Epidemiology of NTS and S. Typhi in Kenya and E. Africa region

Sam Kariuki

Chief Research Scientist, KEMRI and International Fellow, WTSI
Outline of my talk

1. Introduction
2. What we know about field epidemiology of adult and paediatric iNTS in the region
3. iNTS and Typhoid contrasting epidemiology
4. Conclusion and planned studies
Background
Invasive NTS in adults

- NTS bacteraemia is a common, recurrent illness in HIV-infected adults, after TB and pneumococcal bacteremia.
- NTS bacteraemia has a high mortality (47%) and recurrence (43%) rate in HIV-infected adults.
- Recurrence is caused by recrudescence rather than re-infection.
- Predominant serovar from seropositive patients, S. Typhimurium at 58%.
- MDR strains are now common in this population (68%)
Several documented studies on NTS in children

- **Tanzania:** 5/24 children with suspected meningitis and/or septicemia, had meningitis caused by S. Enteritidis, all of whom died.
- **Uganda:** Bacteraemia affects 1 / 6 severely malnourished children
- High mortality especially among the HIV-positive.
- **South Africa:** 59% [94 of 160]) of NTS were blood culture isolates.
- **Malawi:** Case-fatality rates for childhood NTS are also high (21–24%), even when appropriate antibiotics are available (*Gordon et al.* CID 2008)
- **Gambia:** incidence of invasive bacterial infections in children - 1009 (95% CI, 903-1124) cases per 100,000 person-years
Reports from tropical Africa of NTS as a major cause of paediatric bacteraemia

The Gambia 1980s and 2005
Ghana 1990s, 2002
Nigeria 1970s, 90s, 2001
CAR 2002
DRC 1980s, 1990s

Uganda 2006, 2009
Ethiopia 2010-2012
Rwanda 1980s
Tanzania 2007, 2010
Malawi 1996-2010
Mozambique 2001-2006
Recent studies in Kenya


  NTS accounted for 60/155 (39%) of blood culture isolates in the rural and 7/230 (3%) sites. The adjusted incidence in the rural site was 568/100,000 person-years


  Of the 4467 outborn young infants admitted, 748 (17%) died. 11% had IBI (10% bacteremia and 3% bacterial meningitis), with a case fatality of 33%


  iNTS at 18% for children with sickle cell disease


  Overall 170 (51.2%) of children presented with iNTS alone, 28 (8.4%) with gastroenteritis and bacteraemia and 134 (40.4%) with gastroenteritis alone.
Documented Risk Factors
Host factors

- Young age
- Anaemia
- Malaria
- Malnutrition
- HIV

- Sickle cell disease
- Schistosomiasis
- Diabetes
- Malignancy
Environmental factors

- Rainy season
- Water supply
- Crowding
- Hygiene
Seasonal variation of NTS infections

Nairobi; p <0.0001

Numbers

Jan Feb Mar April May June July Aug Sep Oct Nov Dec

Months

Nairobi

Kilifi
Pathogen factors

– Virulence characteristics have been mapped in PIs: type III secretion systems, Vi antigen, lipopolysaccharide and other surface polysaccharides, flagella, and various factors essential for the intracellular life cycle of NTS. DeJong et al. PLoS Pathog. 2012;8(10):e1002933

MDR phenotype is a feature of iNTS

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Range</th>
<th>MIC (µg/ml)</th>
<th>Mode</th>
<th>MIC50</th>
<th>MIC90</th>
<th>% R</th>
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<tbody>
<tr>
<td>Ampicillin</td>
<td>0.25-&gt;256</td>
<td>&gt;256</td>
<td></td>
<td>82</td>
<td>64</td>
<td>48</td>
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<td>Co-amoxyclov</td>
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<td>4</td>
<td></td>
<td>1</td>
<td>16</td>
<td>8</td>
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<tr>
<td>Cefuroxime</td>
<td>2-&gt;256</td>
<td>&gt;256</td>
<td></td>
<td>8</td>
<td>32</td>
<td>30</td>
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<tr>
<td>Ceftriaxone</td>
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<td>0.064</td>
<td></td>
<td>0.5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Gentamicin</td>
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<td>4</td>
<td></td>
<td>1</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>0.064-&gt;32</td>
<td>&gt;32</td>
<td></td>
<td>8</td>
<td>32</td>
<td>46</td>
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<tr>
<td>Chloramphene</td>
<td>0.19-&gt;256</td>
<td>&gt;256</td>
<td></td>
<td>4</td>
<td>32</td>
<td>26</td>
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<tr>
<td>Tetracycline</td>
<td>0.064-&gt;256</td>
<td>3</td>
<td></td>
<td>16</td>
<td>128</td>
<td>49</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>1.5-&gt;256</td>
<td>3</td>
<td></td>
<td>3</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.064-4</td>
<td>0.16</td>
<td></td>
<td>0.06</td>
<td>0.125</td>
<td>0</td>
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</table>

