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

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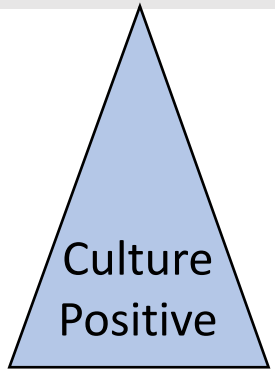
Challenges in Estimating Typhoid Burden

- Surveillance data usually counts culture-positive diagnoses

- Culture-positive cases only represent a fraction of all infections



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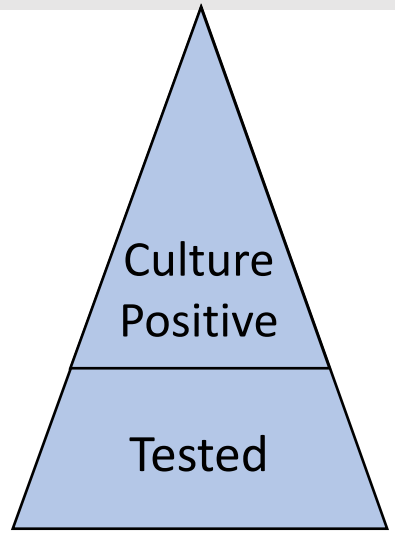

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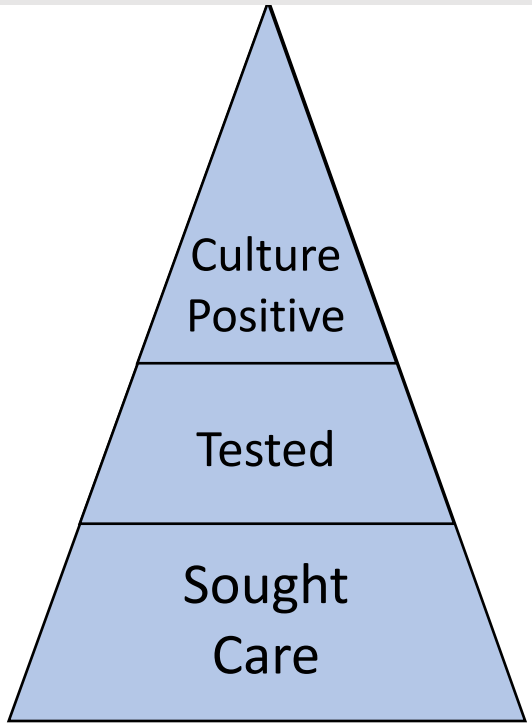

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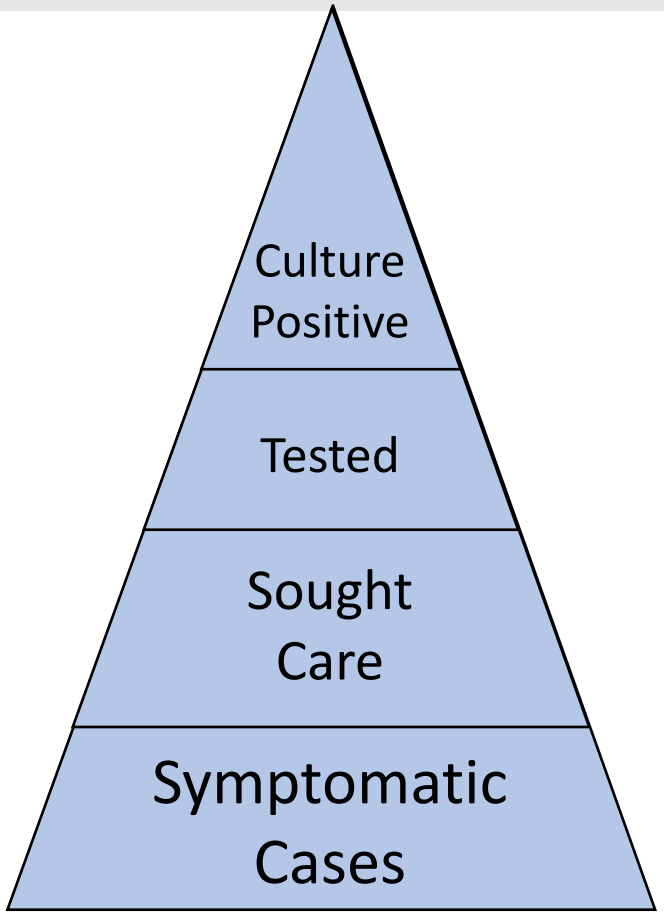

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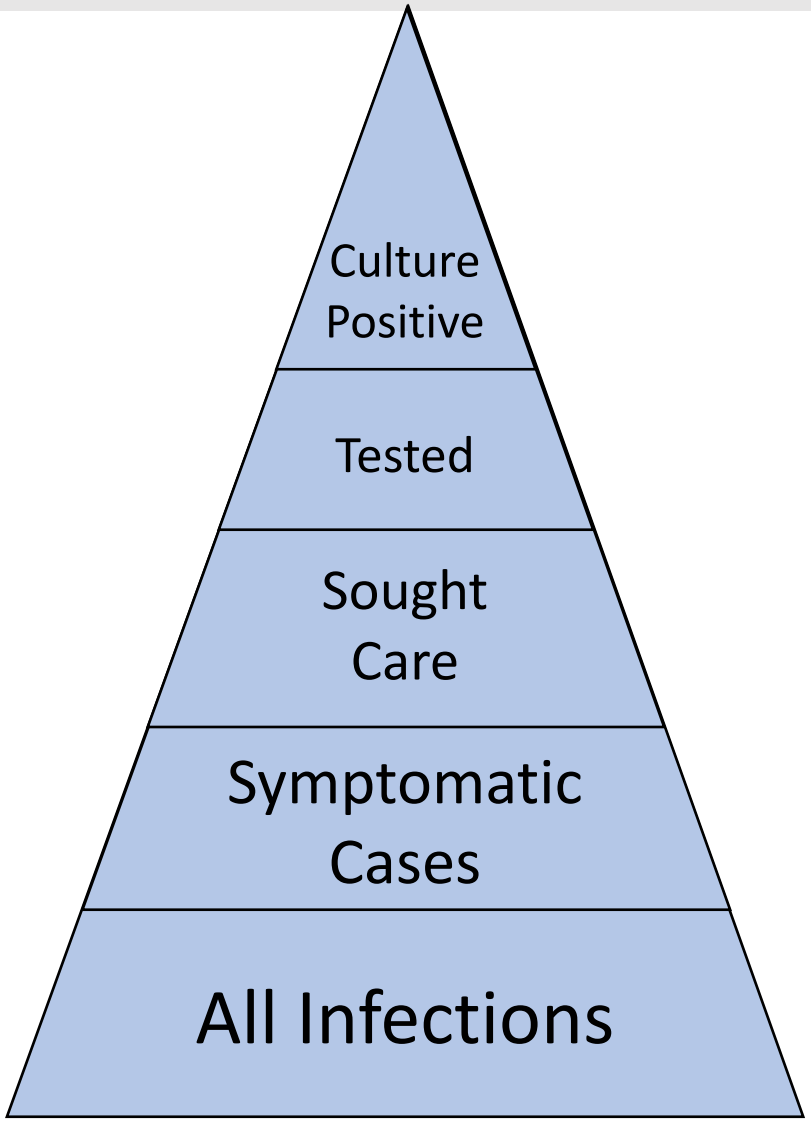
  - **Symptom Frequency**: only some infections result in clinical symptoms

