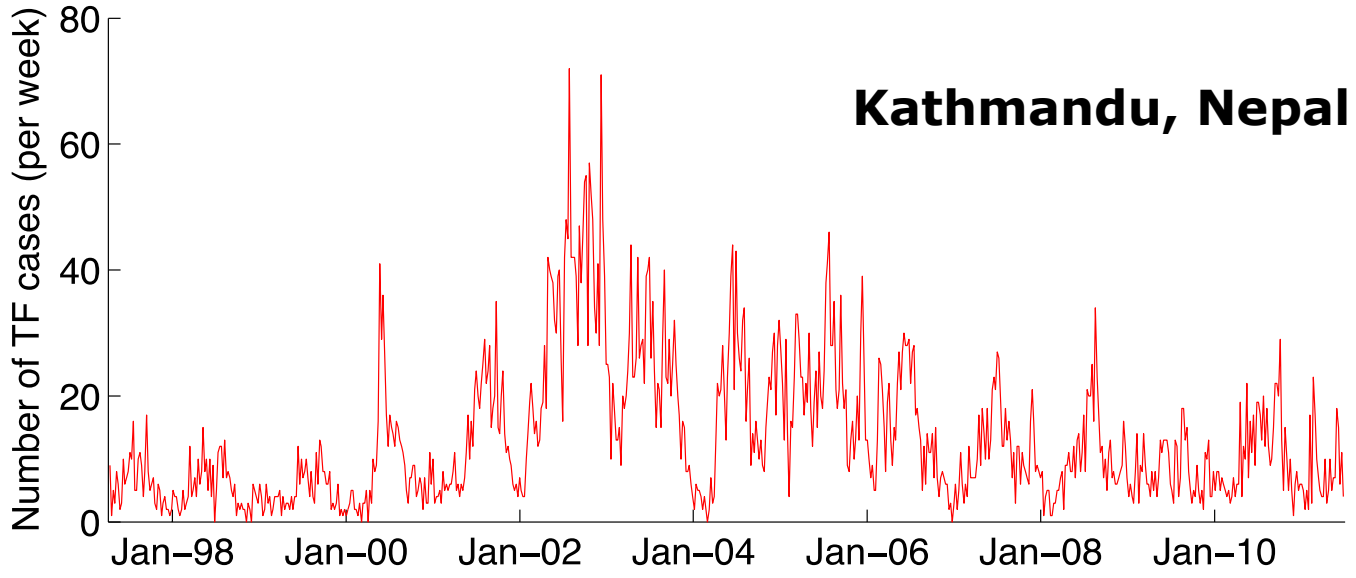
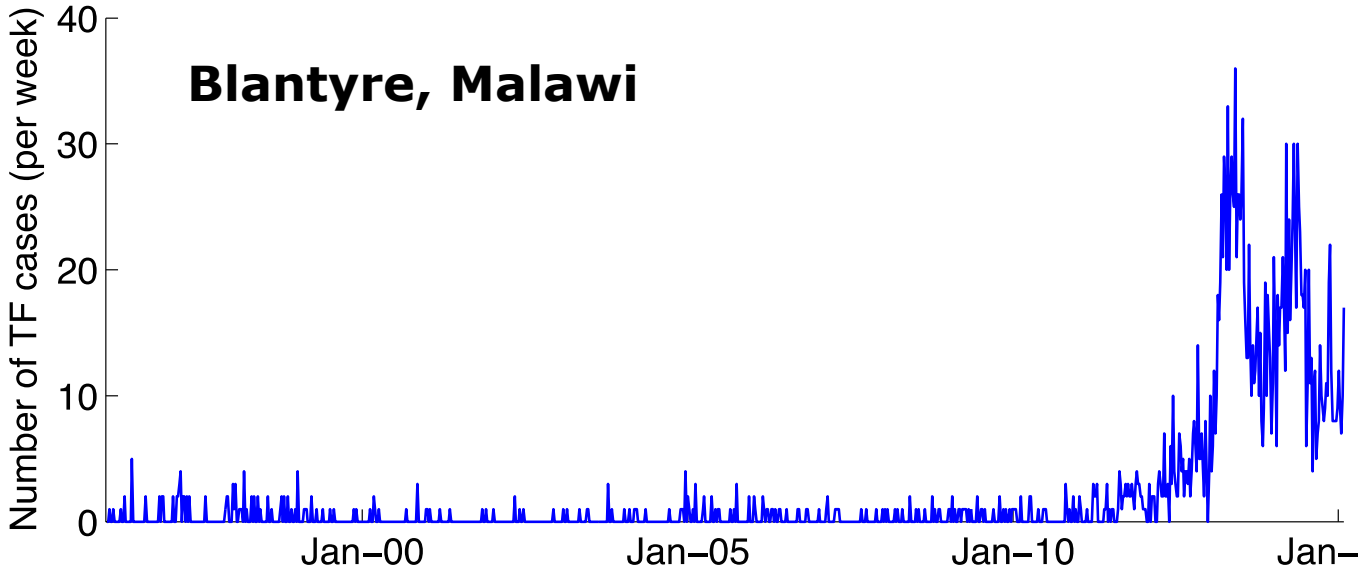


Wong et al, *Nature Genetics* (2015)

A Tale of Two Cities…



Bowles CC et al (in prep)



Feasey NA et al, *PLoS NTD* (2015);
Pitzer VE et al (in prep)

