Bridging the Gap: Environmental and Sero-surveillance for Estimating Typhoid Burden

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Mass General Hospital
Harvard University

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UC Davis School of Medicine
Mahidol University Faculty of Tropical Medicine

Nick Grassly, PhD
Imperial College London

December 06, 2023
Typhoid conjugate vaccines are effective but have yet to be widely adopted.
“Data inequality is our biggest challenge moving forward”

- Kathy Neuzil, ASTMH 2023
The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017

GBD 2017 Typhoid and Paratyphoid Collaborators*
Blood culture confirmed infections

Blood culture performed

Sought care at a surveillance site

Symptomatic infections

All infections (including subclinical)
LATEST ADVANCES IN SEROEPIDEMIOLOGY FOR ENTERIC FEVER

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UC Davis School of Medicine
Department of Immunology and Microbiology
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Seroepidemiology & Environmental Surveillance for Enteric Fever (SEES)
Estimating seroincidence using antibody dynamics

- Seroincidence provides actionable evidence:
  - “The number of **new** infections in this population per year”
- Antibody dynamics only need to be modeled once
- Incorporate heterogeneity in antibody responses (instead of ignore)
- Incorporating signal from multiple antigens/isotypes to improve precision
- Accommodate biological noise and measurement error

Teunis et al, *Stats in Medicine*, 2020
Settings where blood culture surveillance is not available

- Covid serosurvey (DBS) 2020
- 397 samples
Filling the gaps
Integrating HlyE into bead-based multiplex assays

HlyE IgG population responses

Seroincidence = 9.6 (6.2-14.8)

HlyE IgG antibody kinetics among confirmed cases

Seroincidence = 9.3 (6.1-14.1)
Scaling enteric fever serosurveillance: Analytical tools

Open source analytical package for R available on GitHub
https://github.com/UCD-SERG/serocalculator

Analytical training workshops
• Bangkok Aug 2022
• Kigali Dec 2023
• Anywhere you invite us

NIH National Institute of Allergy and Infectious Diseases
Got DBS?
Call us
Extra slides
<table>
<thead>
<tr>
<th>Study Site</th>
<th>Study Name</th>
<th>Age Range (y)</th>
<th>Age&lt; 5 (n)</th>
<th>Total (n)</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>Study Site</td>
<td></td>
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<tr>
<td>Dhaka</td>
<td>SEES</td>
<td>0.5-18</td>
<td>101</td>
<td>401</td>
<td>2019-2021</td>
<td><a href="https://doi.org/10.1016/S2666-5247(22)00114-8">https://doi.org/10.1016/S2666-5247(22)00114-8</a></td>
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<td>Mirzapur</td>
<td></td>
<td></td>
<td>151</td>
<td>596</td>
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<tr>
<td>Kathmandu Valley, Nepal</td>
<td>SEES</td>
<td>0.5-25</td>
<td>186</td>
<td>846</td>
<td>2019-2020</td>
<td><a href="https://doi.org/10.1016/S2666-5247(22)00114-8">https://doi.org/10.1016/S2666-5247(22)00114-8</a></td>
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<tr>
<td>Karachi</td>
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<td>0.5-25</td>
<td>126</td>
<td>494</td>
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<td>Hyderabad</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agogo Ghana</td>
<td>SETA</td>
<td>2-19</td>
<td>18</td>
<td>79</td>
<td>2016</td>
<td><a href="https://doi.org/10.1016/S2666-5247(22)00114-8">https://doi.org/10.1016/S2666-5247(22)00114-8</a></td>
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<tr>
<td>Dosso, Niger</td>
<td>Study Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td></td>
<td></td>
<td>558</td>
<td>558</td>
<td>2020</td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>Study Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Coastal (Ukunda, Msambweni)</td>
<td>CHIKV, DENV</td>
<td>3-18</td>
<td>31</td>
<td>1401</td>
<td>2017</td>
<td><a href="https://bmcinfectdis.biomedcentral.com/articles/10.1007/s12497-017-9569-2">https://bmcinfectdis.biomedcentral.com/articles/10.1007/s12497-017-9569-2</a></td>
</tr>
<tr>
<td>Western sites (Chulaimbo, Kisumu)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vellore, India</td>
<td></td>
<td>0-21</td>
<td>364</td>
<td>1217</td>
<td>2022</td>
<td></td>
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<tr>
<td>Blantyre, Malawi</td>
<td></td>
<td>1-14</td>
<td>387</td>
<td>937</td>
<td>2023</td>
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<tr>
<td>Bo, Sierra Leone</td>
<td>HEAL-SL</td>
<td>2-95</td>
<td>35</td>
<td>455</td>
<td>2022</td>
<td>Jha P et al, in preparation</td>
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<td>Study Site</td>
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<td>California - COVID serosurvey</td>
<td>CA-FACTS</td>
<td>3-50</td>
<td>3</td>
<td>205</td>
<td>2021</td>
<td><a href="https://www.researchsquare.com/article/rs-2548374/v1">https://www.researchsquare.com/article/rs-2548374/v1</a></td>
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<tr>
<td>Boston-Pediatric cohort</td>
<td></td>
<td>1-18</td>
<td>54</td>
<td>80</td>
<td>2017-2020</td>
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</tr>
</tbody>
</table>
Cross-reactive antibody responses in iNTS?

