Typhoid Seroepidemiology for TCV Decision-Making

Meeting Report

Date of Meeting: 18 July 2025

Report Finalized: 06 February 2026

Subject: Expert consultation on the state of evidence for typhoid seroepidemiology and its application in typhoid conjugate vaccine (TCV) decision-making.

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1. Introduction

This formal report summarizes proceedings from the expert consultation convened on 18 July 2025 to review current evidence, methodological considerations, and priority gaps in typhoid seroepidemiology. The meeting aimed to assess the potential for seroepidemiologic tools to inform national decisions on TCV introduction, especially in contexts lacking robust blood culture surveillance.

Typhoid conjugate vaccines (TCVs) are recommended by the World Health Organization for countries with high typhoid burden or significant antimicrobial resistance. However, routine adoption remains limited, partly due to insufficient incidence data from many endemic countries. This report consolidates expert discussions on leveraging serologic surveillance to address these data gaps.

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2. Background

Blood culture remains the gold standard for typhoid diagnosis but is technically demanding, costly, and often unavailable in many low-resource settings. Sensitivity limitations (~60%) and restricted geographic coverage further constrain its utility for national burden estimation. As a result, policymakers frequently face uncertainty when evaluating whether TCV introduction is justified.

Seroepidemiology represents a complementary approach to estimate infection incidence using population-level antibody measurements. By quantifying IgG and IgA responses to *Salmonella* Typhi antigens such as hemolysin E (HlyE) and lipopolysaccharide (LPS), modeled seroincidence can be derived even in the absence of continuous clinical surveillance.

The SEES (SeroEpidemiology and Environmental Surveillance) multi-country study has demonstrated the feasibility of producing comparable typhoid incidence estimates using standardized methods across diverse geographic regions.

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3. Recent Findings

3.1 Transition from IgG to IgA as Primary Marker

Evidence presented at the meeting highlighted limitations in the use of HlyE IgG due to heterogeneity in decay kinetics across continents. IgG waning is slower in high-burden areas, likely influenced by repeated exposures and early-age priming. This variability complicates cross-site comparisons.

Conversely, HlyE IgA demonstrates more consistent kinetics across geographies and age groups, reduced sensitivity to reinfections, and minimal interference from maternal antibodies. These characteristics support its use as the primary analyte for seroincidence estimation.

3.2 Relationship Between Seroincidence and Clinical Incidence

Updated analyses from SEES study sites show that HlyE IgA–derived seroincidence correlates moderately with clinical incidence measures ($R^2 \sim 0.5–0.6$). In most settings, seroincidence exceeds clinical incidence by approximately 25-fold. Divergence is most pronounced in children under two years of age, where several biological and methodological explanations require further investigation.

3.3 Cross-Reactivity Evaluation

Concerns regarding serologic cross-reactivity were systematically examined. According to available data:

- No meaningful elevation of HlyE antibody responses was observed in patients with invasive nontyphoidal *Salmonella* (iNTS), *Shigella flexneri*, extraintestinal pathogenic *E. coli* (ExPEC), or diarrheagenic *E. coli* infections.
- Studies in Malawi confirmed negligible HlyE signal among iNTS patients.

These findings support the antigen's specificity for enteric fever due to *S.* Typhi; however, further validation across age-stratified samples is required.

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4. Geographic Patterns in Seroincidence

4.1 Africa vs. Asia

Experts noted unexpectedly high seroincidence in several African countries, in some cases surpassing levels recorded in highly endemic Asian settings such as Bangladesh and Pakistan. Limited sample sizes in some African surveys warrant cautious interpretation, but the trend underscores the need for expanded surveillance.

4.2 Urban vs. Rural Variations

While clinical typhoid is traditionally associated with urban environments, seroincidence data suggest substantial transmission in rural areas of both Africa and Asia. Examples include higher seroincidence in rural Sierra Leone, Ghana, and Côte d'Ivoire relative to urban districts.

4.3 Age-Related Trends

Across all settings, seroincidence was highest in children under five years, including infants. Data from Niger showed elevated IgA levels even in infants under one year of age. These findings raise questions about early-life exposures not reflected in clinical case reports.

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5. Methodological Considerations

5.1 Sensitivity to Seasonality

Seroepidemiologic estimates may be influenced by timing of survey implementation in settings with seasonal transmission. HlyE IgA profiles reflect exposure over the previous 6–12 months, offering a buffered measure of disease burden compared to point prevalence.

5.2 Laboratory Platform Requirements

Current reliance on kinetic ELISA poses operational challenges due to requirements for high-grade reagents and specialized equipment. Multiplex bead assays such as Luminex offer promise for decentralization but require further validation for HlyE IgA integration.

The publicly available serocalculator tool (https://github\.com/UCD\-SERG/serocalculator\) was acknowledged as a valuable resource for data processing.

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6. Conclusions and Key Recommendations

Experts unanimously agreed that typhoid seroepidemiology can play a meaningful role in informing TCV introduction decisions, provided it is applied with appropriate safeguards.

6.1 Required Qualifications for Use

- Seroepidemiology should *complement* blood culture surveillance, typhoid intestinal perforation data, and wastewater monitoring when available.
- Clinical outcomes remain essential for evaluating optimal vaccination schedules, as the relationship between seroincidence and symptomatic disease—particularly among children under two—remains incompletely understood.
- IgA is preferred over IgG for analytic consistency and interpretability.

6.2 High-Priority Evidence Gaps

1. **Cross-Reactivity:** Expanded validation across pathogens, examining potential variability by location and age group.
2. **Comparative Studies:** Additional paired clinical-serologic incidence studies in a variety of locations and typhoid-risk ecosystems in Africa with sufficient sample sizes to resolve age-specific patterns.
3. **Refinement of Analytical Methods:** Standardization of decay models and best practices.

6.3 Operational Priorities for Scale-Up

- Development of guidance for field implementation, assay selection, and data interpretation.
- Creation of communication tools for policymakers to support understanding of seroepidemiologic evidence.
- Evaluation of TCV impact on seropositivity using archived TyVAC trial samples.
- Advancement of rapid diagnostic test (RDT) development and evaluation, incorporating HlyE IgA and LPS IgA.

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7. Summary Statement

The consultation concluded that HlyE IgA–based seroepidemiology offers a feasible, scalable, and informative surveillance approach, particularly in settings where blood culture capacity is limited. Continued validation, method refinement, and development of supportive tools will be essential to maximizing its utility in guiding national TCV introduction decisions.

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