Emergence of the H58 haplotype

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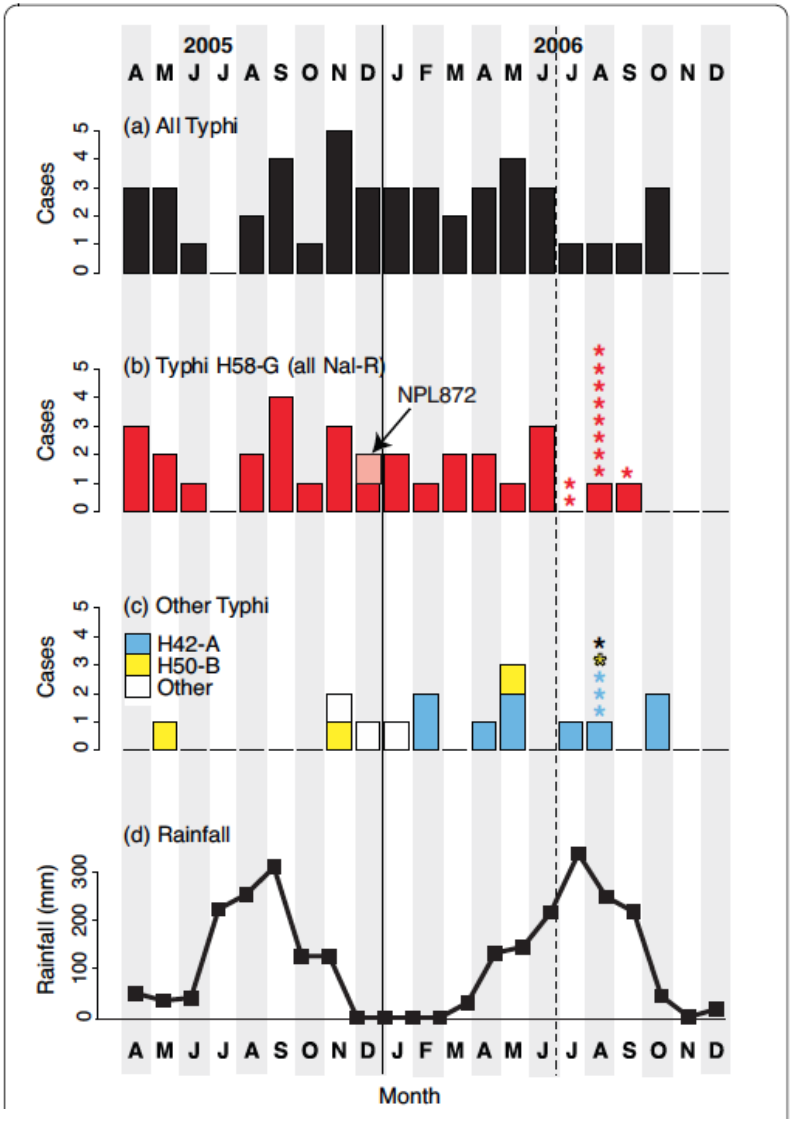
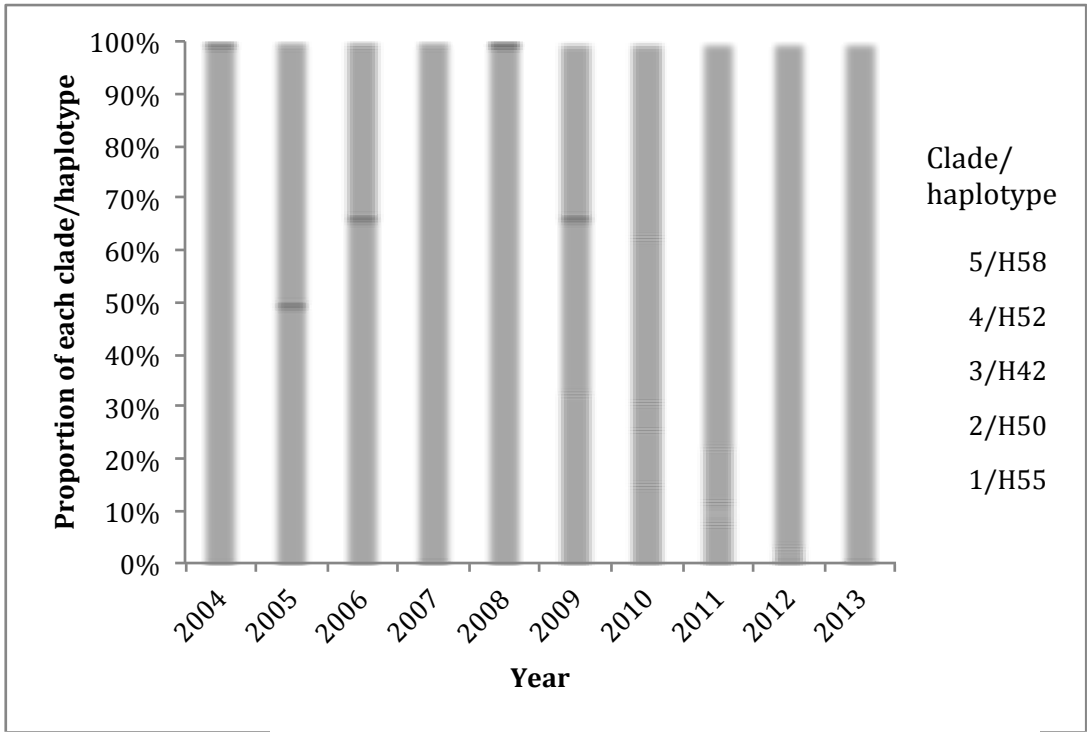
Kathmandu, Nepal



Holt KE et al (2010) *BMC Infect Dis*

Blantyre, Malawi



Feasey NA et al (2015) *PLoS NTD*

Dynamic model structure

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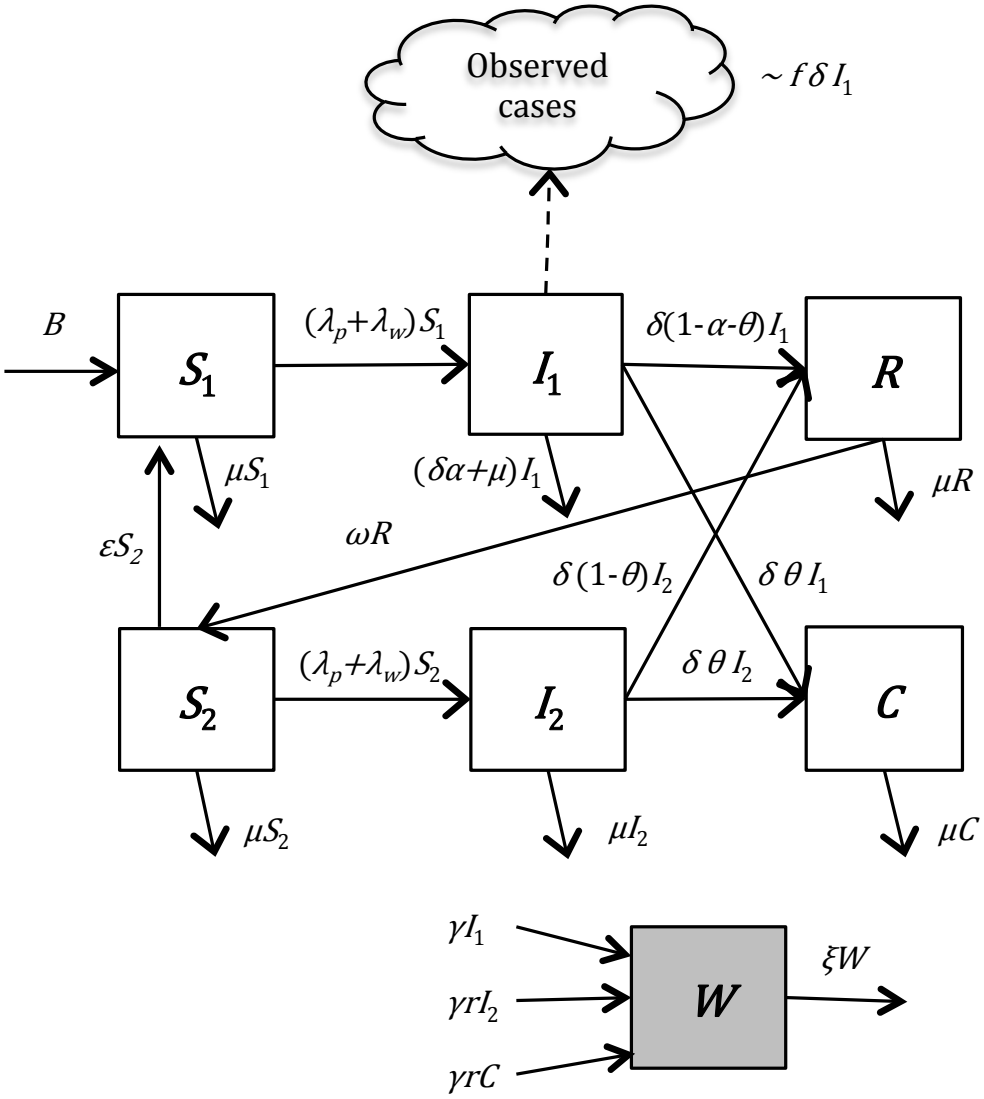