HlyE IgG

- Ghana Neighborhood Controls
- iNTS
- Typhi
- Paratyphi

HlyE IgA

- Ghana Neighborhood Controls
- iNTS
- Typhi
- Paratyphi

**AUC:** 0.97

(95% CI: 0.96-0.99)

LPS IgG

- Ghana Neighborhood Controls
- iNTS
- Typhi
- Paratyphi

LPS IgA

- Ghana Neighborhood Controls
- iNTS
- Typhi
- Paratyphi

**AUC:** 0.88

(95% CI: 0.78-0.99)
Variation in antibody kinetics by:

<table>
<thead>
<tr>
<th>Country</th>
<th>Age</th>
<th>Typhi/Paratyphi A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

*Restrained to Ages 5-15
 Schools as a Platform for Rapid Typhoid Seroepidemiological Assessments: Evidence from Nepal

Shiva Ram Naga
Dhulikhel Hospital, Kathmandu University Hospital
Background

- High typhoid burden in Kathmandu Valley; limited evidence in the other regions of Nepal.
- Blood culture surveillance studies are expensive, logistically intensive, and take many years to complete.
- Serologic surveys are an alternative approach to generate accurate typhoid incidence estimates.
- Schools are a potential alternative population to quickly estimate typhoid burden, but it’s unclear whether they provide a representative sample for assessing community exposure to S. Typhi.
Objectives

- Determine the feasibility of using a school-based sampling frame for typhoid seroepidemiology, evaluating participation rates and resource requirements

- Compare school-based and population-based seroincidence estimates from the same communities to determine whether school-based estimates provide unbiased estimates compared with household-based surveys
Methods

• Random sample of 18 primary and secondary schools
  - 8 in Kavre district
  - 10 in Dolakha district

• Up to 100 children randomly selected from each school

• Inclusion criteria: Age between 4 and 18 years

• Fingerstick capillary blood collected onto filter paper

• HlyE IgG and IgA antibody levels determined by kinetic ELISA

• Estimated seroincidence in each community using previously published methods (Aiemjoy et al, 2022)
## School and Population Sample

<table>
<thead>
<tr>
<th></th>
<th>Population</th>
<th>School</th>
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<tbody>
<tr>
<td></td>
<td>Kathmandu</td>
<td>Kavre</td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>12·0 (5·8–17·8)</td>
<td>10·2 (5·1–15·7)</td>
</tr>
<tr>
<td>Sample size</td>
<td>353</td>
<td>481</td>
</tr>
<tr>
<td>Duration of study, Months</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Research Staff Required</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Consent Rate</td>
<td>76.5%</td>
<td>86.4%</td>
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</tbody>
</table>
RESULTS

Seroincidence by District and Sampling frame
Seroincidence by Timepoints and Sampling site
Conclusions

• Seroincidence estimates derived from school based sampling were similar to those derived from household surveys.

• Participation rates were higher in school based surveys compared with household surveys, and sampling was able to be performed in a fraction of the time and with fewer personnel, markedly reducing costs.

• School-based surveys could enable rapid mapping of typhoid risk in communities where blood culture-based surveillance is not available, as well as monitoring of typhoid exposure trends following vaccine introduction.

• In settings where surveys for helminths or other infections are performed at school, typhoid surveys could be part of an integrated surveillance system to leverage resources and enhance scalability.
Acknowledgements

Nepal Team:-
Dr. Dipesh Tamrakar, Dr. Rajeev Shrestha, Krista Vaidya, Nishan Katuwal, Sabin Bikram Shahi, Nisha Shrestha, Manisha Banjara, Anil Khanal, Urusha Ranjitkar, Sneha Shrestha, Neeru Suwal.