Emergence of ceftriaxone resistant S. Typhimurium in 2010

• Isolate 1. 43 year old hospitalized male Feb, 2010, stool culture done due to diarrhea and septic screen.
• Isolate no 2. date of isolation May 2010 from a hospitalized 1 month old baby, urine and blood culture
• Both Identified as S. Typhimurium
• Sensitive to – Chlor, Ciproxin and Cefoxitin.
• Resistant to Nalidixic acid, Septrin, Ampi, Ceftriaxone and aztreonam. MIC ceftriaxone >256 ; MIC Cipro 0.012
• ESBL CTX-M-18
Environmental reservoirs and transmission routes remain elusive!

Invasive multidrug-resistant non-typhoidal *Salmonella* infections in Africa: zoonotic or anthroponotic transmission?

Samuel Kariuki,¹,² Gunturu Revathi,³ Nyambura Kariuki,³ John Kiiru,¹ Joyce Mwituria,¹ Jane Muyodi,¹ Jane W. Githinji,⁴ Dorothy Kagendo,¹ Agnes Munyalo¹ and C. Anthony Hart²

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⁴Central Veterinary Investigations Laboratory, PO Private Bag, Kabete, Kenya
NTS by age group – Nairobi

Clinical presentation of NTS infection according to age group

![Bar chart showing the clinical presentation of NTS infection by age group. The chart compares the number of children with and without diarrhea or invasive NTS infection across different age groups: 0-1, 1-2, 2-3, and over 3 years old.]

- **No. of children with diarrhoea only**
- **No. with invasive NTS only**
We believe NTS was a problem starting way back in 1970s?

1975-79: 297 invasive isolates

- < 2 years: 45%
- 2-12 years: 32%
- > 13 years: 23%

Mortality for *S. typhimurium*

- Blood isolates (n=93): 18%
- CSF isolates (n=26): 96%

Salmonella infections Kenyatta National Hospital
1970-80


<table>
<thead>
<tr>
<th></th>
<th>Ampicillin</th>
<th>Cotrimoxazole</th>
<th>Chloramphenicol</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.typhimurium</td>
<td>63</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>S.typhi</td>
<td>22</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
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Contrasting Typhoid/NTS incidence

• In urban informal settlement studies:
  • crude incidence of blood culture-confirmed typhoid fever was 247 cases per 100,000 pyo, highest in children 5-to-9 and 2-4 yo (596 and 521 /100,000 pyo)
  • No seasonality noted
  • Not HIV-related
• In typical rural community
  • Crude incidence was 29 cases per 100,000 pyo in Lwak 18–34 year age group (63 cases per 100,000 pyo) and low in 2-4 and 5–9 yo(28 and 18 cases per 100,000 pyo, respectively)
Conclusions

1. ST313 iNTS clade is fast expanding throughout SSA
2. Is iNTS athroponotic? We think so in SSA
3. With Hib and pneumococcal vaccine available, iNTS is likely to be the major bacterial infection in both adults and children
4. MDR phenotype will complicate management
5. Improved detection and early treatment will save lives
Proposed iNTS Project

• To determine geospatial distribution of cases of invasive salmonellosis (iNTS and Typhoid) treated at the clinics in Mukuru slum 15 km east of Nairobi city
• To determine the hotspots for invasive salmonella infection according to genotypes in circulation and evaluate the risk factors associated with high incidence of disease in specific endemic zones.
Study site and population

Mukuru kwa Njenga and Mukuru Reuben are among the many villages in the larger slum

**Catchment population for Mukuru clinic**

<table>
<thead>
<tr>
<th>Description</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total catchment population</td>
<td>89,258</td>
</tr>
<tr>
<td>Children under 1yr (12months)</td>
<td>2,678</td>
</tr>
<tr>
<td>Children under 5 yrs (60months)</td>
<td>11,336</td>
</tr>
<tr>
<td>Children under 15 yrs</td>
<td>27,045</td>
</tr>
<tr>
<td>Adults (24-59yrs)</td>
<td>21,690</td>
</tr>
<tr>
<td>Elderly (over 60yrs)</td>
<td>625</td>
</tr>
</tbody>
</table>
The Invasive Salmonella Study

Expected outcomes of the study will include:

1. incidence, prevalence, and spatial and spatio-temporal clustering of strain types/genotypes of invasive salmonellosis and NTS diarrhea
2. incidence, prevalence, and spatial and spatio-temporal clustering of strains with different antibiotic resistance profiles, and of strains with different resistance genes;
3. maps showing hotspots for the ST and iNTS phenotypes in space and in space-time,
4. associations between potential risk factors and the risk of TF and iNTS disease
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