Sepsis in Africa: clarifying what we know

Neill Adhikari
Critical Care Medicine
Sunnybrook Health Sciences Centre and University of Toronto
28 October 2015
Conflicts of interest

• I have been a consultant to WHO for development and piloting of training materials for care of severely ill patients in resource-limited settings
Objective

- Clarify what we know (and don’t know) about sepsis in sub-Saharan Africa
  - Incidence
  - Deaths
  - Resources
  - Treatments
Population-level data on the scope of sepsis in Africa do not exist
Measuring the burden of sepsis is more difficult...

- It is a syndrome
  - validity and reliability under debate
- Brief prodrome and high short-term mortality
  - limits prevalent cases found in point-prevalence studies
- Not well captured in administrative data
- Incidence depends on availability and intensity of other health services
- No globally validated risk-adjustment models
Sepsis incidence in Africa – measurement challenges

- Clinical databases (none)
  - In high-income countries these are ICU-based, so measured incidence depends on ICU access

- Hospital discharge databases (none)
  - Codes for infection + organ dysfunction
  - Codes for ‘septicemia’ and organ dysfunction

- Death estimates using registries (GBD)
  - Cause of death likely attributed to infection
  - Back-calculate incidence using case-fatality
  - Could capture deaths at home
Factors determining incidence and case-fatality

Adapted from Octavia Peck-Palmer, with permission.
Crude estimate 1

Assumes same age and sex distribution, pathogens, outcomes...

<table>
<thead>
<tr>
<th>Population in 2004 (x10^3)</th>
<th>Total</th>
<th>Infection</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-income countries</td>
<td>8008</td>
<td>468 (6%)</td>
<td>2300–2800</td>
</tr>
<tr>
<td>East Asia and Pacific</td>
<td>14000</td>
<td>1776 (13%)</td>
<td>4500–5700</td>
</tr>
<tr>
<td>Europe and central Asia</td>
<td>5684</td>
<td>284 (5%)</td>
<td>1100–1400</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>3499</td>
<td>474 (14%)</td>
<td>1300–1600</td>
</tr>
<tr>
<td>Middle East and north Africa</td>
<td>2114</td>
<td>299 (14%)</td>
<td>780–970</td>
</tr>
<tr>
<td>South Asia</td>
<td>13778</td>
<td>3993 (29%)</td>
<td>3600–4500</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>11662</td>
<td>6475 (56%)</td>
<td>1800–2200</td>
</tr>
<tr>
<td>World</td>
<td>58772</td>
<td>13777 (23%)</td>
<td>15 000–19 000</td>
</tr>
</tbody>
</table>

*Estimated potential burden of selected critical illnesses per year (x10^3)†

*Lancet 2010; 375: 1339–46*
Differential population burden of sepsis even with crude methods

- high-income countries
  - 20% of world’s population
  - Sepsis: ~2.3 million cases/yr

- low and middle-income countries
  - 80% of the world’s population
  - Sepsis: ~13 million cases/yr (underestimate)

Lancet 265:63-78; Crit Care Med 29:1303-10; Lancet 2010 Oct 09
Supported by data from specific infections

**Mortality**

- **Pneumonia:** 442,521
- **Meningitis:** 51,502
- **“Other Infections”:** 491,489

**DALYs lost**

- **Pneumonia:** 11,415,856
- **Meningitis:** 1,505,700
- **“Other Infections”:** 12,725,926

doi:10.1371/journal.pmed.0050175.g001

Healthcare-associated infection

- Incidence of SSI in Africa 2.5-30.9 / 100 patients (pooled incidence 5.6 /100 patients in LMICs)

*Bull World Health Organ 2011;89:757–765; Lancet 2011; 377: 228–41*
Origin of population-based hospital-treated sepsis studies

27 studies, 7 HICs

AJRCCM 10.1164/rccm.201504-0781OC
Crude estimate 2

• Sepsis incidence /10^5 person-yr
  – 288 (215-386)
  – 437 (334-571) MORE RECENT DATA

• Severe sepsis incidence /10^5 person-yr
  – 148 (98-226)
  – 270 (176-412) MORE RECENT DATA
<table>
<thead>
<tr>
<th>Region</th>
<th>Sepsis cases</th>
<th>Severe sepsis cases</th>
<th>Sepsis deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Income</td>
<td>5.6</td>
<td>3.5</td>
<td>0.96</td>
</tr>
<tr>
<td>East Asia/Pacific</td>
<td>8.9</td>
<td>5.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Europe + Central Asia</td>
<td>1.2</td>
<td>0.73</td>
<td>0.20</td>
</tr>
<tr>
<td>Latin America / Caribbean</td>
<td>2.5</td>
<td>1.6</td>
<td>0.43</td>
</tr>
<tr>
<td>Mid East, N Africa</td>
<td>1.5</td>
<td>0.92</td>
<td>0.25</td>
</tr>
<tr>
<td>S Asia</td>
<td>7.2</td>
<td>4.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>3.9</td>
<td>2.5</td>
<td>0.68</td>
</tr>
<tr>
<td>World</td>
<td>30.9</td>
<td>19.1</td>
<td>5.3</td>
</tr>
</tbody>
</table>

*1 million. Projected from data in AJRCCM 10.1164/rccm.201504-0781OC
The GBD model

- Cause of death database
  - Noise reduction
    - MI ratio
      - Negative binomial/fixed proportion
        - CoDCorrect algorithm
          - YLLs
            - Natural history models

