Understanding Fever and the Acute Febrile Illness Landscape

David Mabey
Clinical Research Department
London School of Hygiene & Tropical Medicine
The “Gate Clinic”, MRC Labs, The Gambia, 1978
The ward at MRC Labs, The Gambia, 1978
Association between malaria and non-typhoid *Salmonella* (NTS) bacteraemia in The Gambia


- 71 cases of NTS bacteraemia; 30 had malaria (42%)
- 45 cases of typhoid; 5 had malaria (11%)

Mean haemoglobin
- In NTS cases: 6.7
- In typhoid cases: 10.3
The Effect of Insecticide-treated Bed Nets on Mortality in Gambian Children


Permethrin-impregnated bednets + weekly malaria chemoprophylaxis during the rainy season reduced mortality of children aged 1-4 years by 63%
Figure 2.1 Estimated malaria case incidence and death rate globally, 2000–2015

Source: WHO estimates
Decline in malaria 2000 - 2015

Bhatt S et al Nature 2015
Increase in use of malaria Rapid Diagnostic Tests (mRDTs)
## IMCI guidelines

| Pink: VERY SEVERE FEBRILE DISEASE | Give first dose of artesunate or quinine for severe malaria  
|-----------------------------------|----------------------------------------------------------|
|                                   | Give first dose of an appropriate antibiotic  
|                                   | Treat the child to prevent low blood sugar  
|                                   | Give one dose of paracetamol in clinic for high fever (38.5°C or above)  
|                                   | Refer URGENTLY to hospital  

| Yellow: MALARIA | Give recommended first line oral antimalarial  
|-----------------|------------------------------------------------|
|                 | Give one dose of paracetamol in clinic for high fever (38.5°C or above)  
|                 | Give appropriate antibiotic treatment for an identified bacterial cause of fever  
|                 | Advise mother when to return immediately  
|                 | Follow-up in 3 days if fever persists  
|                 | If fever is present every day for more than 7 days, refer for assessment  

| Green: FEVER: NO MALARIA | Give one dose of paracetamol in clinic for high fever (38.5°C or above)  
|--------------------------|-------------------------------------------------|
|                          | **Give appropriate antibiotic treatment for an identified bacterial cause of fever**  
|                          | Advise mother when to return immediately  
|                          | Follow-up in 3 days if fever persists  
|                          | If fever is present every day for more than 7 days, refer for assessment  

- Any general danger sign or stiff neck.
- Malaria test POSITIVE.
- Malaria test NEGATIVE
- Other cause of fever PRESENT.
Introduction of Malaria RDTs increases prescription of antibiotics

Hopkins H et al. BMJ 2017; 356:1054

Ratios for antibiotic prescription in randomised studies comparing patients in control settings with patients in settings where malaria rapid diagnostic test intervention was implemented.
Beyond Malaria — Causes of Fever in Outpatient Tanzanian Children

Valérie D’Acremont, M.D., Ph.D., Mary Kilowoko, M.P.H., Esther Kyungu, M.D., M.P.H., Sister Philipina, R.N., Willy Sangu, A.M.O., Judith Kahama-Maro, M.D., M.P.H.,* Christian Lengeler, Ph.D., Pascal Cherillod, Ph.D., Laurent Kaiser, M.D., and Blaise Genton, M.D., Ph.D.

• 2 sites (Ifakara and Dar es Salaam)
• 2 months – 10 years
• Low malaria endemicity (around 9% in febrile children)
• Recorded temperature >38°C
• 23 symptoms, travel history, risk factors, 49 clinical signs
• 5 ml blood and pooled nasal and throat
• Final diagnosis based on predefined clinical and micro criteria using computer
1005 children – 1232 diagnoses

D’acremont et al NEJM 2014
133 children with severe illness - 160 diagnoses

D'acremont et al NEJM 2014
### Table 1. Prevalence and Outcome of Community-Acquired Bacteremia among Hospitalized Children, According to Age.*

