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?

• 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
• **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
Emergence of the H58 haplotype

A Tale of Two Cities...

Kathmandu, Nepal

Number of TF cases (per week)

Jan-98 Jan-00 Jan-02 Jan-04 Jan-06 Jan-08 Jan-10

Bowles CC et al (in prep)

Blantyre, Malawi

Number of TF cases (per week)

Jan-00 Jan-05 Jan-10 Jan-15

Emergence of the H58 haplotype

Kathmandu, Nepal

- **(a) All Typhi**: 2005 and 2006 data showing cases per month.
- **(b) Typhi H58-G (all NaI-F)**: 2005 and 2006 data with specific months highlighted.
- **(c) Other Typhi**: Cases per month with different clades indicated.
- **(d) Rainfall**: Graph showing rainfall per month with peaks.

Blantyre, Malawi

- **Proportion of each clade/haplotype**: Graph showing the proportion of each clade/haplotype per year.
- **Clade/haplotype**:
  - 5/H58
  - 4/H52
  - 3/H42
  - 2/H50
  - 1/H55


Holt KE et al (2010) *BMC Infect Dis*
Dynamic model structure

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?

- 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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- Both would lead to an increase in $R_0$
Epidemic drivers: Kathmandu, Nepal

- 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

Documented increase in fluoroquinolone resistance

Max $\Psi \approx 19 \text{ wks}$

Bowles CC et al (in prep)
Epidemic drivers: Blantyre, Malawi

- Assume the duration of infectiousness increases coincident with the emergence of MDR strains
Assume the transmission rate increases coincident with the emergence of H58 haplotype.
What might happen in the future?
Caveats

• 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
Kathmandu – Influx of susceptible migrant male workers from low-incidence rural regions
Epidemic drivers: Migration & resistance

Typhoid Fever in Kathmandu with Migration and an increase in 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

Documented increase in fluoroquinolone resistance

Max $\Psi \approx 7$ wks

Weekly migration for 2 years

Data

Model

Bowles CC et al (in prep)
Alternative explanations

**Blantyre** –

Increasing population density
Cross-immunity from *S. enteritidis*
Environmental or other interaction among *Salmonella* species?
Sources of uncertainty

• 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?
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