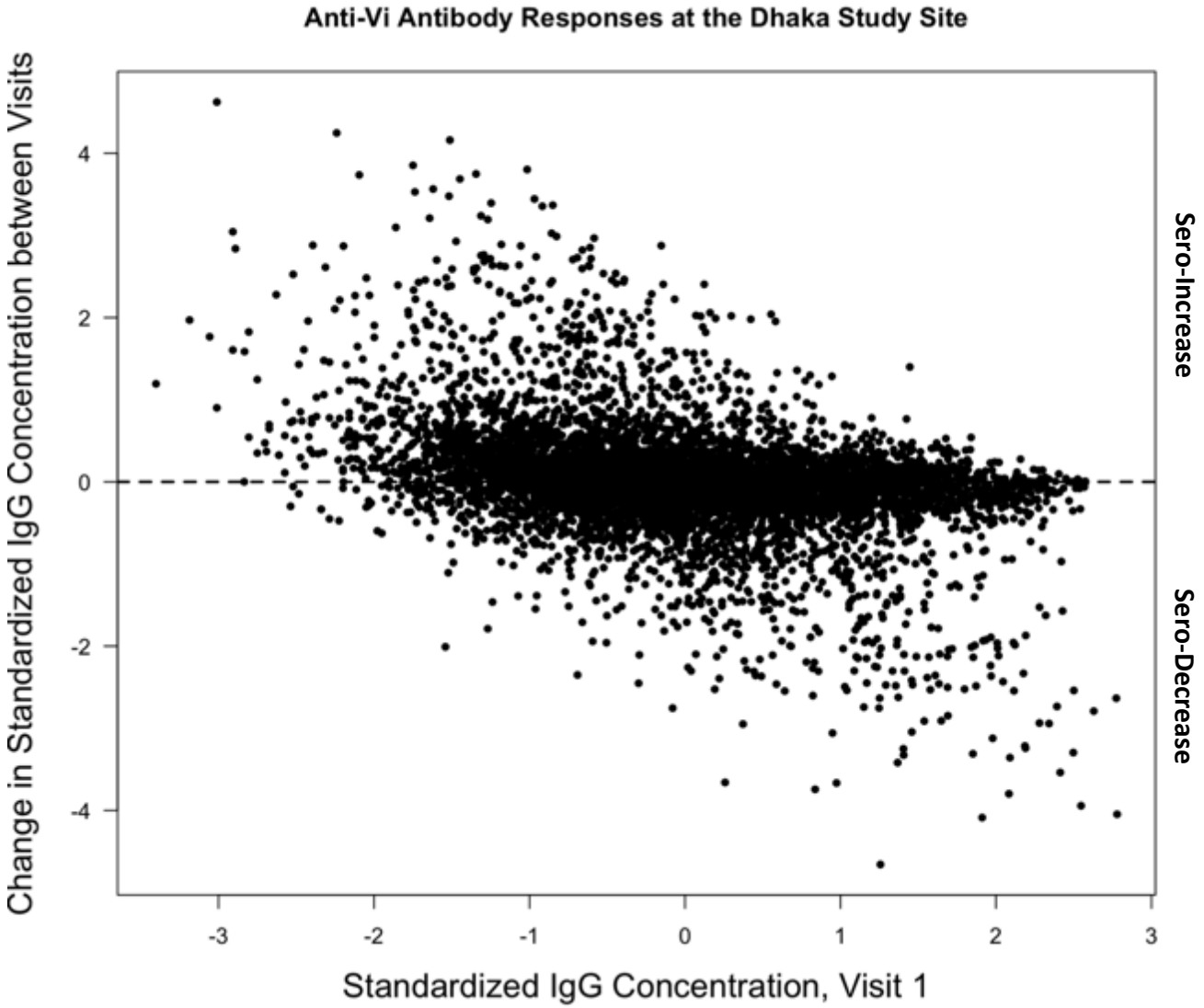


Research Question:

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

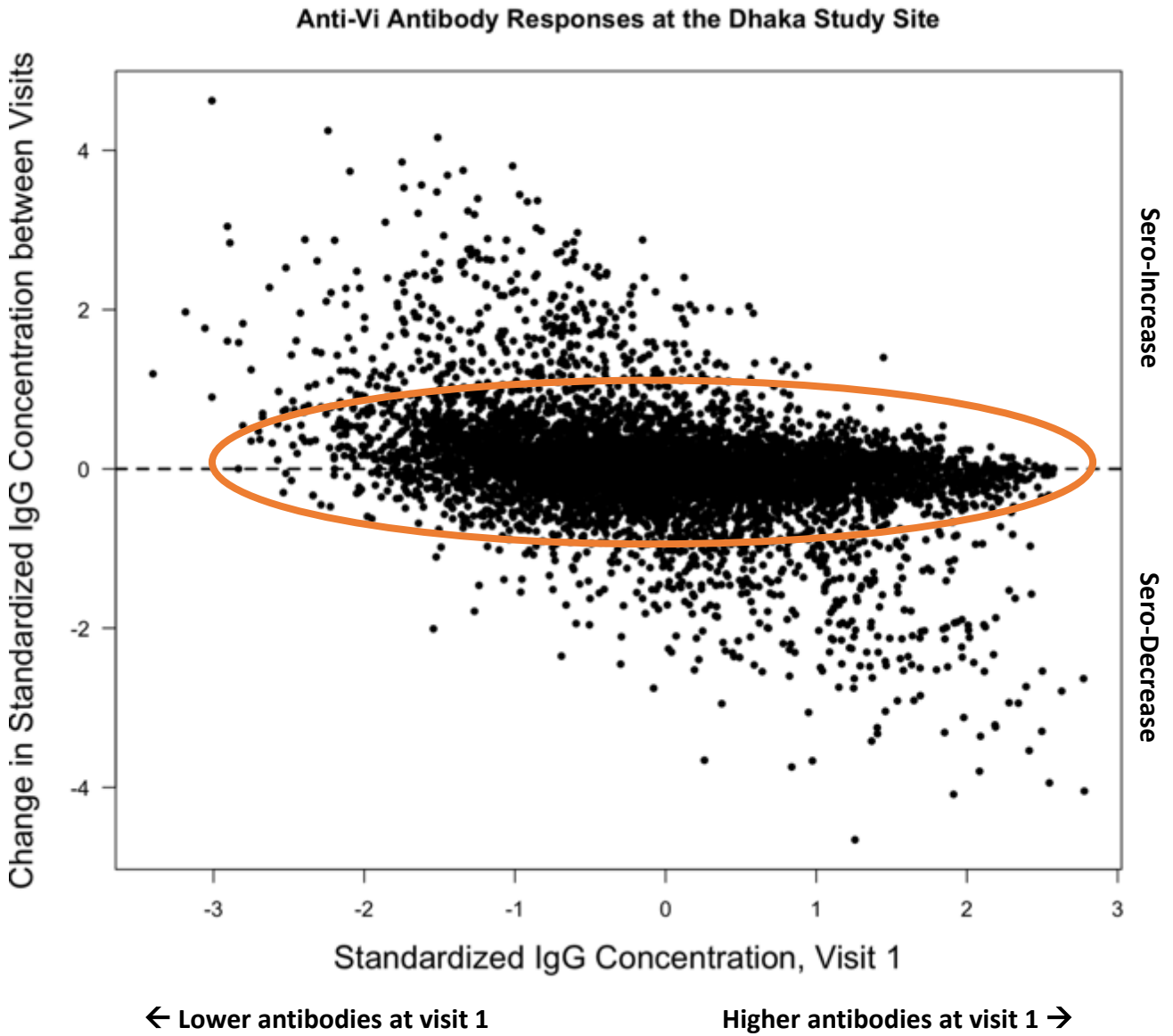
Settings and Data

- 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



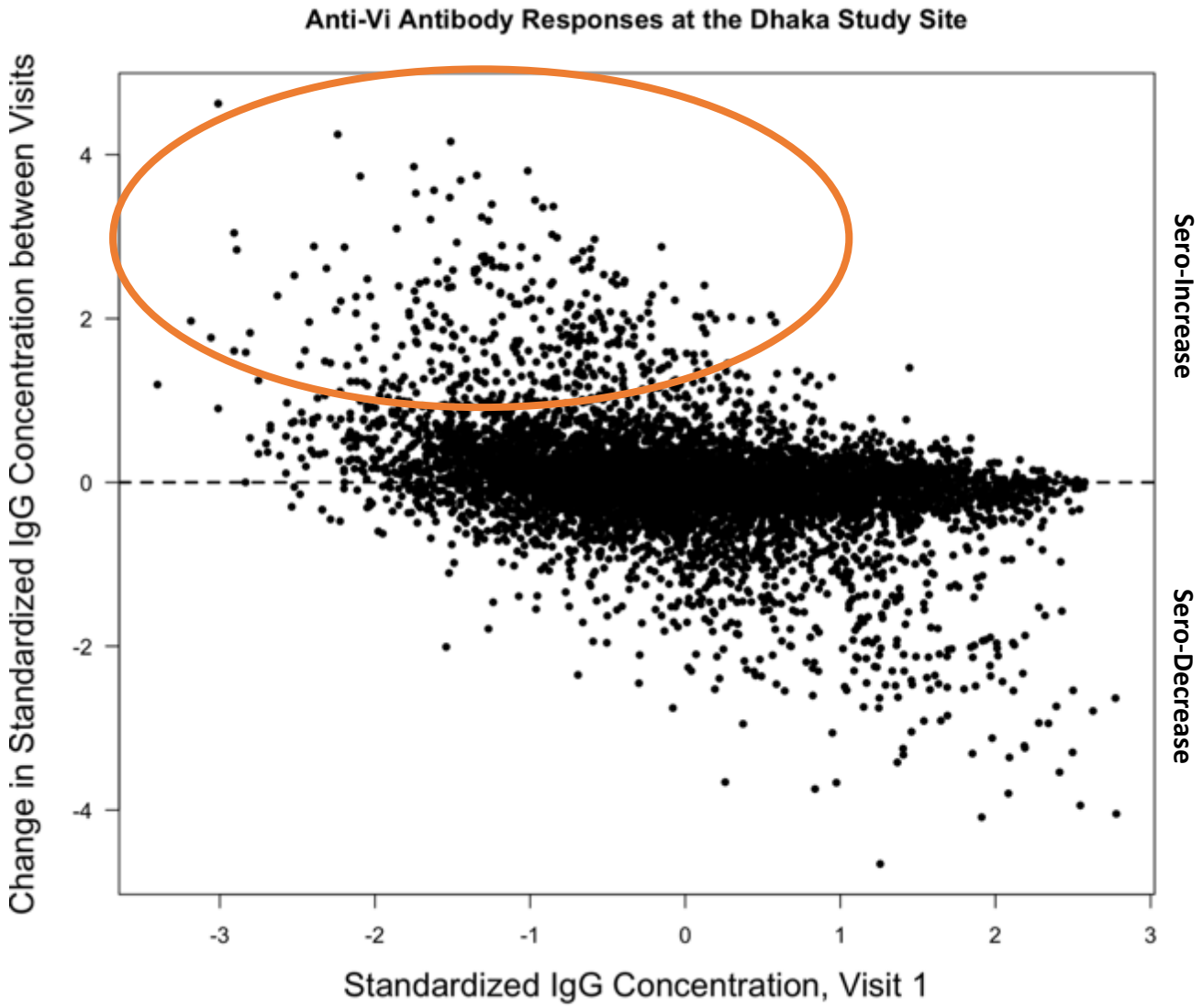
Settings and Data

Little change in IgG between visits