<table>
<thead>
<tr>
<th>Age</th>
<th>All Patients</th>
<th>Patients with Bacteremia</th>
<th>Patients without Bacteremia</th>
<th>Patients with Bacteremia (95% CI)</th>
<th>Deaths Involving Bacteremia (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Deaths</td>
<td>Total</td>
<td>Deaths</td>
<td>percent</td>
</tr>
<tr>
<td>&lt;7 days</td>
<td>867</td>
<td>117</td>
<td>65</td>
<td>247</td>
<td>13.5 (11.5–16.0)</td>
</tr>
<tr>
<td>7–59 days</td>
<td>916</td>
<td>111</td>
<td>29</td>
<td>51</td>
<td>12.1 (10.1–14.4)</td>
</tr>
<tr>
<td>60–364 days</td>
<td>4,354</td>
<td>301</td>
<td>86</td>
<td>152</td>
<td>6.9 (6.2–7.7)</td>
</tr>
<tr>
<td>≥1 yr</td>
<td>10,433</td>
<td>565</td>
<td>128</td>
<td>426</td>
<td>5.4 (5.0–5.8)</td>
</tr>
<tr>
<td>All ages</td>
<td>16,570</td>
<td>1094</td>
<td>308</td>
<td>876</td>
<td>6.6 (6.2–7.0)</td>
</tr>
</tbody>
</table>
# Bacteremia among Children Admitted to a Rural Hospital in Kenya


## Table 1. Prevalence and Outcome of Community-Acquired Bacteremia among Hospitalized Children, According to Age.*

<table>
<thead>
<tr>
<th>Age</th>
<th>All Patients</th>
<th>Patients with Bacteremia</th>
<th>Patients without Bacteremia</th>
<th>Patients with Bacteremia (95% CI)</th>
<th>Deaths Involving Bacteremia (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Deaths</td>
<td>Total</td>
<td>Deaths</td>
<td>percent</td>
</tr>
<tr>
<td>&lt;7 days</td>
<td>867</td>
<td>117</td>
<td>750</td>
<td>247</td>
<td>13.5 (11.5–16.0)</td>
</tr>
<tr>
<td>7–59 days</td>
<td>916</td>
<td>111</td>
<td>805</td>
<td>51</td>
<td>12.1 (10.1–14.4)</td>
</tr>
<tr>
<td>60–364 days</td>
<td>4,354</td>
<td>301</td>
<td>4,053</td>
<td>152</td>
<td>6.9 (6.2–7.7)</td>
</tr>
<tr>
<td>≥1 yr</td>
<td>10,433</td>
<td>565</td>
<td>9,868</td>
<td>426</td>
<td>5.4 (5.0–5.8)</td>
</tr>
<tr>
<td>All ages</td>
<td>16,570</td>
<td>1094</td>
<td>15,476</td>
<td>876</td>
<td>6.6 (6.2–7.0)</td>
</tr>
</tbody>
</table>

*percent

- All ages: 28% bacteremia, 6% death.

---

*Note: The table provides the prevalence and outcome of community-acquired bacteremia among hospitalized children, categorized by age. The data includes the total number of patients, those with bacteremia, those without bacteremia, and the associated percentages and confidence intervals for patients with bacteremia and deaths involving bacteremia.*
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Odds Ratio (95% Confidence Interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td>None‡</td>
<td>1.00</td>
</tr>
<tr>
<td>Any organism</td>
<td>2.02 (1.65–2.47)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>1.85 (1.36–2.52)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>1.31 (0.76–2.26)</td>
</tr>
<tr>
<td>Group A streptococci</td>
<td>3.28 (1.75–6.15)</td>
</tr>
<tr>
<td>Group B streptococci§</td>
<td>1.15 (0.45–3.00)</td>
</tr>
<tr>
<td>Nontyphoidal salmonella species</td>
<td>1.68 (1.15–2.44)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>1.16 (0.75–1.79)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>4.73 (3.15–7.10)</td>
</tr>
</tbody>
</table>

