SEROEPIDEMIOLOGY FOR EVALUATING THE IMPACT TYPHOID VACCINE INTERVENTIONS

Together We Can Take on Typhoid

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Wisdom of the Land
<table>
<thead>
<tr>
<th>Location</th>
<th>Number of participants</th>
<th>Ages of participants</th>
<th>Study design</th>
<th>Length of follow-up</th>
<th>Blood-culture confirmed typhoid cases</th>
<th>Vaccine efficacy</th>
<th>Vaccine safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal</td>
<td>20,019</td>
<td>9 months to &lt;16 years</td>
<td>Randomized 1:1</td>
<td>24 months</td>
<td>TCV: 13, Meningococcal A: 62</td>
<td>79%</td>
<td>Meets safety standards ✓</td>
</tr>
<tr>
<td>Malawi</td>
<td>27,882</td>
<td>9 months to &lt;12 years</td>
<td>Randomized 1:1</td>
<td>18-24 months</td>
<td>TCV: 10, Meningococcal A: 61</td>
<td>84%</td>
<td>Meets safety standards ✓</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>61,567</td>
<td>9 months to &lt;16 years</td>
<td>Cluster* randomized 1:1</td>
<td>18 months</td>
<td>TCV: 29, JE: 192</td>
<td>85%</td>
<td>Meets safety standards ✓</td>
</tr>
</tbody>
</table>

*In cluster randomized trials, groups of participants (known as clusters) are randomized as opposed to individual participants being randomized.
Blood culture confirmed infections

Blood culture performed

Sought care at a surveillance site

Symptomatic infections

All infections (including subclinical)
Seroincidence: a new tool for capturing enteric fever infection burden based on anti-HLyE antibody responses
Can seroepidemiology be used to efficiently characterize overall/total/indirect effects of TCV introduction?
Outcomes

**Overall effect**: Seroincidence in intervention arm vs. control arm

**Total effect**: Seroincidence among vaccinated individuals in the intervention arm vs. unvaccinated individuals in the control arm

**Indirect effect**: Seroincidence incidence in unvaccinated individuals in the intervention arm vs. control arm
Sero incidence of X per 1000 person-years
Effect size = 60%
Sample size = 500
Starting seroincidence = 200 per 1000
Intervention effect of 60%; Sample size = 800; Age 1-5
Intervention effect of 60%; Sample size = 800; Age 1-5
100% power to detect an intervention effect of 60% 2 years post-intervention with a sample size of 2000 1-15 year-olds (1000 per arm)
85% power to detect an intervention effect of 60% 2 years post-intervention with a sample size of 1200 1-15 year-olds (600 per arm)
100% power to detect an intervention effect of 60% 2 years post-intervention with a **sample size of 800** 1-5 year-olds (400 per arm)
Antibody levels measured in a cross-sectional population sample can be translated into an estimate of the frequency with which seroconversions (infections) occur in the sampled population. In other words, the presence of many high antibody titres indicates that many individuals likely experienced infection recently and the burden of disease is high in the population, while low titres indicate a low frequency of infections in the sampled population and therefore a lower burden of disease.

The `serocalculator` package was designed to use the longitudinal response characteristics using a set of modeled parameters characterizing the longitudinal response of the selected serum antibodies.

### Installing R

The `serocalculator` package is written in R, a free, open-source software program. The end user of this package must have access to a working installation of the R software. We recommend installing base R and a Graphical User Interfaces (GUI) for R such as RStudio.

If you need to download and install R and/or RStudio, we recommend following the tutorial below from *Hands On Programming in R* by Garrett Grolemund:

**Installing R and RStudio:** [https://rstudio-education.github.io/hopr/starting.html](https://rstudio-education.github.io/hopr/starting.html)

### Installing the Serocalculator Package

The `serocalculator` package must be installed in R before first use. As of November 21, 2023, `serocalculator` is still in development. To install the development version, you must
Generate a simulated cross-sectional sample and estimate seroincidence

Enteric Fever using HlyE IgG and/or HlyE IgA

Source: vignettes/articles/simulate_xsectionalData.Rmd

This vignette shows how to simulate a cross-sectional sample of seroresponses for incident infections as a Poisson process with frequency \( \lambda \). Responses are generated for the antibodies given in the antigen_isos argument.

Age range of the simulated cross-sectional record is \( \text{lifespan} \).

The size of the sample is \( nrep \).

Each individual is simulated separately, but different antibodies are modelled jointly.

Longitudinal parameters are calculated for an age: \( \text{age.fx} \) (fixed age). However, when \( \text{age.fx} \) is set to NA then the age at infection is used.

The boolean \( \text{renew.params} \) determines whether each infection uses a new set of longitudinal parameters, sampled at random from the posterior predictive output of the longitudinal model. If set to \( \text{FALSE} \) a parameter set is chosen at birth and kept, but: 1. the baseline antibody levels (\( y_b \)) are updated with the simulated level (just) prior to infection, and 2. when \( \text{is.na(age.fx)} \) then the selected parameter sample is updated for the age when infection occurs.

There is also a variable \( \text{n.mc} \): when \( \text{n.mc=}0 \) then a random MC sample is chosen out of the posterior set (1:4000). When \( \text{n.mc} \) is given a value in 1:4000 then the chosen number is fixed and reused in any subsequent infection. This is for diagnostic purposes.
Conclusions

+ Through simulation, we show that seroepidemiology could be an efficient and rapid way to evaluate TCV interventions
+ Young children provide the most informative data for detecting intervention effects
+ Approach for both trials and pre/post designs
Extra slides
Outcomes

- **Overall effect**: Seroincidence in intervention arm vs. control arm
- **Total effect**: Seroincidence among vaccinated individuals in the intervention arm vs. unvaccinated individuals in the control arm
- **Indirect effect**: Seroincidence incidence in unvaccinated individuals in the intervention arm vs. control arm
Variation in antibody kinetics by:

Country          Age          Typhi/Paratyphi A

Days since fever onset

ELISA units

Days since fever onset

Age strata

*Restricted to Ages 5-15
No differences in antibody responses among hospitalized vs non-hospitalized cases
Vi IgG responses barely elevated in cases compared with population No increase across age
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Cross-reactive antibody responses in iNTS?

- **HlyE IgG**
  - Ghana Neighborhood Controls
  - iNTS
  - Typhi
  - Paratyphi

- **HlyE IgA**
  - Ghana Neighborhood Controls
  - iNTS
  - Typhi
  - Paratyphi

**HlyE IgA**
- Typhi vs iNTS
- **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

**LPS IgA**
- Typhi vs iNTS
- **AUC: 0.88**
- (95% CI: 0.78-0.99)
No differences in antibody responses among hospitalized vs non-hospitalized cases.