Essential features:

- Loss of immunity to subclinical infection
- Primary vs secondary infection
- Chronic carriers
- Balance between "short cycle" transmission via contamination of food, etc in the immediate environment
- …and "long cycle" transmission via contaminated water
  - May be more seasonal

Why is typhoid incidence increasing in Malawi?

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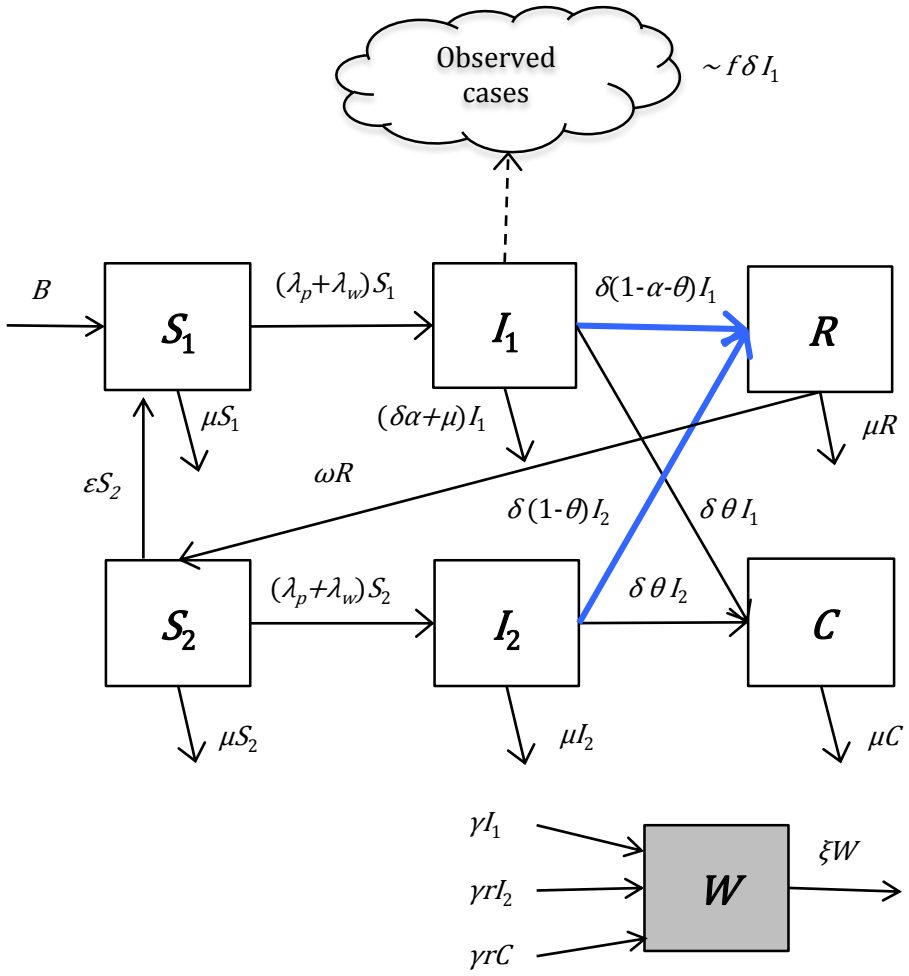
- Increased prevalence of drug-resistant strains
  - Longer duration of infectiousness



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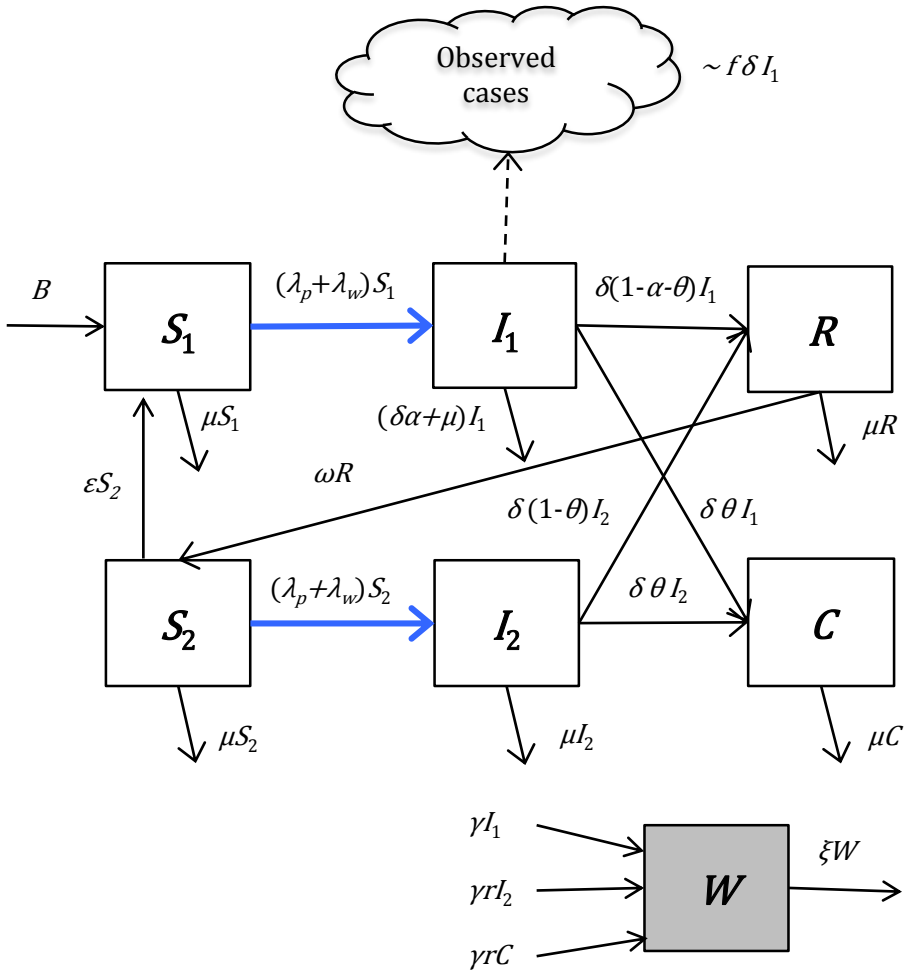
- Emergence of the H58 haplotype, which is more "fit"/transmissible than previous strains
  - Increase in the transmission rates