**Bacterial bloodstream infections in Africa**


---

**North Africa**

Two studies covering 14 locations
10,330 patients, 10.2% with BSI
HIV was not reported.
All studies were primarily in adults
Three commonest isolates: Salmonella 49.9%
(5 Escherichia coli Typhi 9.6%),
*Erwinia* spp 25.8%, *Staphylococcus aureus* 7.7%

---

**East Africa**

Seven studies covering nine locations
21,317 patients, 7.6% with BSI
18.6% of included patients tested for HIV
23.7% of 3,445 tested were seropositive for HIV-1
Four studies were primarily in children and four were primarily in adults
Three commonest isolates:
*Streptococcus pneumoniae* 21.2%,
Salmonella 17.9% (non-typhoidal 88.1%),
*Escherichia coli* 9.5%

---

**West and central Africa**

Six studies covering five locations
5,887 patients, 12.4% with BSI
5.4% of included patients tested for HIV
65.2% of 1,102 tested were seropositive for HIV-1 or HIV-2
Five studies were primarily in children and one was primarily in adults
Three commonest isolates: Salmonella 10.8% (non-typhoidal 87.0%),
*S pneumoniae* 18.0%, *S aureus* 17.2%

---

**Southern Africa**

Seven studies covering five locations
23,893 patients, 9.8% with BSI
5.0% of included patients tested for HIV
59.8% of 1,294 tested were seropositive for HIV-1
Four studies were primarily in children and three were primarily in adults
Three commonest isolates: Salmonella 29.0%
(non-typhoidal 97.0%), *Streptococcus pneumoniae* 24.0%,
*S aureus* 9.4%
Organisms isolated from Blood Cultures in Blantyre, Malawi, 1998-2016

*Musicha P et al. Lancet Infect Dis 2017; 17: 1042*

194,539 blood cultures, of which 29,183 (15%) were positive

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella</em> (non-typhi)</td>
<td>36%</td>
<td>30%</td>
<td>50%</td>
<td>40%</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td><em>Strep. pneumoniae</em></td>
<td>15%</td>
<td>17%</td>
<td>17%</td>
<td>20%</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td><em>S. typhi</em></td>
<td>10%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>27%</td>
<td>43%</td>
</tr>
<tr>
<td><em>E.coli</em></td>
<td>9%</td>
<td>9%</td>
<td>7%</td>
<td>10%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>7%</td>
<td>7%</td>
<td>5%</td>
<td>5%</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>4%</td>
<td>7%</td>
<td>3%</td>
<td>4%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td><em>Cryptococcus</em></td>
<td>3%</td>
<td>1%</td>
<td>3%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Bacteraemia in Kenyan children with sickle-cell anaemia: a retrospective cohort and case-control study

Thomas N Williams, Sophie Uyoga, Alex Macharia, Carolyne Ndila, Charlotte F McAuley, Daniel H Opi, Salim Mwarumba, Julie Makani, Albert Komba, Moses N Ndiritu, Shahnaaz K Sharif, Kevin Marsh, James A Berkley, J Anthony G Scott

<table>
<thead>
<tr>
<th>Gram positive</th>
<th>Isolates from children without sickle-cell anaemia (%)</th>
<th>Isolates from children with sickle-cell anaemia (%)</th>
<th>Proportion of isolates in children with sickle-cell anaemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumonia</td>
<td>425 (25.9%)</td>
<td>44 (40.7%)</td>
<td>10.4%</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>173 (10.5%)</td>
<td>6 (5.6%)</td>
<td>3.5%</td>
</tr>
<tr>
<td>Group A streptococci</td>
<td>82 (5.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>35 (2.1%)</td>
<td>1 (0.9%)</td>
<td>2.9%</td>
</tr>
<tr>
<td>Other gram-positive organisms†</td>
<td>82 (5.0%)</td>
<td>4 (3.7%)</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram negative</th>
<th>Isolates from children without sickle-cell anaemia (%)</th>
<th>Isolates from children with sickle-cell anaemia (%)</th>
<th>Proportion of isolates in children with sickle-cell anaemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-typhi Salmonella species</td>
<td>192 (11.7%)</td>
<td>19 (17.6%)</td>
<td>9.9%</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>100 (6.1%)</td>
<td>13 (12.0%)</td>
<td>13.0%</td>
</tr>
<tr>
<td>Haemophilus influenzae other</td>
<td>27 (1.6%)</td>
<td>2 (1.9%)</td>
<td>7.4%</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>138 (8.4%)</td>
<td>7 (6.5%)</td>
<td>5.1%</td>
</tr>
<tr>
<td>Acinetobacter species</td>
<td>136 (8.3%)</td>
<td>7 (6.5%)</td>
<td>5.1%</td>
</tr>
<tr>
<td>Pseudomonas species</td>
<td>81 (4.9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>57 (3.5%)</td>
<td>1 (0.9%)</td>
<td>1.8%</td>
</tr>
<tr>
<td>Other gram-negative organisms†</td>
<td>113 (6.9%)</td>
<td>4 (3.7%)</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Overall

