Incidence, presentation and outcomes of *Salmonella* bacteraemia among young children in sub-Saharan Africa: MAL055 RTS,S-AS01 Salmonella Ancillary Study

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10th International Conference on Typhoid and Other Invasive Salmonelloses, Kampala, Uganda

5 April 2017
First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership∗

Table 3. Serious Adverse Events after the First Dose of a Study Vaccine in the Intention-to-Treat Population, According to Age Category.∗

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>5–17 Mo</th>
<th>6–12 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RTS,S/AS01 Vaccine (N = 5949)</td>
<td>Rabies Vaccine (N = 2974)</td>
</tr>
<tr>
<td></td>
<td>no. of children</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Salmonella sepsis</td>
<td>41</td>
<td>0.7 (0.5–0.9)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>48</td>
<td>0.8 (0.6–1.1)</td>
</tr>
</tbody>
</table>

Average follow-up 18 months and 9 months

Approx. 500 cases of *Salmonella* bacteraemia per 100,000 PYO
11 sites selected to represent diversity of malaria endemicity in sub-Saharan Africa

Children randomised into 3 groups:
- RTS,S-AS01 3 doses + booster
- RTS,S-AS01 3 doses
- Comparator vaccine

Cohorts: 6-12 weeks & 5-17 months
Median follow-up: 38 & 48 months
Duration: 2009 to 2014

Passive surveillance
Blood cultures for febrile admissions
WGS of isolates (ongoing)
AMR profiling (ongoing)

The RTS,S-AS01 phase 3 trial: MAL055
Main exclusion criteria included
- Malnutrition requiring hospitalisation
- Severe anaemia (<5 g/dL)

15,460 children enrolled

Mean baseline Hb = 10.3 g/dl (IQR 9.3 to 11.2).
Mean height-for-weight z score = 0.2 (IQR -0.7 to 1.1)
HIV not systematically tested

Incidence of clinical malaria
- (min) Kilifi, Kenya 0.05 cases per person year
- (max) Siaya, Kenya 4.41 and 5.41 per person year

Our Aim: Use data from MAL055 to determine incidence of *Salmonella* bacteraemia in children under five years across sub-Saharan Africa. Workshop held in Nairobi, Kenya, September 2016.
Incidence and Prevalence

257 episodes of *Salmonella* bacteraemia.
50,280 person years of observation

**Incidence***: per 100,000 PYO (95% CIs)

- All *Salmonella*: 534 (471, 604)  
- *S. Typhi*: 66.5 (45.5, 93.9)  
- NTS: 461 (402, 526)  
- *S. Typhimurium*: 283 (237, 334)  
- *S. Enteritidis*: 133 (102, 170)

**Prevalence***: approx 60% of all bacteraemias

*subject to confirmation*
Incidence by Study Site

Cases per 100,000 PYO

Study Site
- Nanoro, Burkina Faso
- Kintampo, Ghana
- Agogo, Ghana
- Kombewa, Kenya
- Siaya, Kenya
- Korogwe, Tanzania
- Lilongwe, Malawi
- Manhica, Mozambique

Lines = 95% CIs
Incidence by Age – cases per 100,000 PYO (95% CIs)

<table>
<thead>
<tr>
<th></th>
<th>Typhimurium</th>
<th>Enteritidis</th>
<th>Typhi</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 months</td>
<td>517 (362-716)</td>
<td>216 (121-356)</td>
<td>14.4 (0.363-80.1)</td>
<td>43.1 (8.9-126.0)</td>
</tr>
<tr>
<td>12-24 months</td>
<td>438 (335-566)</td>
<td>168 (107-253)</td>
<td>80.6 (40.2-144)</td>
<td>95.2 (50.7-162)</td>
</tr>
<tr>
<td>24-60 months</td>
<td>236 (183-301)</td>
<td>109 (74-156)</td>
<td>80.0 (50.2-121)</td>
<td>32.7 (15.0-62.2)</td>
</tr>
<tr>
<td>Overall</td>
<td>283 (237-334)</td>
<td>133 (102-170)</td>
<td>66.5 (45.5-93.9)</td>
<td>45.7 (28.7-69.3)</td>
</tr>
</tbody>
</table>
Incidence by Age

Cases per 100,000 PYO

Age (months)
Incidence Association with Malaria and HIV by Site

Graphs showing incidence of Salmonella Typhi and NTIS cases per 100,000 PYO by site. The graphs include sites such as Siaya, Kintampo, Kombewa, Agogo, Korogwe, Lilongwe, and Manhica. The x-axis represents clinical malaria cases per 1,000 PYO, and the y-axis represents Salmonella cases per 100,000 PYO.

Another graph shows adult HIV prevalence with sites Siaya, Kintampo, Kombewa, Agogo, Korogwe, Lilongwe, and Manhica, with the x-axis representing HIV prevalence and the y-axis representing Salmonella cases per 100,000 PYO.
Fatality Outcomes

Following *Salmonella* bacteraemia

Throughout study
Salmonella bacteraemia association with malaria

83.8% cases are aparasitaemic at presentation

Positive association with number of malaria infections/year:

<table>
<thead>
<tr>
<th>Infections</th>
<th>Incidence</th>
<th>Incidence Ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 infections</td>
<td>136</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>0-1 infections</td>
<td>300</td>
<td>2.09</td>
<td>0.009</td>
</tr>
<tr>
<td>1-2 infections</td>
<td>774</td>
<td>5.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;2 infections</td>
<td>1217</td>
<td>8.50</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Non-significant reduction in bacteremia in RTS,S-AS01 group compared with comparator vaccine

- incidence rate ratio = 0.83 (95% CI 0.63-1.10)
Conclusions

- *Salmonella* is a major and persistent cause of bacteremia among children under five years across sub-Saharan Africa.

- 3 commonest serovars:
  1. S. Typhimurium
  2. S. Enteritidis
  3. S. Typhi

- iNTS disease 7x higher incidence than typhoid fever

- A *monovalent typhoid vaccine* could have prevented 12.5% of bacteraemias in this study.

- A *trivalent Salmonella vaccine* could have prevented 90.3% of bacteraemias in this study.

- A vaccine able to protect against all three serovars could have a major public health impact.
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