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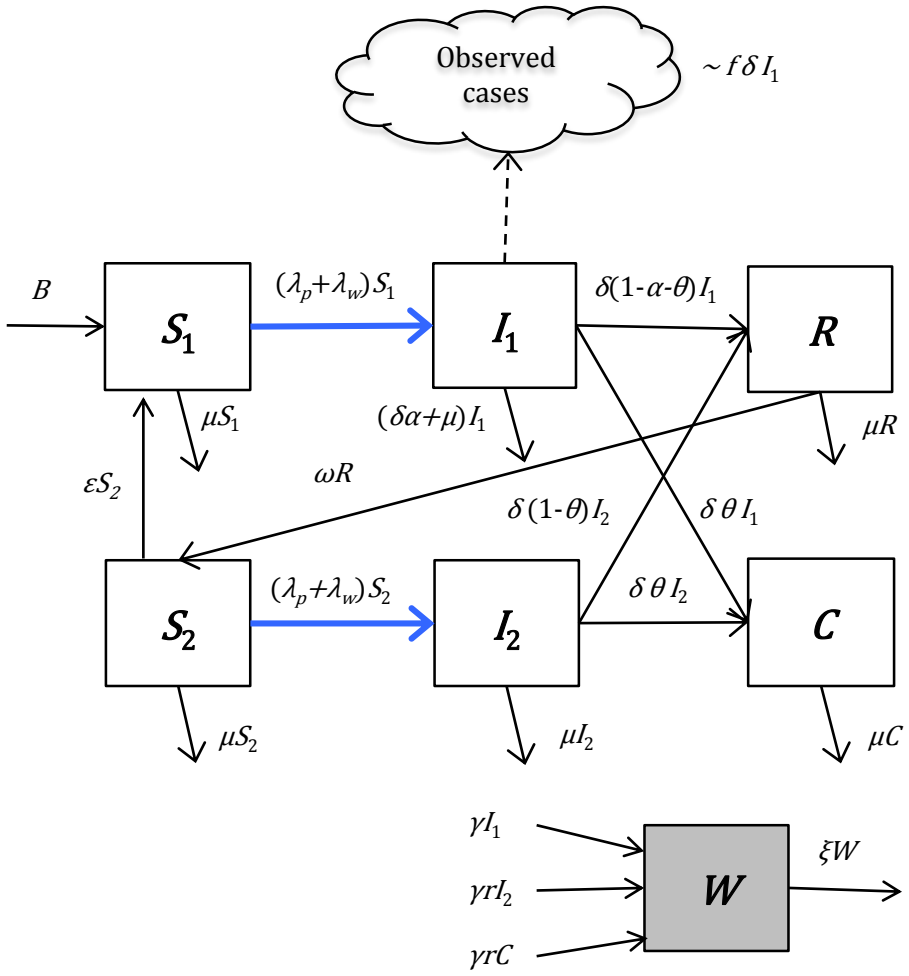
  - Increase in the transmission rates
- Both would lead to an increase in R_0



Epidemic drivers: Kathmandu, Nepal

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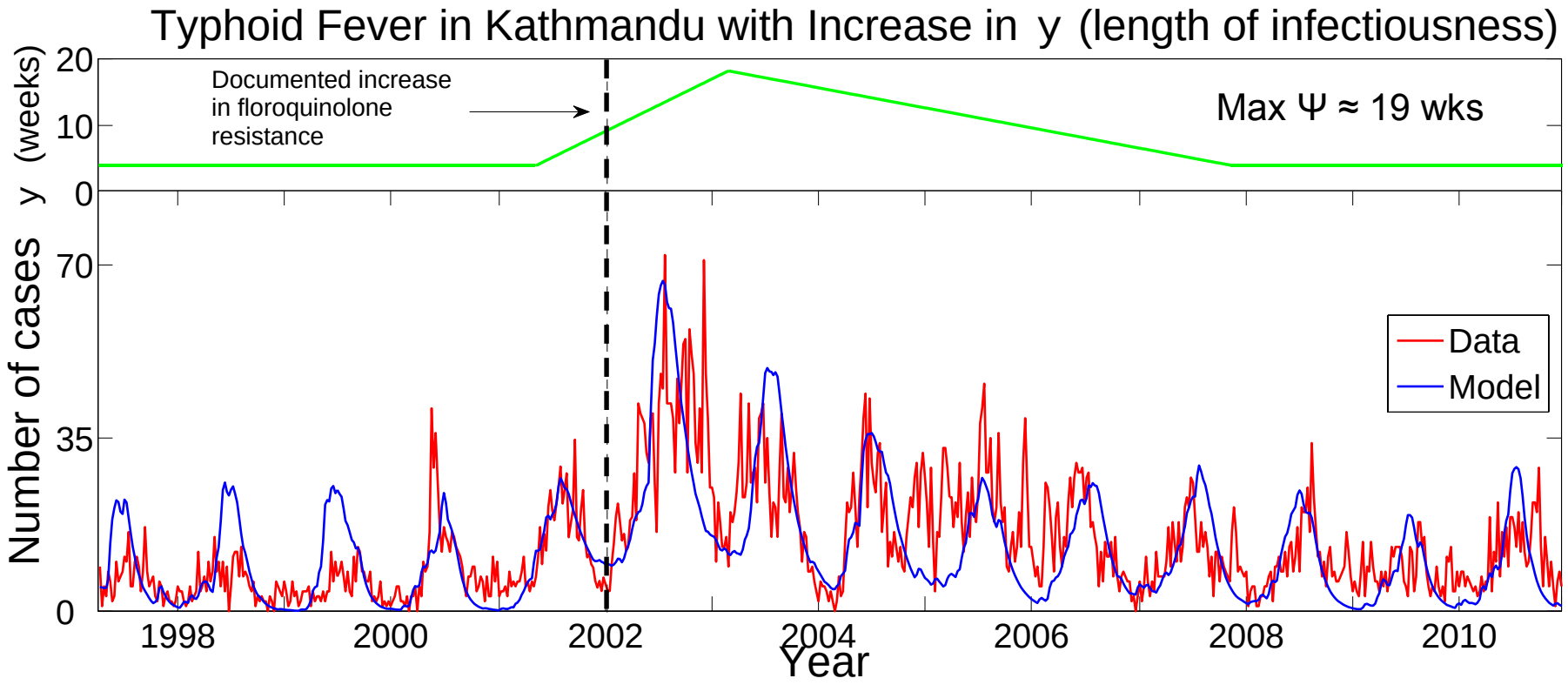