| Any organism          | 1641 (100.0%)                                          | 108 (100.0%)                                        | 6.6%                                                          |

Sickle Cell Disease

- OR 26.3 for bacteraemia
- Bacterial etiology similar to non-Sickle children
- Association strongest for:
  - *Streptococcus pneumoniae*
  - Non-Typhi *Salmonella*
  - *Haemophilus influenzae*
Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study

<table>
<thead>
<tr>
<th>Nosocomial (total [%])</th>
<th>Health-care-associated* (total [%])</th>
<th>Community-acquired (total [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-negative organisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>44 (21%)</td>
<td>16 (11%)</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>43 (20%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td><em>Klebsiella spp</em> (other)</td>
<td>9 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>16 (8%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td><em>Pseudomonas spp</em> (other)</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><em>Acinetobacter spp</em></td>
<td>19 (9%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td><em>Non-typhi Salmonella spp</em></td>
<td>3 (1%)</td>
<td>10 (7%)</td>
</tr>
<tr>
<td><em>Salmonella typhi</em></td>
<td>2 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><em>Other enterobacteriaceae</em></td>
<td>8 (4%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>2 (1%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td><em>Other Gram-negative organisms</em></td>
<td>4 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Gram-positive organisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>20 (9%)</td>
<td>22 (16%)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>3 (1%)</td>
<td>23 (16%)</td>
</tr>
<tr>
<td><em>Group A streptococci</em></td>
<td>1 (1%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td><em>Group B streptococci</em></td>
<td>2 (1%)</td>
<td>18 (13%)</td>
</tr>
<tr>
<td><em>Group D streptococci</em></td>
<td>18 (9%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td><em>Other gram-positive organisms</em></td>
<td>1 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeasts</td>
<td>31 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Total pathogens!</td>
<td>212 (100%)</td>
<td>141 (100%)</td>
</tr>
</tbody>
</table>

Data are number of episodes. *Health-care-associated infection was defined as bacteraemia within the first 48 h of admission to hospital when within 28 days of discharge from hospital or hospital birth. Contaminants were grown from 19.5% of samples collected in the first 48 h after admission and 13.2% of samples obtained 48 h or more after admission. These proportions did not differ significantly (p=0.11).

Table 3: Pathogens causing paediatric bacteraemia in Kilifi District Hospital, 2002-09

**Nosocomial bacteraemia**

- Incidence 40x higher than community acquired bacteraemia
- Risk increasing 27%/year
- Mortality twice as high as community acquired bacteraemia (53% vs 24%)
- Longer hospital stay

Aiken A et al., Lancet 2011
DOI:10.1016/S0140- 6736(11)61622-X
Febrile Paediatric Admissions to Muheza Hospital

Nadjm B et al BMJ 2010;340:c1350
Muheza Hospital

Nadjm B et al BMJ 2010;340:c1350
Risk factors for bacteraemia in African children

- Malnutrition
- HIV infection
- Sickle cell disease
- Admission to hospital
- ? Malaria
Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study


Lancet 2011; 378: 1316-23
Case-control study

• Children aged 3 months to 3 years
• Recruited between Sept 1999 and July 2002
• 292 cases admitted with bacteraemia
• 2 healthy controls for each case, matched for age, sex and location
• Sickle haemoglobin phenotype determined for cases and controls by electrophoresis
Results of case-control study

