Advances in serology for enteric fever diagnostics and sero-surveillance

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December 2023
Impact of lack of rapid diagnostics for enteric fever

Over diagnosis and over-prescribing of anti-typhoid antimicrobials

- Driven emergence of antimicrobial resistance
  - Specifically, fluoroquinolone resistance in Asia
  - Now there is emergence of extensively drug resistant *Salmonella Typhi* (XDR) = MDR + FQ + 3rd gen. cephalosporin resistance

Surveillance equity gaps

- Many LMICs lack incidence data
- Major gaps exist across Africa, Asia, and the Middle East and central America.
- May lead to vaccine equity gaps
Current enteric fever diagnostics lack sensitivity and specificity

Blood Culture

Result takes 2 days
Requires laboratory capacity
60% sensitive

PCR

DNA extraction

Amplification

Results

Antibody-based assays

Lack of specificity

Requires laboratory capacity
Current enteric fever diagnostics lack sensitivity and specificity

**Blood Culture**

- 60% sensitive
- Result takes 2 days
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**PCR**

- DNA extraction
- Amplification
- Results

**Antibody-based assays**

- Lack of specificity
Current enteric fever diagnostics lack sensitivity and specificity

**Blood Culture**

60% sensitive  
Result takes 2 days  
Requires laboratory capacity

**PCR**

DNA extraction  
Amplification  
Results

Requires laboratory capacity

**Antibody-based assays**

Lack of specificity
Biomarker screens identified seroresponses with better diagnostic accuracy

Charles RC et al., CVI 2010 Aug;17(8):1188-95

Assessment of the sensitivity and specificity of Anti-HlyE and LPS IgA

Sensitivity of 90% and specificity of 92%
DPP Typhoid Assay

- Generate a rapid test on detecting IgA antibody responses targeting LPS and HlyE of S. Typhi and S. Paratyphi A

DPP® Test Cassette  DPP® Micro Reader

Specificity of 96% and sensitivity of 90%.

*Kumar et al. 2020. mSphere 5:e00253-20.
Prospective Study of DPP in Bangladesh

Dr. Sira Jam Munira

CHRF team

A) Study Design

Enrollment

≥ 3 days of fever

Bangladesh Shisu Hospital

n = 501

Samples collected

Venous blood (N=501)

Capillary blood (N=299)

NP swab (N=416)

Diagnostic assays performed

- Blood culture
- Molecular assays (qPCR)
  - Influenza A/B
  - RSV
  - Dengue
  - Rickettsia spp.
- Serologic assays
  - DPP Typhoid Assay
  - Widal
  - Test/A Typhoid IgM

B) Classification of cohort

Enteric fever case
N=77

S. Typhi
N=62
S. Paratyphi A
N=15

Alternative etiology
N=70

Dengue
N=23
Rickettsia
N=7

Blood culture negative
N=424

Influenza
N=34
RSV
N=7

No infectious etiology
N=354
DPP Typhoid Assay

• We used Bayesian latent class models incorporating the results from all the typhoid and alternative etiology diagnostics to estimate the true sensitivity and specificity of DPP Typhoid

• The AUC for the DPPT in distinguishing typhoid from alternative etiologies was 97% (95% CI: 94-99%).

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Balanced accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPPT assay</td>
<td>93% (87 - 97)</td>
<td>89% (85 - 93)</td>
<td>91% (87 - 94)</td>
</tr>
<tr>
<td>Test-It</td>
<td>54% (49 - 59)</td>
<td>100% (100 – 100)</td>
<td>77% (74 - 79)</td>
</tr>
<tr>
<td>Widal ≥ 1:160</td>
<td>48% (43 - 53)</td>
<td>92% (90 – 94)</td>
<td>70% (67 - 73)</td>
</tr>
<tr>
<td>Blood culture</td>
<td>62% (55 - 69)</td>
<td>100% (100 – 100)</td>
<td>81% (78 - 85)</td>
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</tbody>
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Using HlyE Ig for sero-surveillance

- Serological surveillance may be a more versatile and cost-effective approach to evaluating the burden of disease
- Overcomes some of the limitations of current culture-based surveillance
- Available for countries that lack infrastructure for culture-based surveillance
Took longitudinal data from >1400 cases and used Bayesian hierarchical modeling to estimate the antibody kinetics of HlyE.

We then apply the cross-sectional data to estimate time-since infection and incidence.

Aiemjoy et al, *Lancet Microbe*, 2022
Comparison of estimates for crude and adjusted clinical enteric fever incidence with typhoidal *Salmonella* seroincidence

Aiemjoy et al, *Lancet Microbe*, 2022
Conclusion

Diagnostics
• We have promising new diagnostic tools based on the detection of IgA responses to LPS and HlyE

• Today Poster #70

• December 7th at 11 am

Serosurveillance
• We have a new tools for sero-surveillance tools for enteric fever based on the antibody detection

• Today at 1:30
  • Bridging the gap: environmental and eero-surveillance for estimating typhoid burden and supporting vaccine introduction.
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