- Model provides a good fit to the data and can explain the increase in cases in 2002
- But increase in infectious period is unrealistically long

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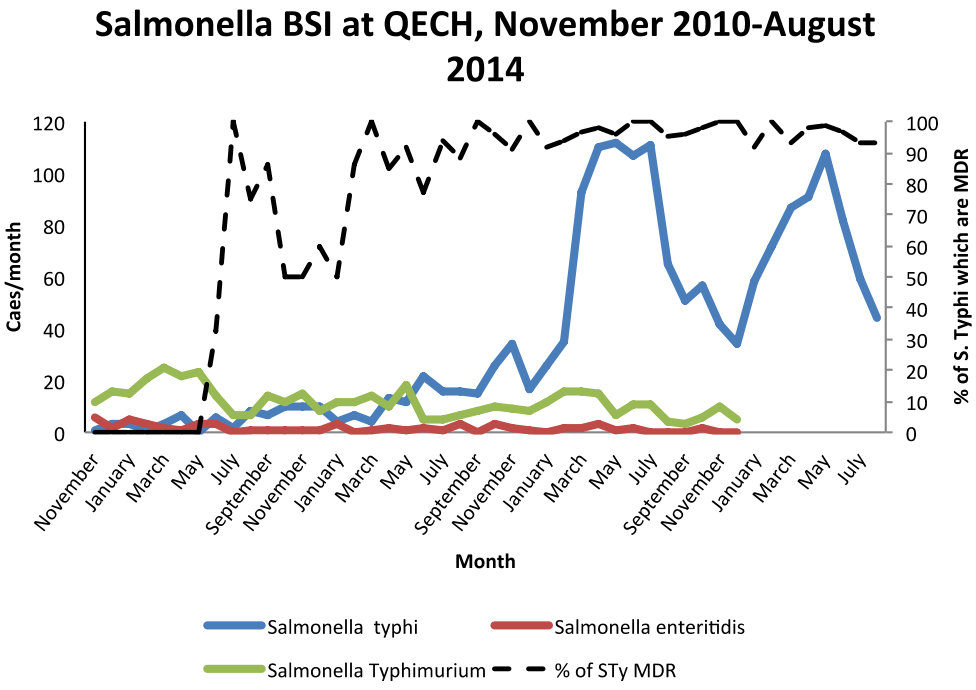
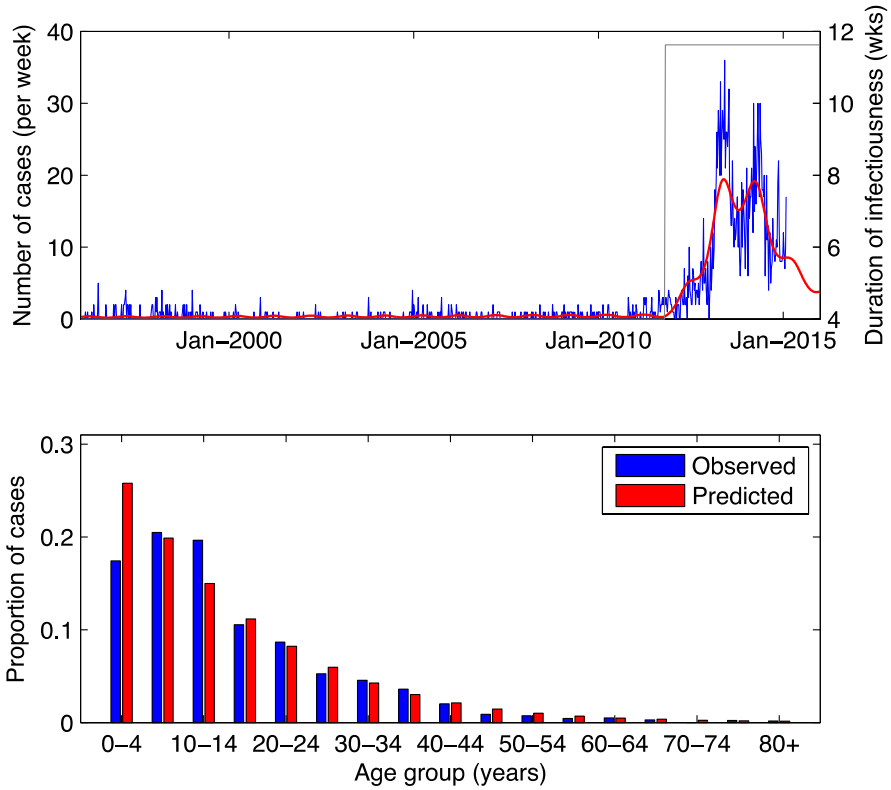
Bowles CC et al (in prep)

