Epidemiology and disease burden of typhoid fever and iNTS disease in sub-Saharan Africa

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Coalition against Typhoid meeting
Kampala, Uganda
4 April 2017
Salmonella infections – major cause of global morbidity and mortality

Ivanoff (1994)  
17 million cases and 600,000 deaths

Crump (2004)  
21.7 million cases and 216,000 deaths

Buckle (2012)  
26.9 million cases

Mogasale (2014)  
20.6 million cases and 222,000 deaths

2008 - Need for epidemiological information on invasive Salmonella disease in sub-Saharan Africa (sSA) expressed by WHO

2009 - Consortium established to investigate invasive Salmonella disease burden sSA

2010 – Surveillance implemented in sSA: The Typhoid Surveillance in Africa Program (TSAP)
Typhoid Fever Surveillance in Africa Program (TSAP) - methods

- Mar 2010 to Jan 2014
- 13 African sites
- 13,431 febrile patients sampled
- Standardized procedures
  - inclusion criteria
  - laboratory
  - case definition
  - healthcare utilization
  - database

S. Typhi and iNTS positivity

Blood culture
Typhoid Fever Surveillance in Africa Program (TSAP) – major findings

**Typhoid fever disease**

- Overall adjusted incidences – two to three times higher compared to previous estimates (10-100 cases/100,000 people).

- In some settings – adjusted rates comparable to data from Asia. (Ghana, Burkina Faso, and Kenya).

- Greatest burden – in children aged 2-14 years.

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Burkina Faso, Nioko II</th>
<th>Burkina Faso, Polesgo</th>
<th>Guinea Bissau, Bandim</th>
<th>Ghana, AAN</th>
<th>Tanzania, Moshi rural</th>
<th>Tanzania, Moshi urban</th>
<th>Kenya, Kibera</th>
<th>Madagascar, Imerintsatoska</th>
<th>Madagascar, Isotry</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
<td>148 (48 - 458)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
</tr>
<tr>
<td>2 to 4</td>
<td>251 (107 - 590)</td>
<td>1,890 (1,202 – 2,972)</td>
<td>53 (13 - 208)</td>
<td>1,079 (762 – 1,528)</td>
<td>0 (0 - 0)</td>
<td>1,028 (472 – 2,237)</td>
<td>490 (264 - 912)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
</tr>
<tr>
<td>5 to 14</td>
<td>315 (191 - 519)</td>
<td>485 (263 - 896)</td>
<td>18 (5 - 72)</td>
<td>314 (230 - 430)</td>
<td>18 (8 - 44)</td>
<td>103 (54 – 199)</td>
<td>489 (338 - 709)</td>
<td>171 (81 - 360)</td>
<td>62 (11 - 359)</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>227 (148 - 350)</td>
<td>719 (500 – 1,035)</td>
<td>20 (8 - 53)</td>
<td>389 (310 - 486)</td>
<td>18 (7 - 42)</td>
<td>155 (94 – 256)</td>
<td>419 (308 - 569)</td>
<td>95 (45 - 201)</td>
<td>42 (7 - 247)</td>
</tr>
<tr>
<td>≥15</td>
<td>0 (0 - 0)</td>
<td>107 (46 - 252)</td>
<td>4 (1 - 20)</td>
<td>n.a.</td>
<td>28 (8 - 95)</td>
<td>201 (99 - 408)</td>
<td>141 (82 - 243)</td>
<td>20 (4 - 103)</td>
<td>42 (12 - 151)</td>
</tr>
<tr>
<td>All</td>
<td>104 (68 - 161)</td>
<td>383 (274 - 535)</td>
<td>10 (4 - 22)</td>
<td>n.a.</td>
<td>20 (10 - 41)</td>
<td>168 (111 – 253)</td>
<td>284 (217 - 371)</td>
<td>58 (29 - 114)</td>
<td>42 (15 - 119)</td>
</tr>
</tbody>
</table>


iNTS disease

- Overall adjusted incidences – comparable to previous reports.
- Greatest burden – in children aged 0-5 years.
- Most common serovars
  1. S. Typhimurium (40%, 38/94)
  2. S. Enteriditis (12%, 11/94)
  3. S. Dublin (11%, 10/94)