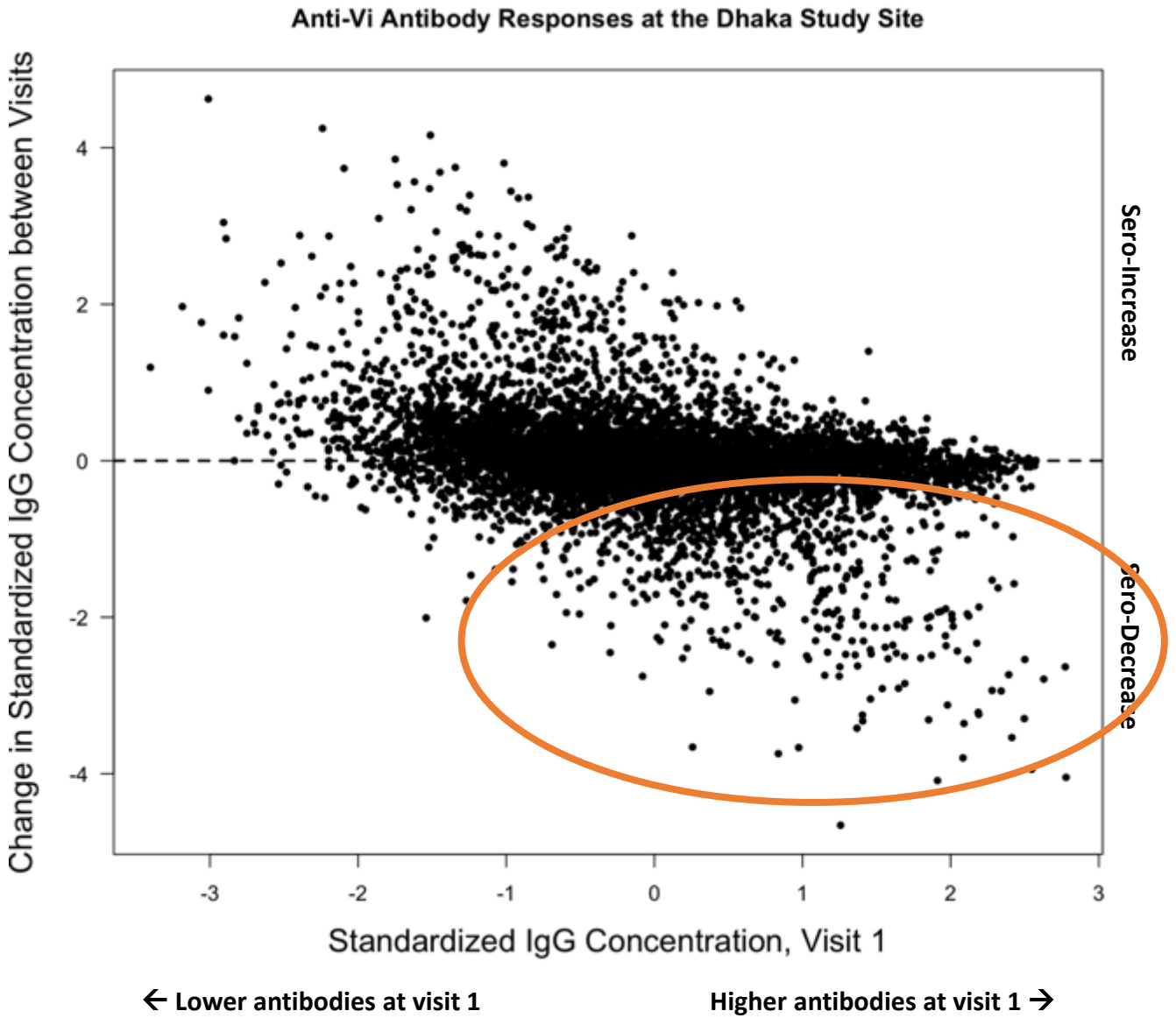
Settings and Data

Low IgG at visit 1,
large increase at visit 2

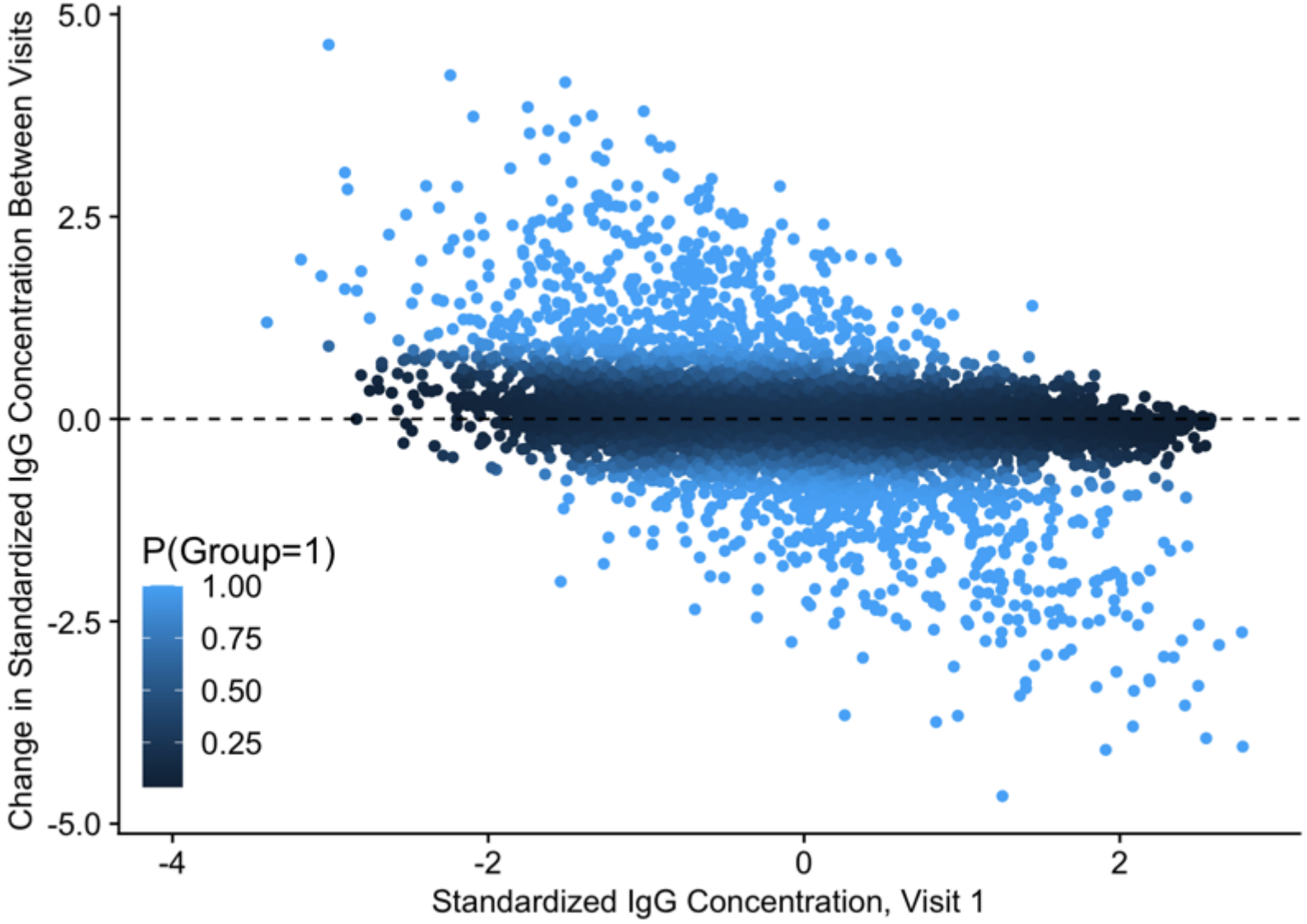


Settings and Data

High IgG at visit 1, large decrease at visit 2



Classifying Antibody Responses with Mixture Models