UC Davis:-
Dr. Kristen Aiemjoy

Harvard Medical School
Dr. Richelle Charles

Stanford Team:-
Dr. Jason Andrews, Christopher Leboa

SABIN Team:-
Dr. Denise Garrett, Dr. Jessica Seidman, Alice Carter, Kate Doyle

Funded by:-

Bill & Melinda Gates Foundation
Thank You
Enteric fever seroincidence estimates using cross-sectional rapid serosurveys in Bangladesh

Presented by
Sira Jam Munira
Child Health Research Foundation
Study design

For Dhaka and Mirzapur*
- From June 2019 to June 2021
- Collected dried blood spot samples

For the remaining areas
- January to June 2022, 3-5 days for each survey
- Collected venous whole blood samples
- Additional benefits to participants-
  Blood grouping and Hepatitis B/C tests,
  Science camps

*Aiemjoy et al., The Lancet Global Health, 2022

Child Health Research Foundation
Characteristics of the study participants

**Age distribution**

- Dhaka
- Mirzapur
- Chittagong
- Dinajpur
- Sylhet
- Satkhira
- Faridpur

**Sex distribution**

- Male: 1630 (54.9%)
- Female: 1339 (45.1%)

- <5
- 05-15
- 16+
Anti-HlyE IgG response among study participants

By study communities

By age
Enteric fever seroincidence among study participants

<table>
<thead>
<tr>
<th>Study areas</th>
<th>Seroincidence per 100 person-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhaka</td>
<td>64.4 (55.4- 75.0)</td>
</tr>
<tr>
<td>Mirzapur</td>
<td>39.0 (34.8- 43.8)</td>
</tr>
<tr>
<td>Chittagong</td>
<td>30.1 (26.4- 34.4)</td>
</tr>
<tr>
<td>Dinajpur</td>
<td>27.3 (23.9- 31.1)</td>
</tr>
<tr>
<td>Sylhet</td>
<td>24.3 (21.3- 27.8)</td>
</tr>
<tr>
<td>Satkhira</td>
<td>21.0 (18.5- 23.9)</td>
</tr>
<tr>
<td>Faridpur</td>
<td>20.7 (18.2- 23.6)</td>
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</tbody>
</table>
Enteric fever seroincidence by age group
To detect high enteric fever burden areas

To detect priority age groups for enteric fever
Thank you
Mapping Typhoid Transmission
Geospatial Analysis and Seroepidemiology for TCV Prioritization

Dr. Abdul Momin Kazi, MBBS, MPH, PhD (Cand)
Assistant Professor (Research)
Department of Pediatrics & Child Health
The Aga Khan University, Karachi, Pakistan
Data Sources

1. Impact Assessment of Typhoid conjugate vaccine following introduction in Routine Immunization Program of Pakistan (IATRP)
   - October 2020 to September 2023
   - Total cases tested: 30,503
   - XDR-positive: 18,603
   - Hospital and Lab based data

2. Serosurveillance and Environmental Surveillance for Enteric Fever (SEES)
   - March 2018 to June 2022
   - Population-based: 794
   - School-based: 1363
   - Campaign
     - November 2019
     - Routine Immun

3. (SEAP) Phase II & III, and ITRIPP study
   - January 2017 to September 2023
   - Total cases tested: 61,936
   - XDR-positive: 35,543
   - January 2020
Extracting Geospatial information from Hospital and Lab Data

**Hospitals**
- Aga Khan University Hospital
- Liaquat University of Medical and Health Science Hospital, Hyderabad
- Aga Khan Maternal and Childcare Center AKMCCC, AKU
- Children’s hospital and Institute of Child Health
- Shifa International Hospital
- Qasimabad Hospital, Hyderabad
- Bhittai Hospital, Hyderabad
- Kharadar General Hospital
- National Institute of Child Health
- Jinnah Postgraduate Medical center

**Labs**
- Aga Khan University Lab network – allover Pakistan
- Liaquat University of Medical and Health Science (LUMHS) Laboratory Network
- Chughtai Lab Network
- Shaukat Khanum Hospital Laboratory Network
October 2020 to September 2023
Sindh Cities
Punjab Cities

Legend
Cases per 100,000 people
- No Data
- 0.1 - 1
- 1.1 - 10
- 10.1 - 100
- 100.1 - 197

<table>
<thead>
<tr>
<th>Sindh Cities</th>
<th>Density over 100,000 people</th>
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<tr>
<td>Hyderabad</td>
<td>197</td>
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<tr>
<td>Karachi</td>
<td>41</td>
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<tr>
<td>Jamshoro</td>
<td>47</td>
</tr>
<tr>
<td>Larkana</td>
<td>33</td>
</tr>
<tr>
<td>Mirpur Khas</td>
<td>19</td>
</tr>
<tr>
<td>Sukkur</td>
<td>10</td>
</tr>
<tr>
<td>Qambar Shahdadkot</td>
<td>5</td>
</tr>
<tr>
<td>Sujawal</td>
<td>2</td>
</tr>
<tr>
<td>Tando Allahyar</td>
<td>5</td>
</tr>
<tr>
<td>Tando Muhammad Khan</td>
<td>16</td>
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<table>
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<tr>
<th>Punjab Cities</th>
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<tr>
<td>Lahore</td>
<td>9</td>
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<tr>
<td>Faisalabad</td>
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<tr>
<td>Gujranwala</td>
<td>1</td>
</tr>
<tr>
<td>Multan</td>
<td>1</td>
</tr>
<tr>
<td>Rawalpindi</td>
<td>1</td>
</tr>
<tr>
<td>Sheikhupura</td>
<td>3</td>
</tr>
<tr>
<td>Chiniot</td>
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Karachi Districts