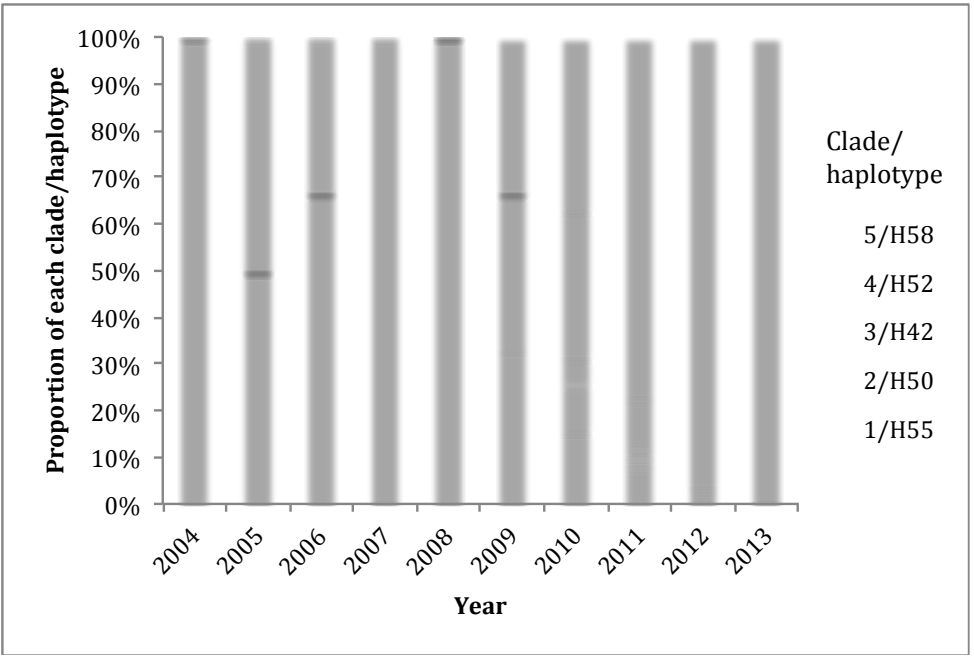
Epidemic drivers: Blantyre, Malawi

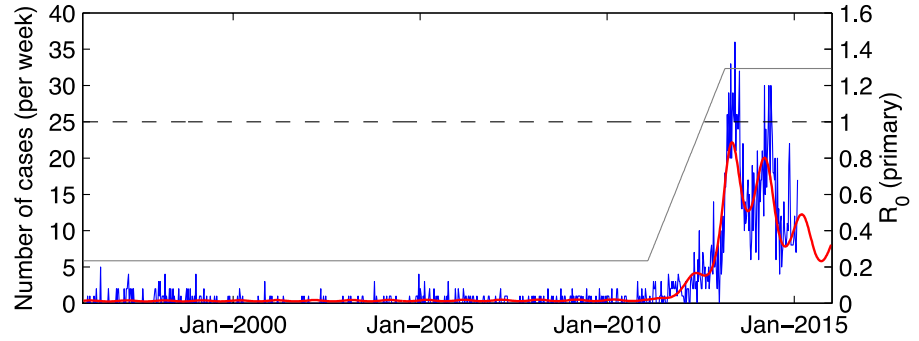


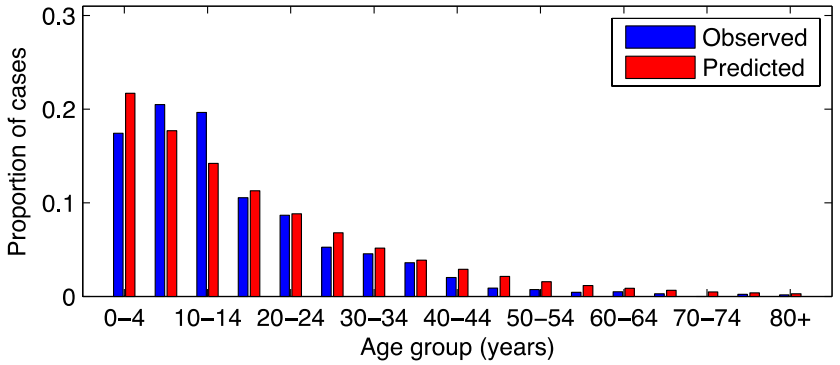


- Assume the duration of infectiousness increases coincident with the emergence of MDR strains

Epidemic drivers: Blantyre, Malawi







- Assume the transmission rate increases coincident with the emergence of H58 haplotype

What might happen in the future?

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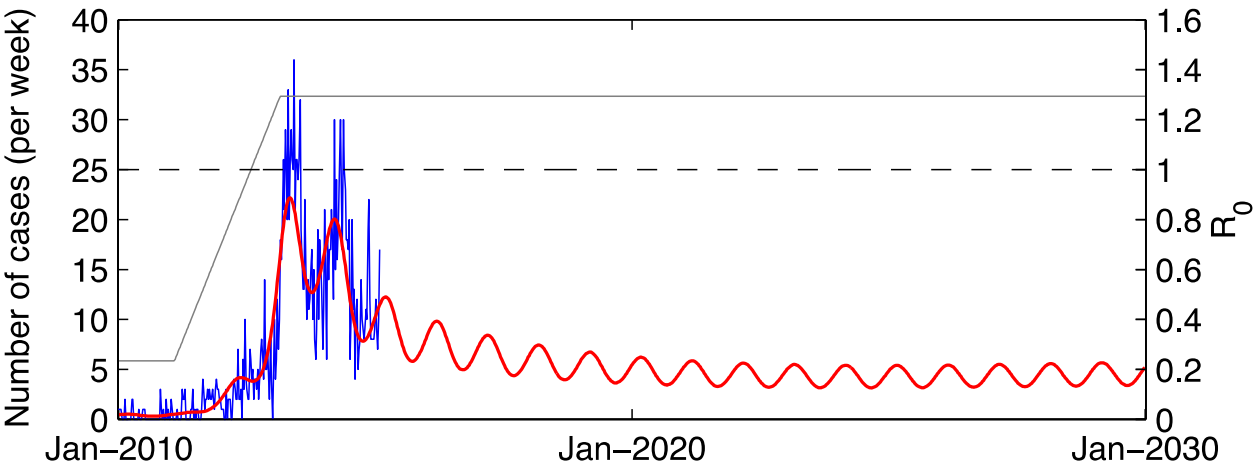