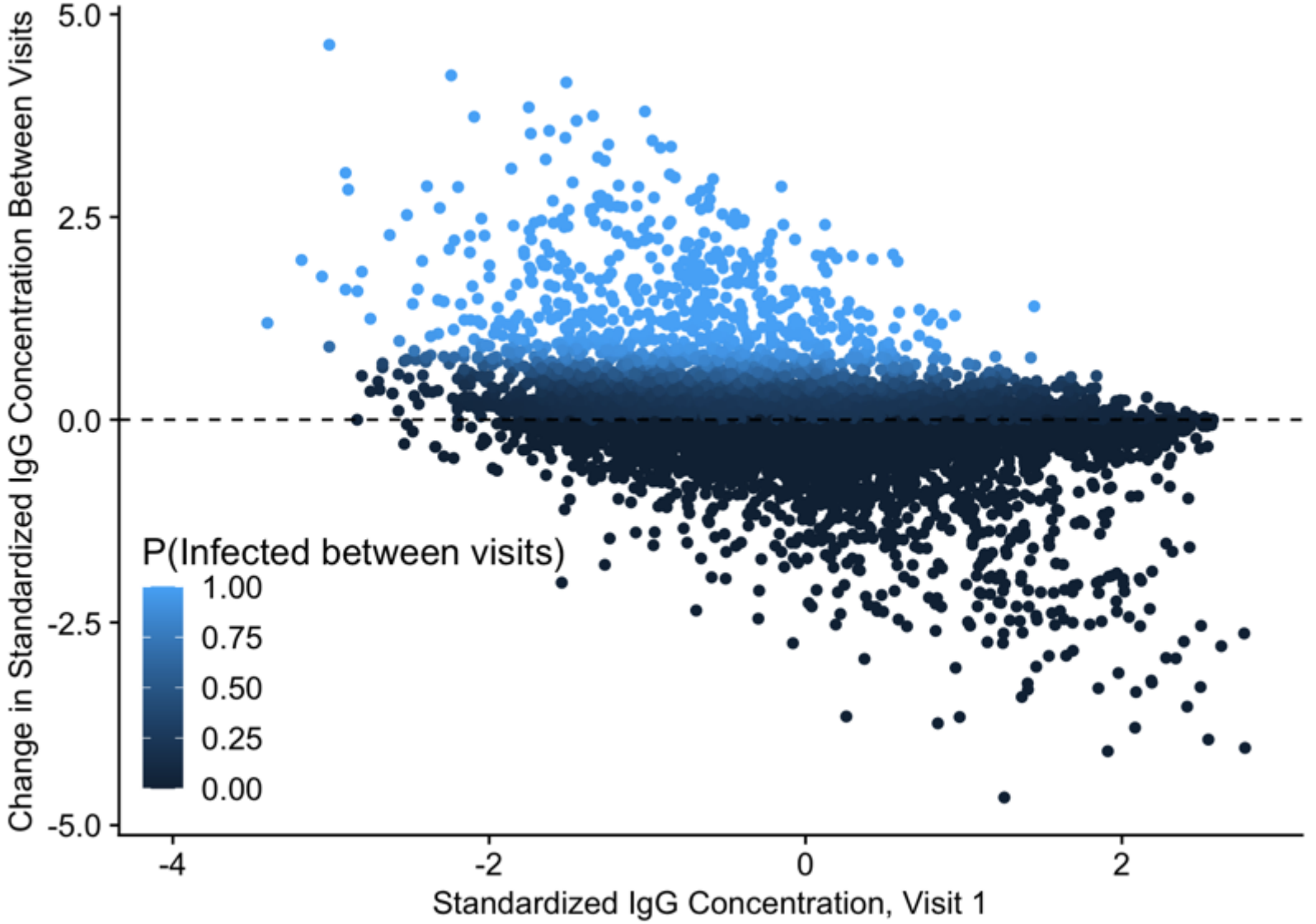


Apply a mixture of regression models to distinguish 2 groups of participants

- 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 increased between visits:

- Possibly infected
- P(infected) = P(Group=1)

If IgG decreased between visits:

- Assume uninfected
- P(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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- 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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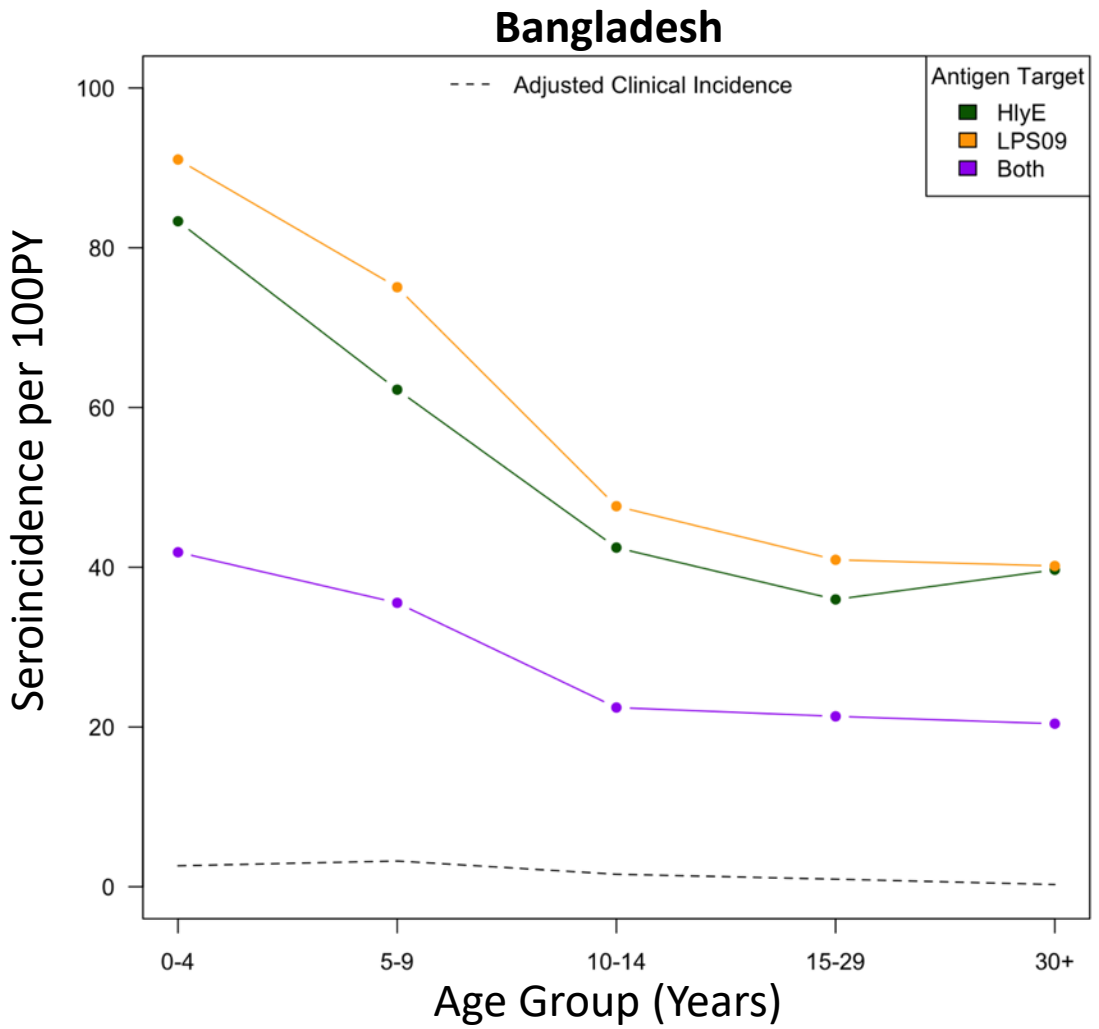
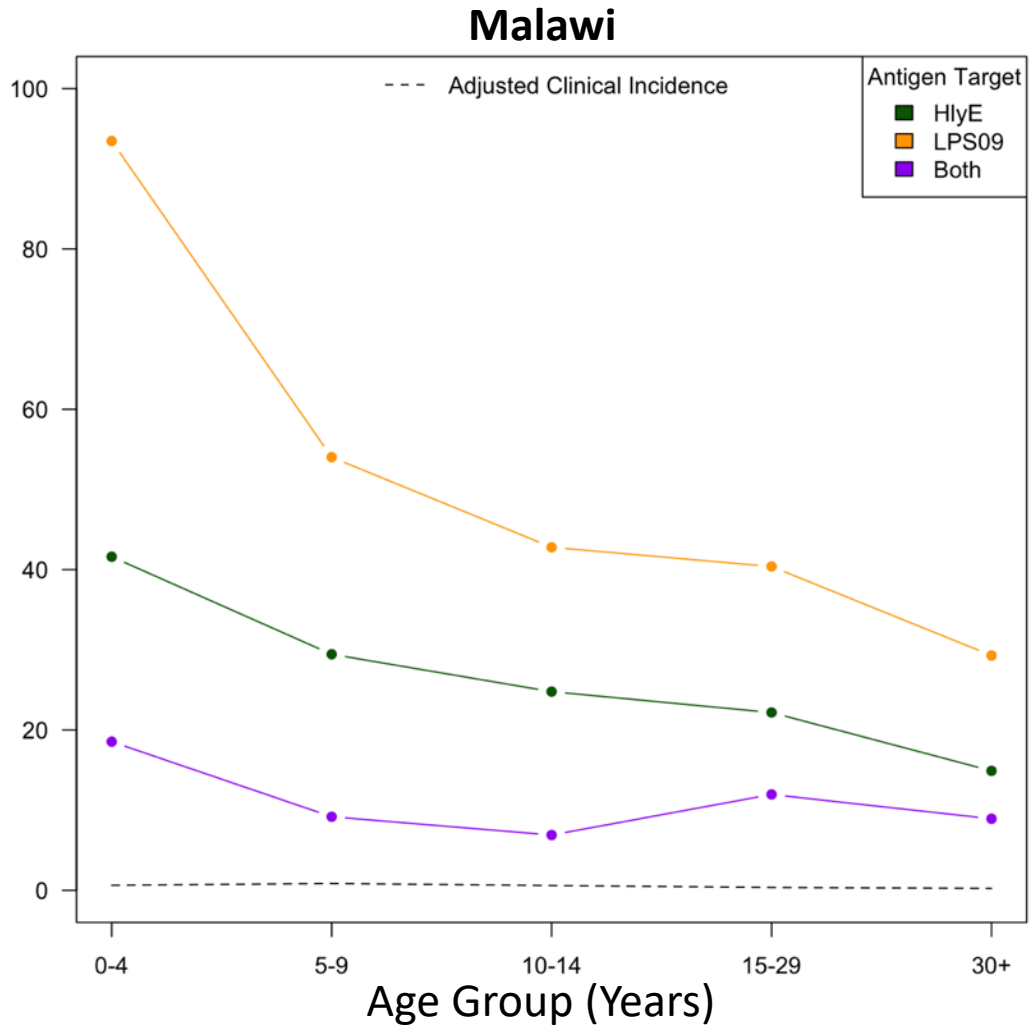
- Link infection status to person-time → estimate seroincidence in an MCMC framework

Seroincidence by Age:

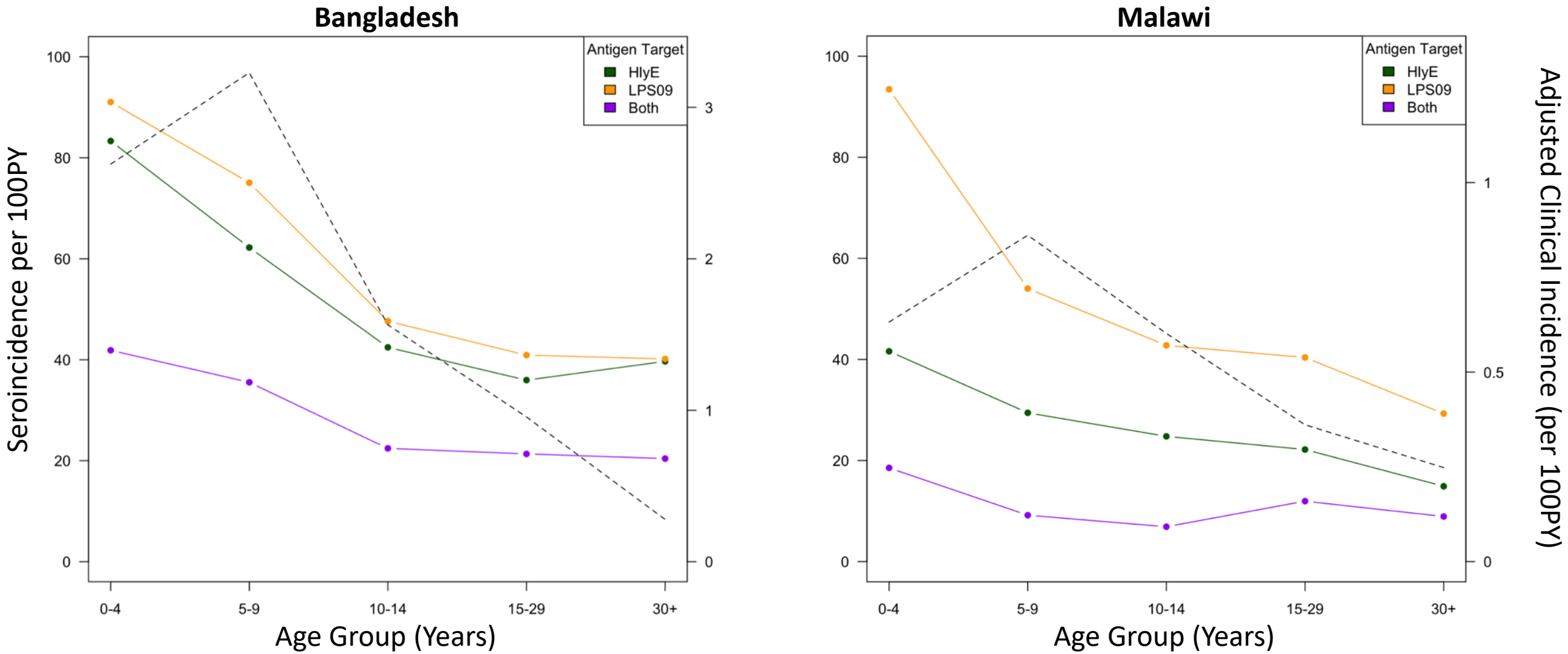
- Seroincidence >> clinical incidence
- Bangladesh: similar HlyE and LPS09 seroincidence estimates
- Malawi: LPS09 >> HlyE seroincidence
- Both countries: comparable LPS09 seroincidence