<table>
<thead>
<tr>
<th>Karachi Districts</th>
<th>XDR Cases</th>
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</thead>
<tbody>
<tr>
<td>Karachi South</td>
<td>1918</td>
</tr>
<tr>
<td>Karachi East</td>
<td>1426</td>
</tr>
<tr>
<td>Karachi Central</td>
<td>1221</td>
</tr>
<tr>
<td>Karachi West</td>
<td>722</td>
</tr>
<tr>
<td>Malir</td>
<td>619</td>
</tr>
<tr>
<td>Karachi Cantonment</td>
<td>258</td>
</tr>
<tr>
<td>Kemari</td>
<td>202</td>
</tr>
<tr>
<td>Korangi</td>
<td>167</td>
</tr>
</tbody>
</table>
Karachi
Districts Population Cases per 100,000 people
Karachi South 1,416,936 135
Karachi East 2,610,998 55
Karachi West 1,560,284 46
Karachi Central 2,971,626 41
Malir 1,812,104 34
Karachi Cantonment 873,955 30
Kemari 2,348,599 9
Korangi 2,457,019 7
Number of XDR-positive Cases
Seasonality Maps
Serosurveillance

Legend
No. of cases
- No Data
- 1 - 10
- 11 - 100
- 101 - 591

XDR-Typhoid Cases in Pakistan
n = 1,990
Conclusions

• Hyderabad had the highest clinical (blood culture) incidence and seroincidence

• Serosurveillance is a strategy to efficiently fill in the gaps in areas where blood culture is not available

• In Lyari, where we had both population-based and school-based serosurveys, seroincidence estimates were comparable
Acknowledgements

Dr. Farah Qamar
Study and field team

Parents and families

GIS team
Syeda Aliya Hassan
Ayub Khan
Sero-incidence of Enteric Fever based on Targeted Serosurveillance in Blantyre, Malawi

Jonathan Mandolo (PhD student)
Liverpool School of Tropical Medicine
Malawi Liverpool Wellcome Programme
This was a cross sectional study in Ndirande, Blantyre, Malawi between Dec 2022 to June 2023.

The target was to recruit 1300 individuals of 1 to 14 years based on adjusted clinical incidence.

Recruited 966 of age groups 1-2 and 3-4, 5-9, 10-14 years.
Laboratory Methods

Labeled IgG

HlyE IgG from Serum

HlyE antigen

Created with BioRender.com, Aiemjoy et al, BPLoS Negl Trop Dis., 2020
Data Analysis

- Antibody dynamics from a longitudinal cohort of 1,420 blood culture–confirmed enteric fever cases in Nepal, Ghana, Bangladesh, Pakistan were used.

- Age-stratified incidence rates were estimated using the age-specific antibody response parameters.

Aiemjoy et al, BPLoS Negl Trop Dis., 2020
### Participants demographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>Value, N = 966 (%)</th>
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<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td></td>
<td>6 (3 -11)</td>
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<tr>
<td>Age group</td>
<td>1 to 2 years</td>
<td>183 (18.94)</td>
</tr>
<tr>
<td></td>
<td>3 to 4 years</td>
<td>204 (21.12)</td>
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<tr>
<td></td>
<td>5 to 9 years</td>
<td>287 (29.71)</td>
</tr>
<tr>
<td></td>
<td>10 to 14 years</td>
<td>292 (30.23)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>476 (49.28)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>490 (50.72)</td>
</tr>
</tbody>
</table>
Increase in HlyE IgG levels by age suggesting hyperendemicity
Seroincidence by demographic characteristics

Higher force of infection in younger Children
Higher Seroincidence rate than clinical-incidence rate in Urban Malawi

(Feasey et al. unpublished)
Conclusion

• Higher Salmonella typhi Seroincidence rate than clinical incidence estimates in Urban Malawi

• Malawi amongst the high Enteric fever burden countries

• The approach has a potential to expand the geographical scope of typhoidal Salmonella surveillance and generate incidence estimates in Malawi
Way Forward

- Analyse samples from other sites of Malawi to have a proper national burden of Enteric fever
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Dr Armelle Forrer
Professor Melita Gordon
Infection and Immunity Group
SEROSURV study participants