Estimating the Seroincidence of Typhoidal *Salmonella* Infection in the STRATAA Study

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Challenges in Estimating Typhoid Burden

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  - **Care-seeking**: only some symptomatic cases are medically attended (care-seeking)
  - **Symptom Frequency**: only some infections result in clinical symptoms
Research Question:

Can we use serology to directly estimate the incidence of typhoidal salmonella infection (the base of the burden pyramid)?
**Settings and Data**

- Paired serology data from STRATAA study sites
  - Blantyre, Malawi: 4,004 participants
  - Dhaka, Bangladesh: 6,684 participants

- **7 antigen targets**
  - **HlyE, LPS09, LPS02, Flic, CdtB, Vi, YncE**

- **IgG concentration**:
  - ELISA fluorescence intensity
  - Z-score standardized by antigen batch, then log10 transformed

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**Anti-Vi Antibody Responses at the Dhaka Study Site**

- **Change in Standardized IgG Concentration between Visits**

  - Lower antibodies at visit 1 ➙ Higher antibodies at visit 1 ➘
Little change in IgG between visits
Low IgG at visit 1, large increase at visit 2
High IgG at visit 1, large decrease at visit 2
Classifying Antibody Responses with Mixture Models

Apply a mixture of regression models to distinguish 2 groups of participants

- Group 1 (blue): significant change in IgG between visits
- Group 2 (black): minimal change in IgG between visits

Output for each participant: probability of belonging to group 1 vs 2
Inferring Infection Status

If IgG decreased between visits:
- Assume uninfected
- \( P(\text{infected}) = 0 \)

If IgG increased between visits:
- Possibly infected
- \( P(\text{infected}) = P(\text{Group}=1) \)

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- Assume uninfected
- \( P(\text{infected}) = 0 \)
Estimating Seroincidence

• Approach #1: single-antigen estimation
  • LPS09 estimate: consider infected if large ↑ in anti-LPS09 IgG between visits
  • HlyE estimate: consider infected if large ↑ in anti-HlyE IgG between visits
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  • LPS09 estimate: consider infected if large ↑ in anti-LPS09 IgG between visits
  • HlyE estimate: consider infected if large ↑ in anti-HlyE IgG between visits

• Approach #2: multiple-antigen estimation
  • Combined estimate: consider infected if large ↑ in anti-LPS09 AND anti-HlyE IgG between visits
  • More conservative than single-antigen estimates
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• Link infection status to person-time → estimate seroincidence in an MCMC framework
Seroincidence by Age:

- Seroincidence >> clinical incidence
- Bangladesh: similar HlyE and LPS09 seroincidence estimates
- Malawi: LPS09 >> HlyE seroincidence
- Both countries: comparable LPS09 seroincidence
• Clinical incidence declines much more rapidly with age than seroincidence
• Unlike clinical incidence, seroincidence is higher in ages 0-4 than 5-9
Relative Burden: Bangladesh vs Malawi

- Higher disease burden in Bangladesh than Malawi
  - Disparity shrinks with age, disappears by mid-adulthood
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- Seroincidence based on LPS09 and HlyE captures this pattern better than LPS09 or HlyE alone
• As part of the SEAP study, Aimejoy et al. estimated seroincidence in a section of Dhaka a few kilometers south of Mirpur (the STRATAA site).

• STRATAA (paired IgG) and SEAP (cross-sectional IgG/IgA) seroincidence estimates are comparable in magnitude and trend
  • CI’s overlap (not shown)
  • Slightly different age groups
Key Findings

• Seroincidence was much higher than the incidence of typhoid fever at all study sites, even after adjusting for underdetection of cases
  • Most infections are likely asymptomatic, especially in adults

• HlyE seroincidence captures age-specific differences in typhoid fever incidence between Bangladesh and Malawi relatively well, particularly when combined with LPS09

• In Mirpur, seroincidence estimates were similar between the STRATAA and SEAP studies, despite different approaches
  • paired vs cross-sectional serology
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