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Burkina Faso, Nioko II</th>
<th>Burkina Faso, Polesgo</th>
<th>Guinea Bissau, Bandim</th>
<th>Ghana, AAN</th>
<th>Tanzania, Moshi rural</th>
<th>Tanzania, Moshi urban</th>
<th>Kenya, Kibera</th>
<th>Madagascar, Imerintsiatosika</th>
<th>Madagascar, Isotry</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>753 (460 – 1,233)</td>
<td>431 (162 - 1147)</td>
<td>291 (176 - 482)</td>
<td>1,733 (1,373 – 2,188)</td>
<td>0 (0 - 0)</td>
<td>427 (125 – 1,461)</td>
<td>49 (7 - 350)</td>
<td>100 (18 – 562)</td>
<td>0 (0 - 0)</td>
</tr>
<tr>
<td>2 to 4</td>
<td>753 (460 – 1,233)</td>
<td>630 (288 – 1,380)</td>
<td>53 (13 - 208)</td>
<td>1,908 (1,469 – 2,479)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
<td>49 (7 - 348)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
</tr>
<tr>
<td>5 to 14</td>
<td>236 (133 - 420)</td>
<td>0 (0 - 0)</td>
<td>53 (14 - 97)</td>
<td>147 (93 - 232)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
<td>17 (2 - 124)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>475 (352 - 640)</td>
<td>255 (138 - 470)</td>
<td>116 (69 - 161)</td>
<td>742 (631 - 873)</td>
<td>0 (0 - 0)</td>
<td>26 (8 - 88)</td>
<td>31 (10 - 95)</td>
<td>18 (3 – 99)</td>
<td>0 (0 - 0)</td>
</tr>
<tr>
<td>≥15</td>
<td>35 (13 - 96)</td>
<td>54 (16 - 179)</td>
<td>0 (0 - 0)</td>
<td>n.a.</td>
<td>28 (8 - 95)</td>
<td>0 (0 - 0)</td>
<td>33 (10 - 101)</td>
<td>0 (0 - 0)</td>
<td>0 (0 - 0)</td>
</tr>
<tr>
<td>All</td>
<td>237 (178 – 316)</td>
<td>144 (83 - 249)</td>
<td>37 (24 - 57)</td>
<td>n.a.</td>
<td>7 (2 - 23)</td>
<td>19 (5 - 64)</td>
<td>32 (14 - 70)</td>
<td>9 (2 – 50)</td>
<td>0 (0 - 0)</td>
</tr>
</tbody>
</table>

Antimicrobial resistance patterns

- High number of MDR S. Typhi isolates – 47% (64/135)
- High number of MDR NTS isolates – 48% (45/94)

<table>
<thead>
<tr>
<th></th>
<th>Burkina Faso</th>
<th>Guinea-Bissau</th>
<th>Senegal*</th>
<th>Ghana</th>
<th>Ethiopia</th>
<th>Madagascar</th>
<th>South Africa</th>
<th>Tanzania</th>
<th>Kenya</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total S Typhi isolates, N</td>
<td>16</td>
<td>3</td>
<td>7</td>
<td>30</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>9</td>
<td>54</td>
<td>135</td>
</tr>
<tr>
<td>Isolate with antimicrobial resistance, n (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>20 (67%)</td>
<td>2 (67%)</td>
<td>NR</td>
<td>0</td>
<td>8 (89%)</td>
<td>41 (76%)</td>
<td>71 (53%)</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>3 (10%)</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>4 (44%)</td>
<td>24 (44%)</td>
<td>31 (23%)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2 (11%)</td>
<td>NR</td>
<td>NR</td>
<td>23 (77%)</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>5 (56%)</td>
<td>43 (80%)</td>
<td>73 (54%)</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>2 (11%)</td>
<td>NR</td>
<td>NR</td>
<td>24 (80%)</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>8 (89%)</td>
<td>43 (80%)</td>
<td>77 (57%)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>1 (50%)</td>
<td>0</td>
<td>11 (70%)</td>
<td>12 (9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Multidrug resistance‡</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>19 (63%)</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>5 (56%)</td>
<td>40 (74%)</td>
<td>64 (47%)</td>
</tr>
<tr>
<td>Total INTS isolates, N</td>
<td>14</td>
<td>8</td>
<td>4</td>
<td>59</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>94</td>
</tr>
</tbody>
</table>

- Isolate with antimicrobial resistance, n (%)†

- Multidrug resistance‡

Resistant isolates are reported per country, rather than per site. No Salmonella enterica serotype Typhi (S. Typhi) or INTS isolates were cultured in Sudan. INTS = invasive non-typoidal Salmonella. NR = no resistant isolates identified. †Seven S Typhi, four INTS, and three S minnesota serotype Paratyphi (S Paratyphi) isolates. One of the 5 Paratyphi isolates was resistant to ciprofloxacin. Includes isolates fully and intermediately resistant against the respective drug, as defined by the Clinical Laboratory and Standards Institute guidelines 2013. ‡Defined as resistance against ampicillin or amoxicillin AND chloramphenicol AND co-trimoxazole.