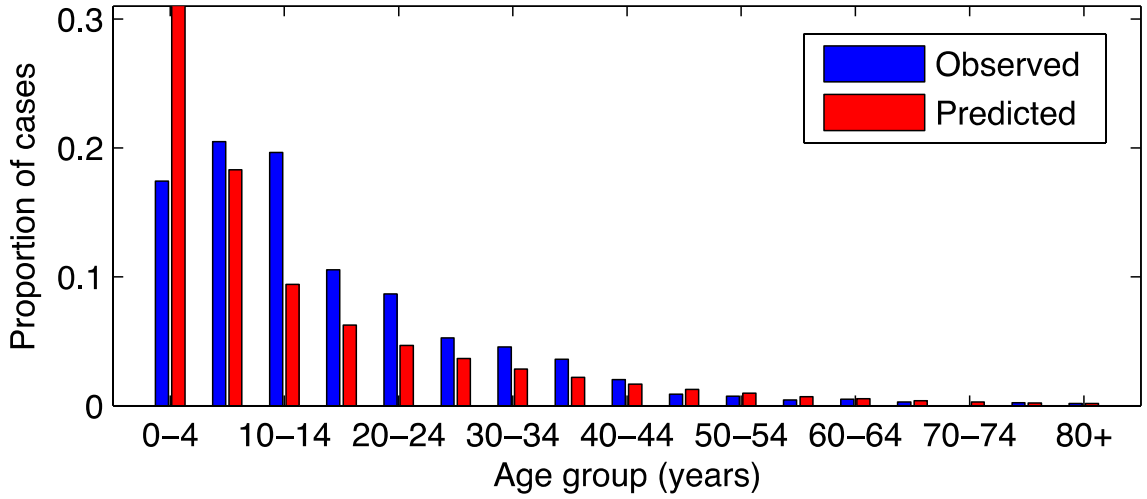

Caveats

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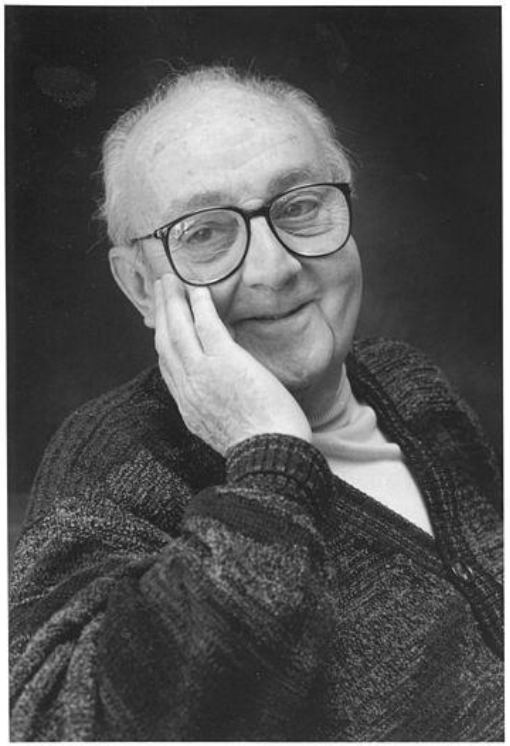
- Simplified model
  - Homogeneous mixing
  - No differences in risk by age
  - Not explicitly modeling multiple strains
  - ….
- Need to determine whether adding "realism" to model will result in qualitatively different predictions



"All models are wrong, but some are useful"

--George E.P. Box

Alternative explanations

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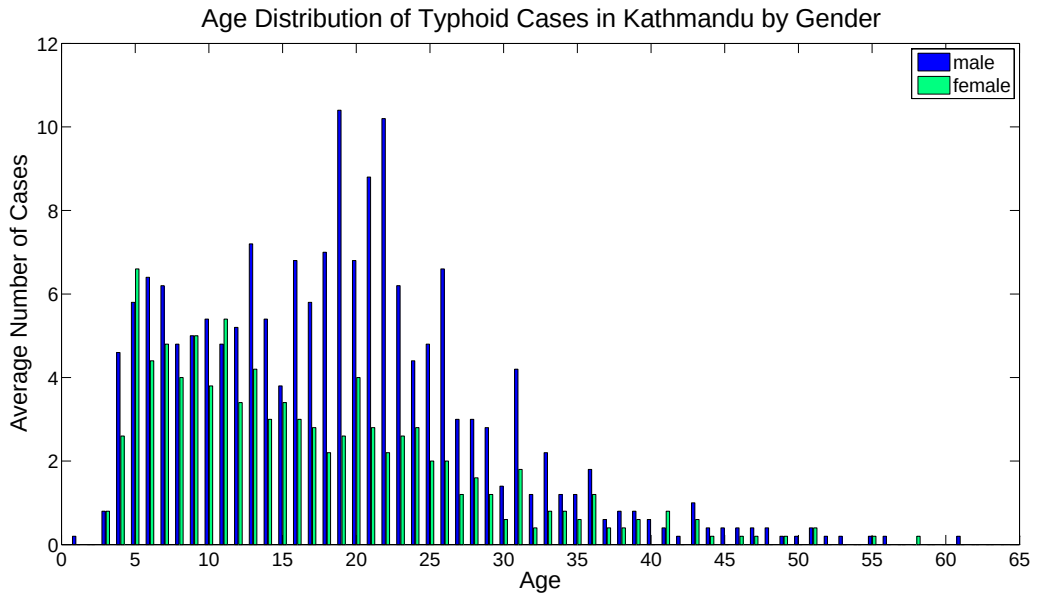
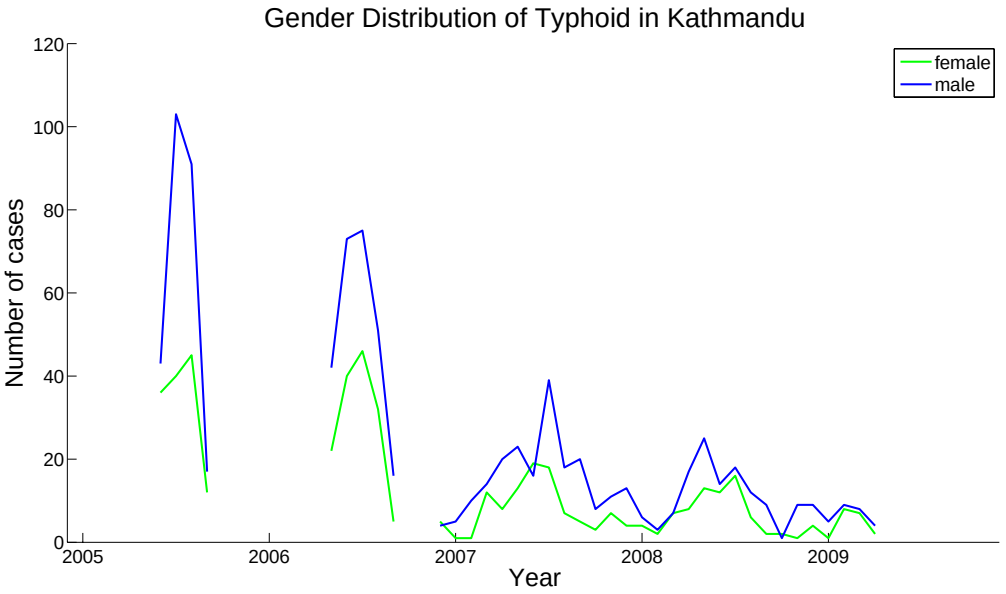
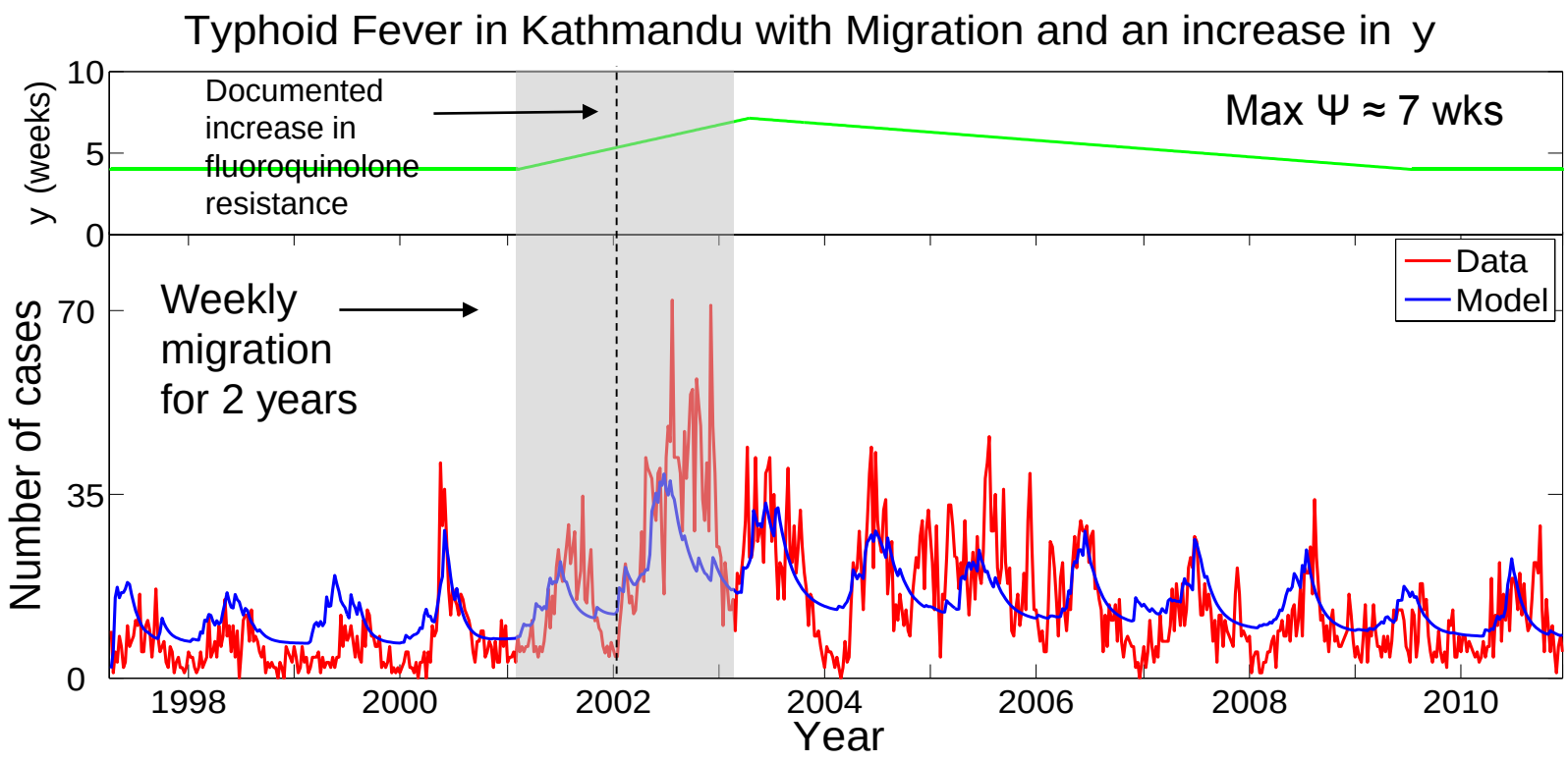
Kathmandu –