Bacteraemia was associated with
- HIV
- Malnutrition
- Sickle cell disease
- Leucocyte haemoglobin pigment

Sickle trait (HbA/S) was negatively associated with bacteraemia (OR 0.36, 95% CI 0.20-0.65)

Is this because sickle trait protects against malaria?
Relation between falciparum malaria and bacteraeemia in Kenyan children: a population-based, case-control study and a longitudinal study


![Graph showing the relation between malaria incidence and odds ratio for HbAS over the years 1999 to 2007.](Lancet 2011;378:1316-23.)
Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study


Conclusions

• Malaria is a risk factor for invasive bacterial infection
• Therefore a severely ill febrile child with or without malaria should be given an antibiotic

Which one?
Emergence of resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole among *Salmonella enteritidis* and *S. typhimurium* in Malawi, 1998–2004

Publications on AMR in Africa 1990-2013

Publications on AMR in Africa 2013-6

Tadesse BT et al. BMC Infectious Diseases 2017; 17: 616
Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998–2016): a surveillance study

Patrick Musicha, Jennifer E Cornick, Naor Bar-Zeev, Neil French, Clemens Masesa, Brigitte Denis, Neil Kennedy, Jane Malilewa, Melita A Gordon, Chisomo I. Msfupa, Robert S Heyderman, Dean B Everett, Nicholas A Feasey

S. pneumoniae

S. aureus

First-line antibiotics

RFL = resistant to penicillin, cotrimoxazole, chloramphenicol
A) *Escherichia coli*. (B) *Klebsiella* spp. (C) Other *Enterobacteriaceae*. (D) *S. pneumoniae*. (E) *Staphylococcus aureus*. (F) Other *Streptococcus and Enterococcus* spp.

RFL=resistant to all first-line antimicrobials, which include chloramphenicol and co-trimoxazole, plus ampicillin for Gram-negative pathogens and penicillin for Gram-positive pathogens.
# Resistance in NTS from Blood Cultures in Western Kenya


<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistant/Tested, No. (%)</th>
<th>Salmonella B (n = 72)$^a$</th>
<th>Salmonella D (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>64/68 (94.1)</td>
<td>27/30 (90)</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>54/72 (75)</td>
<td>28/30 (93.3)</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin + clavulanate</td>
<td>44/67 (65.7)</td>
<td>13/27 (48.1)</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>17/72 (23.6)</td>
<td>0/30 (0)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1/71 (1.4%)</td>
<td>0/30 (0)</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>0/42 (0)</td>
<td>0/15 (0)</td>
<td></td>
</tr>
<tr>
<td>A, Au, C</td>
<td>36/64 (56.3)</td>
<td>13/30 (43.3)</td>
<td></td>
</tr>
<tr>
<td>A, Au, C, Gen, Cx</td>
<td>17/64 (26.6)</td>
<td>0/30 (0)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Resistance in NTS from Blood Cultures in Western Kenya
Ceftriaxone Resistant *Salmonella* from Blood Cultures in Western Kenya