Table 3: Antimicrobial resistance patterns of Salmonella enterica serotype Typhi and INTS isolates across sites

25 manuscripts published and several planned for 2017
Updated estimates mean annual typhoid fever incidence (/100,000)
- decreased from 526 to 376 in East Africa
- increased from 160 to 411 in West Africa

→ average annual incidence of 328/100,000 people in Africa
(an increase of 28/100,000 from the previous estimate)

Typhoid and iNTS disease burden in children and infants

### Invasive *Salmonella* infections in young children across TSAP\(^1\) sites

<table>
<thead>
<tr>
<th>Age Group in years</th>
<th># of enrolled patients</th>
<th># of patients by age group</th>
<th>S. Typhi Crude Cases</th>
<th>S. Typhi Cases adjusted for recruitment(^2)</th>
<th>S. Typhi Adjusted incidence per 100,000 PYO (95% CI)</th>
<th>INTS Crude Cases</th>
<th>INTS Cases adjusted for recruitment(^2)</th>
<th>INTS Adjusted incidence per 100,000 PYO (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>1,217</td>
<td>8,658</td>
<td>1</td>
<td>1</td>
<td>41 (38.4-43.7)</td>
<td>14 (15)*</td>
<td>33</td>
<td>81.6 (75.5-261.0)</td>
</tr>
<tr>
<td>1 to 2</td>
<td>1,057</td>
<td>9,322</td>
<td>4</td>
<td>7</td>
<td>314 (7.6-130.5)</td>
<td>27</td>
<td>77</td>
<td>138.3 (72.4-731.8)</td>
</tr>
<tr>
<td>2 to 3</td>
<td>818</td>
<td>6,407</td>
<td>7</td>
<td>19</td>
<td>1,229 (34.0-445.0)</td>
<td>13</td>
<td>35</td>
<td>143.0 (45.1-451.4)</td>
</tr>
<tr>
<td>3 to 4</td>
<td>685</td>
<td>5,557</td>
<td>13</td>
<td>27</td>
<td>1,913 (55.3-689.6)</td>
<td>15</td>
<td>38</td>
<td>108.9 (66.4-656.7)</td>
</tr>
<tr>
<td>4 to 5</td>
<td>575</td>
<td>4,800</td>
<td>12 (16)*</td>
<td>28</td>
<td>242.2 (99.9-800.1)</td>
<td>2</td>
<td>8</td>
<td>47.1 (12.4-179.1)</td>
</tr>
<tr>
<td>Total</td>
<td>4,352</td>
<td>34,174</td>
<td>37 (41)*</td>
<td>82</td>
<td></td>
<td>71 (73)*</td>
<td>191</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Ethiopia, South Africa and Smegail are excluded in the analysis because no person time information is available in these sites.

\(^2\)Crude cases were adjusted for recruitment proportion (number of patients analyzed divided by number of patients with febrile illness from study area who visited a recruitment health facility, multiplied by 100).

### Invasive *Salmonella* infections in young children by TSAP region

<table>
<thead>
<tr>
<th>Age Group in years</th>
<th>S. Typhi # of adjusted cases</th>
<th>S. Typhi Adjusted incidence per 100,000 PYO (95% CI)</th>
<th>INTS # of adjusted cases</th>
<th>INTS Adjusted incidence per 100,000 PYO (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>0</td>
<td>464.5 (14.8-985.4)</td>
<td>1</td>
<td>41.4 (5.3-122.9)</td>
</tr>
<tr>
<td>1 to 2</td>
<td>5</td>
<td>1,254 (548.1-1650.9)</td>
<td>2</td>
<td>56.8 (15.7-274.8)</td>
</tr>
<tr>
<td>2 to 3</td>
<td>18</td>
<td>831.2 (578.9-1144.0)</td>
<td>1</td>
<td>45.5 (6.0-344.9)</td>
</tr>
<tr>
<td>3 to 4</td>
<td>22</td>
<td>1,205 (845.2-1717.0)</td>
<td>5</td>
<td>203.8 (82.9-568.5)</td>
</tr>
<tr>
<td>4 to 5</td>
<td>18</td>
<td>297.9 (230.1-553.9)</td>
<td>10</td>
<td>457.1 (241.2-865.8)</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td></td>
<td>19</td>
<td>6</td>
</tr>
</tbody>
</table>

\(^1\)TSAP West Region includes Burkina Faso, Ghana and Guinea Bissau.

\(^2\)TSAP East Region includes Kenya, Madagascar, Sudan and Tanzania.