Influx of susceptible migrant male workers from low-incidence rural regions





Epidemic drivers: Migration & resistance



- Both antibiotic resistance and migration likely played a role in altered typhoid dynamics from 2002-2003
  - Need strategies to better control antibiotic distribution
  - Migrants may be an essential part of a successful vaccination campaign

Bowles CC et al (in prep)

Alternative explanations

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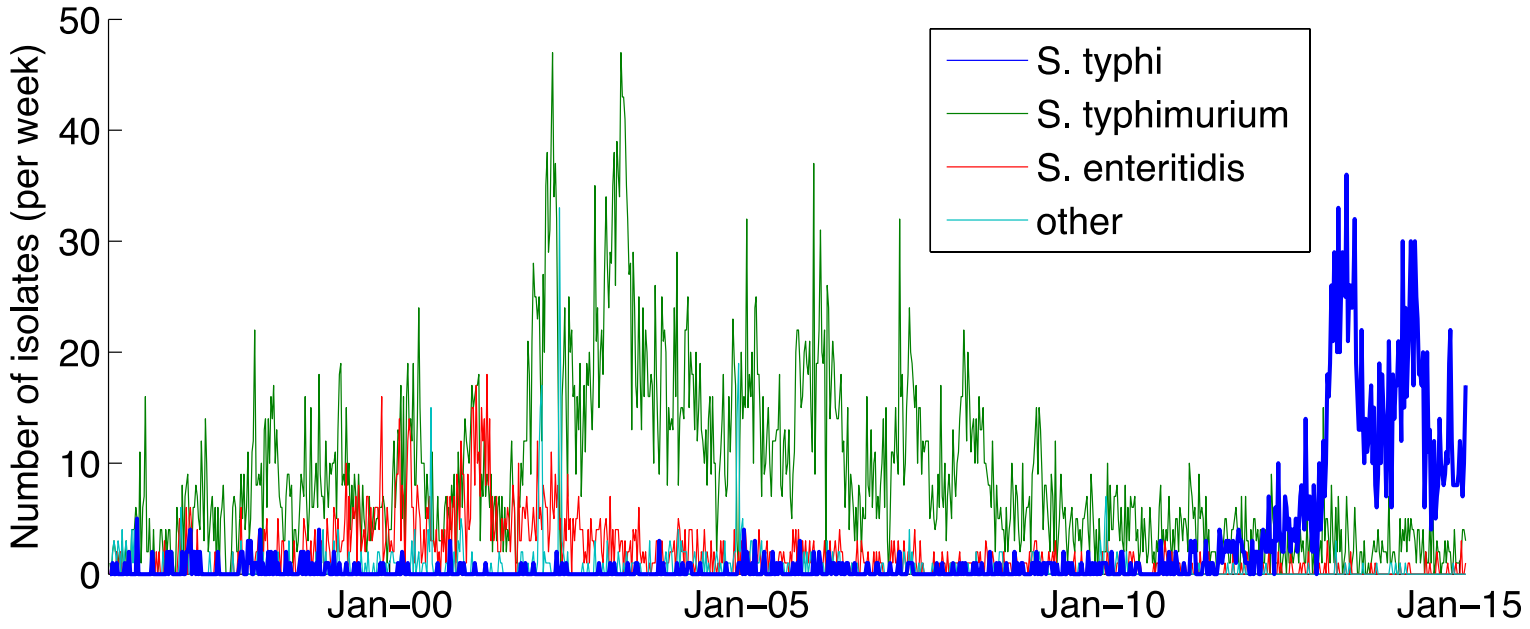
Blantyre –

Increasing population density

Cross-immunity from *S. enteritidis*

Environmental or other interaction among *Salmonella* species?



Sources of uncertainty

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- What is the true burden of typhoid?
  - Need for better diagnostics
- What is the prevalence of chronic carriers and their role in transmission?
  - How does this vary among settings?
- Is natural immunity maintained through repeated exposure to subclinical infections in endemic settings?

Acknowledgements

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BILL & MELINDA GATES foundation

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FOGARTY

U.S. Department of Homeland Security

PRINCETON UNIVERSITY

OUCRU Oxford University Clinical Research Unit Viet Nam

Malawi-Liverpool-Wellcome Trust Clinical Research Programme

COALITION AGAINST TYPHOID