## Antibiotic Susceptibility of *Salmonella* Strains from Blood Cultures in Bukavu, DRC


<table>
<thead>
<tr>
<th>Antibiotiques</th>
<th>Sensitive (%)</th>
<th>Intermediate (%)</th>
<th>Resistant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacine</td>
<td>46(76,6)</td>
<td>1(1,7)</td>
<td>13(21,7)</td>
</tr>
<tr>
<td>Amoxicilline</td>
<td>7(11,7)</td>
<td>-</td>
<td>53(88,3)</td>
</tr>
<tr>
<td>Augmentin</td>
<td>3(5)</td>
<td>-</td>
<td>57(95)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>49(81,7)</td>
<td>-</td>
<td>10(18,3)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>48(80)</td>
<td>2(3,3)</td>
<td>10(16,7)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>44(73,3)</td>
<td>-</td>
<td>16(26,7)</td>
</tr>
<tr>
<td>Chloramphénicol</td>
<td>5(8,3)</td>
<td>-</td>
<td>55(91,7)</td>
</tr>
<tr>
<td>Ciprofloxacine</td>
<td>55(91,7)</td>
<td>-</td>
<td>5(8,3)</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>6(10)</td>
<td>-</td>
<td>54(90)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>12(20)</td>
<td>4(6,7)</td>
<td>44(73,3)</td>
</tr>
<tr>
<td>Gentamicine</td>
<td>7(11,7)</td>
<td>-</td>
<td>53(32)</td>
</tr>
<tr>
<td>Négram</td>
<td>1(1,7)</td>
<td>-</td>
<td>59(98,3)</td>
</tr>
<tr>
<td>Norfloxacine</td>
<td>48(80)</td>
<td>-</td>
<td>12(20)</td>
</tr>
</tbody>
</table>
The African Meningitis Belt
Meningococcal Meningitis in the Meningitis Belt

Mustapha M and Harrison L. Hum Vaccin Immunother 2018; 14: 1107

Serogroup A conjugate vaccine rolled out in 2010
Febrile illness in Moshi


• Prospective study, 2 hospitals
• 870 consecutive admissions with fever (children and adults)
• 528 clinical malaria (60%)
• 14 confirmed (1.6%)
• 118 bacterial zoonoses (26%)
  • 16 brucellosis
  • 40 leptospirosis
  • 24 Q fever
  • 36 Rickettsia
• 55 chikungunya

None of the above were included in the differential diagnosis
Leptospirosis in Africa

2.3% - 19.8% of inpatients with non-specific febrile illness had leptospirosis
(Data from 11 studies)
Ugandan HIV+ Patients admitted with severe sepsis

Jacob ST et al. PLoS One 2013; 8: e70205

368 patients

Median CD4 count

- 17 in *MTb* + cases
- 64 in others
Urine Antigen Detection to diagnose TB

Lipoarabinomannan (LAM)
Determine TB-LAM Ag
Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study

Stephen D Lawn, Andrew D Kerkhoff, Monica Vogt, Robin Wood
Sensitivity of LAM POC test


Specificity >98%
all strata

Diagnostic sensitivity (%)
Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial  


RCT comparing standard of care with standard of care + urine testing by LAM POCT and GenExpert
2600 HIV + adults admitted to hospital in Malawi and South Africa
Primary outcome: Mortality at 56 days

Results
72% of study subjects taking ART
Median CD4 count 227
Mortality overall was 21% in the standard of care group vs 18% in the intervention group (p=0.074)
Mortality significantly reduced in the intervention group in those with CD4<100 (p=0.036)
And in those with severe anaemia (p=0.021)
Invasive bacterial infections in Africa

• High incidence, especially in children
• High mortality
• Risk factors
  • HIV
  • Malnutrition
  • Sickle cell disease
  • Hospital admission
  • Malaria
Conclusions

Great progress has been made in the past 20 years
• 40% reduction in incidence of malaria between 2000 and 2015
• Vaccinations rolled out (Hib, pneumococcus, meningococcus)
• Antiretroviral treatment rolled out
• POC tests for malaria, HIV, TB, cryptococcal meningitis
• Identification of biomarkers associated with bacterial infections
• Clinical algorithms shown to reduce antibiotic prescription without affecting outcomes
Many challenges remain

• Rapid spread of antimicrobial resistance in major pathogens
• Incidence of malaria is no longer declining
• Serotype replacement when vaccines are rolled out
• Difficult access in regions with conflict
• Uncertain funding environment

For the clinician
Which febrile outpatients need an antibiotic?
Which antibiotic should I give to a febrile inpatient?
The Way Forward

• Further studies on causes of fever in different populations
• Roll out of global surveillance for antimicrobial susceptibility
• Development and evaluation of new vaccines
• Evaluation of new biomarkers to identify patients who need antibiotics in different settings
• Development and evaluation of new POC diagnostic tests
• Development and evaluation of new clinical algorithms for the management of fever in different settings
• New strategies for the control and elimination of malaria