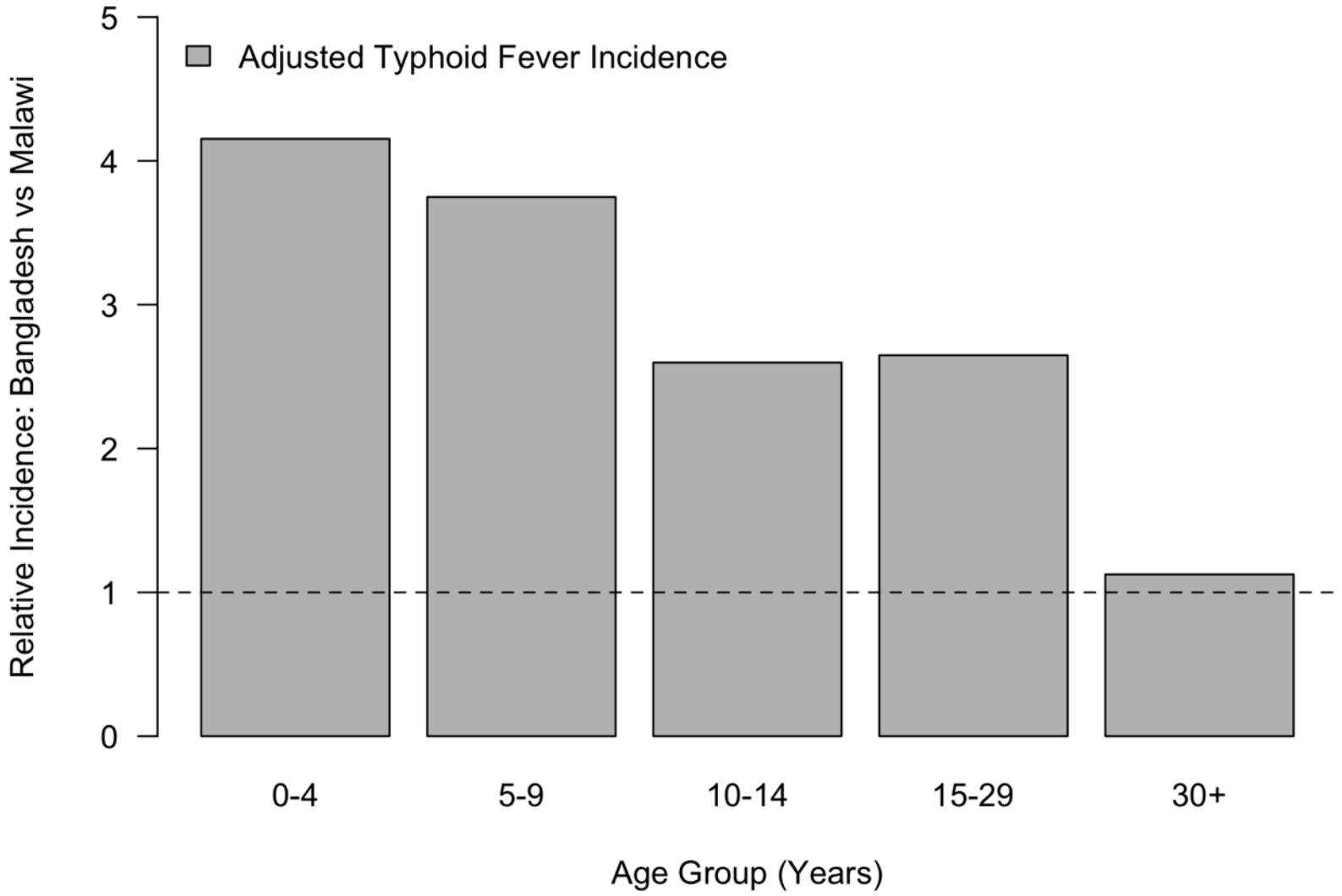


Seroincidence by Age:

- 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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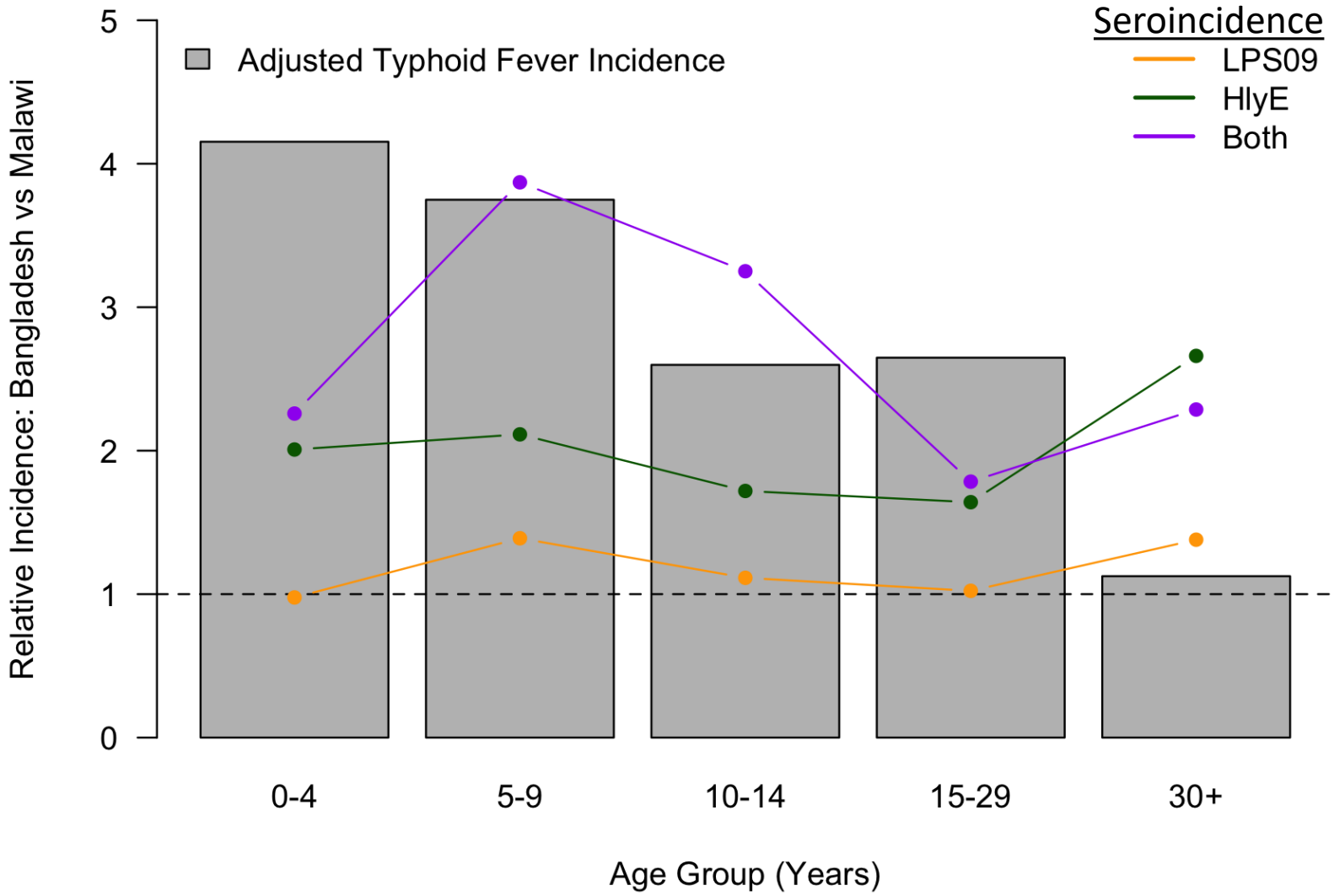
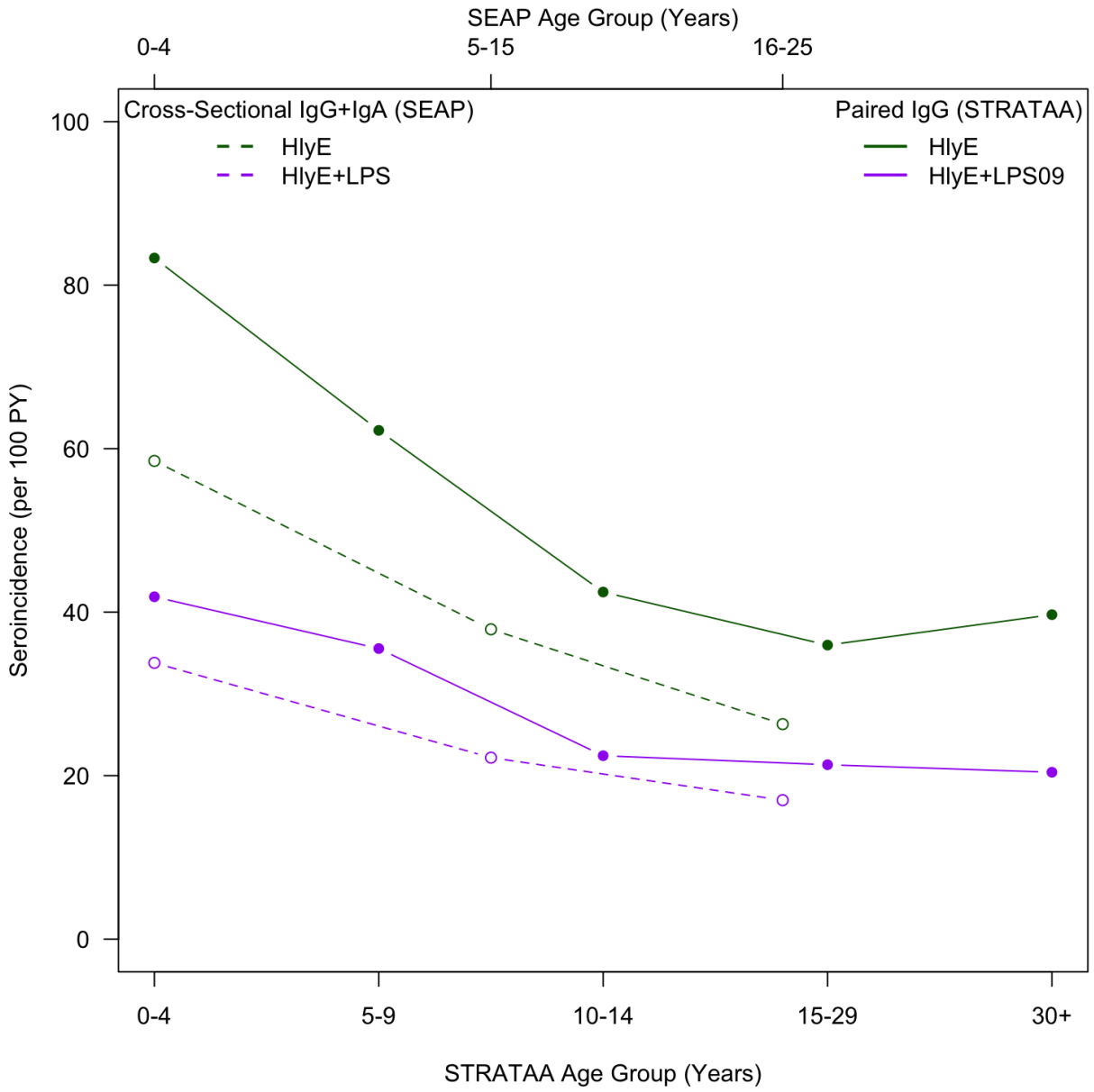


- Higher disease burden in Bangladesh than Malawi
  - Disparity shrinks with age, disappears by mid-adulthood
- Seroincidence based on **LPS09 and HlyE** captures this pattern better than **LPS09** or **HlyE** alone

Comparison to Cross-Sectional and Seroincidence in Dhaka, Bangladesh



- 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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