Higher risk for typhoid fever disease with increasing age

Higher risk of both diseases at sites located in West Africa

Higher risk of iNTS disease in infants and very young children
Positive correlation between frequency proportions of malaria and iNTS disease – observed at the TSAP sites endemic for malaria¹

Widal test – Commonly used in many countries

- Measures agglutinating antibodies specific to S. Typhi
- Difficult to know if the patient is in the acute phase
- Patients rarely demonstrate a 4-fold increase
- Not rapid (takes 14 days)
- Not standardized
- Negative in 30% of culture-confirmed cases
- Often done in a single tube
- Lacks sensitivity and specificity
Number of TF cases in the study area 2010

Annual reports Ministry of Heath Gezira State, 2010
Sudan, 2010

<table>
<thead>
<tr>
<th>Laboratory results</th>
<th>Nioklo II, Burkina Faso</th>
<th>Polesgo, Burkina Faso</th>
<th>Bandim, Guinea-Bissau</th>
<th>Pikine, Senegal</th>
<th>Asante Akim North, Ghana</th>
<th>East Wad Medani, Sudan</th>
<th>Butajira, Ethiopia</th>
<th>Imerintriotsika, Madagascar</th>
<th>Isoto, Madagascar</th>
<th>Pieternitzburg, South Africa</th>
<th>Moshi Urban District, Tanzania</th>
<th>Moshi Rural District, Tanzania</th>
<th>Kibera, Kenya*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood culture, N</td>
<td>918</td>
<td>756</td>
<td>1021</td>
<td>1058</td>
<td>2651</td>
<td>644</td>
<td>847</td>
<td>976</td>
<td>1501</td>
<td>1128</td>
<td>406</td>
<td>274</td>
<td>1251</td>
</tr>
<tr>
<td>Total contaminated blood cultures, n (% of N)</td>
<td>220 (24%)</td>
<td>145 (19)</td>
<td>125 (12%)</td>
<td>96 (9%)</td>
<td>182 (7%)</td>
<td>54 (8%)</td>
<td>90 (11%)</td>
<td>6 (1%)</td>
<td>49 (3%)</td>
<td>192 (17%)</td>
<td>8 (2%)</td>
<td>13 (5%)</td>
<td>16 (1%)</td>
</tr>
<tr>
<td>Total positive blood cultures, n (% of N)</td>
<td>29 (3%)</td>
<td>31 (4)</td>
<td>30 (3%)</td>
<td>31 (3%)</td>
<td>175 (7%)</td>
<td>16 (2%)</td>
<td>26 (3%)</td>
<td>11 (1%)</td>
<td>30 (2%)</td>
<td>51 (5%)</td>
<td>17 (4%)</td>
<td>11 (4%)</td>
<td>110 (9%)</td>
</tr>
<tr>
<td>Positive for malaria, n (% of all patients tested)</td>
<td>430/908 (47%)</td>
<td>444/744 (60%)</td>
<td>206/525 (39%)</td>
<td>297/1058 (28%)</td>
<td>1139/2651 (43%)</td>
<td>254/632 (40%)</td>
<td>110/822 (13%)</td>
<td>19/955 (2%)</td>
<td>2/274</td>
<td>0</td>
<td>4/406</td>
<td>2/274</td>
<td>226/956 (24%)</td>
</tr>
</tbody>
</table>

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**Table 1: Demographics and laboratory results of the sites in the Typhoid Fever Surveillance in Africa Program**

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Widal test does not reflect bloodculture-based results
Lessons learnt in conducting typhoid surveillance

- **Site selection**
  - Selection bias
  - Representativeness
  - Determining a denominator, catchment area
  - Local capacity

- **Quality of data**
  - Protocol adherence
  - Difficult to screen all febrile patients
  - Period of surveillance: Variable disease burden in adjacent sites/between years
  - Severe cases in tertiary care facilities

- **Case definition/diagnostics**
  - Limited resources for blood culture
  - Large volume of blood required
  - Contamination
  - Antibiotic pre-treatment
  - Logistics of sample transport
Most comprehensive standardized analysis of the incidence and antimicrobial resistance patterns of invasive *Salmonella* infections in sub-Saharan Africa

Results used by key stakeholders to decide on potential subsidies for typhoid fever vaccines

Results underscore the need for preventive measures, including vaccines

Emphasize the potential increase of drug-resistance *Salmonella* strains in the region

Need to further assess the severity and mortality of the disease
Severe Typhoid in Africa Program (SETA) – filling the gaps on severity and mortality

Filling the gaps on severity and mortality

- Network of surveillance sites across 6 countries in sSA
- To estimate the severity, immune response, long-term sequelae and the associated costs of invasive *Salmonella* infections in sub-Saharan Africa
- Further assessment of the incidence in infants
- Essential evidence for key stakeholders (WHO, GAVI) to develop prevention strategies including a strategy for advent typhoid vaccines.
Invasive *Salmonella* infections in sub-Saharan Africa

- TSAP results - invasive *Salmonella* infections are a major cause of invasive bacterial febrile illness in the sampled locations, specially in children, with incidence rates higher than previously estimated.

- This evidence will be used by key stakeholders to make decisions on introduction of available and advent vaccines against typhoid fever disease.

- Knowledge gaps on disease severity, mortality and associated costs are being assessed by SETA.
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- Ralf Krumkamp
- Denise Dekker
- Jürgen May
- Christian G. Meyer
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