- Redistribute
  - Cause mapping
    - Cancer registries
      - Verbal autopsy data
        - Vital registration (ICD 9, BTL, ICD 10)
          - Maternal surveillance
            - Household surveys
              - Other (ie, burial or mortuary and census)
              - Maternal census
              - Police data
                - National registries
                  - Case fatality rate
                  - Prevalence
                  - Intervention coverage
                  - Cause-specific mortality
### GBD – multiple data sources

<table>
<thead>
<tr>
<th>Source Type</th>
<th>All geographies</th>
<th>GBD 2013</th>
<th>Difference</th>
<th>GBD 2013</th>
<th>National</th>
<th>State, province, or region*</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital registration</td>
<td>2798</td>
<td>5039</td>
<td>2241†</td>
<td>2765</td>
<td>2112</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>Cancer registry</td>
<td>2715</td>
<td>3860</td>
<td>1145</td>
<td>1216</td>
<td>979</td>
<td>1665</td>
<td></td>
</tr>
<tr>
<td>Sibling history</td>
<td>1557</td>
<td>1798</td>
<td>241</td>
<td>1788</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Police records</td>
<td>1129</td>
<td>1433</td>
<td>304</td>
<td>1429</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Surveillance</td>
<td>128</td>
<td>1430</td>
<td>1302</td>
<td>73</td>
<td>1074</td>
<td>283</td>
<td></td>
</tr>
<tr>
<td>Verbal autopsy</td>
<td>486</td>
<td>538</td>
<td>52</td>
<td>110</td>
<td>0</td>
<td>428</td>
<td></td>
</tr>
<tr>
<td>Survey or census; hospital; burial or mortuary</td>
<td>154</td>
<td>146</td>
<td>-8‡</td>
<td>94</td>
<td>0</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8967</strong></td>
<td><strong>14244</strong></td>
<td><strong>5277</strong></td>
<td><strong>7475</strong></td>
<td><strong>4166</strong></td>
<td><strong>2603</strong></td>
<td></td>
</tr>
</tbody>
</table>

GBD=Global Burden of Disease Study. *Data were analysed at the state level for Mexico, the province level for China, and the region level for the UK. †Significant increase because of incorporation of subnational sites in China, Mexico, and the UK. ‡Decrease caused by omission of World Health Survey data where adequate vital registration data was available for GBD 2013.

**Table 1:** Number of site-years in database by source type

*Lancet 2015; 385: 117-71*
Reasonable data density

Lancet 2015; 385: 117-71
Where is sepsis?

Third, a crucial aspect of enhancing the comparability of data for cause of death is to deal with uninformative, so-called garbage codes. **Garbage codes** are codes for which deaths are assigned that cannot or should not be considered as the underlying cause of death—for example, heart failure, ill-defined cancer site, senility, ill-defined external causes of injuries, and **septicaemia**.

*Lancet 2015; 385: 117-71*
Case-fatality – is this also happening in Africa?

Figure 1. Mean Annual Mortality in Patients With Severe Sepsis

- Mortality, %: 30-40
- No. of patients:
  - 2000: 2708
  - 2001: 3783
  - 2002: 4668
  - 2003: 5221
  - 2004: 6375
  - 2005: 6987
  - 2006: 7627
  - 2007: 8529
  - 2008: 8797
  - 2009: 10277
  - 2010: 11367
  - 2011: 12213
  - 2012: 12512

Malaria deaths

Figure 2: Trends in global malaria deaths by age and geographical region, 1980 to 2010

Lancet 2012; 379: 413–31
Will there be a positive side effect on bacteremia?
Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis

Elizabeth A Reddy, Andrea V Shaw, John A Crump

- 22 studies, 58296 patients
- BSI in 13.5% adults, 8.2% children
- Isolates
  - S. enterica 29.1%
  - S. pneumoniae 18.3%
- HIV+ 53.5% adults, 18.5% children
Etiology of Severe Febrile Illness in Low- and Middle-Income Countries: A Systematic Review

PLoS ONE 10(6): e0127962

Namrata Prasad¹, David R. Murdoch², Hugh Reyburn³, John A. Crump¹*

- 45 studies, 22 locations, 54 578 patients
- 18%: pathogen identified
- 11%: positive blood culture
- 23-44%: malaria
- Up to 23%: dengue and other viruses
- 6%: mycobacteria
Resource variations
Resource variation exists in HICs

ICU beds/hospital beds  Sepsis mortality/ICU beds

Crit Care Med 36:2787-93
...and in LMICs
Table 4  Acute care supply per 100 deaths due to acute illnesses

<table>
<thead>
<tr>
<th>Acute care service</th>
<th>Boston</th>
<th>Paris</th>
<th>Recife</th>
<th>Bogota</th>
<th>Liaocheng</th>
<th>Chennai</th>
<th>Kumasi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals</td>
<td>0.32</td>
<td>0.15</td>
<td>0.32</td>
<td>0.23</td>
<td>0.04</td>
<td>0.20</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospital beds (capacity for IV fluids and medications)</td>
<td>52.66</td>
<td>62.00</td>
<td>46.30</td>
<td>44.70</td>
<td>23.43</td>
<td>27.27</td>
<td>11.67</td>
</tr>
<tr>
<td>Hospital beds (with oxygen capacity)</td>
<td>52.66</td>
<td>62.00</td>
<td>46.30</td>
<td>30.75</td>
<td>23.43</td>
<td>25.07</td>
<td>1.17</td>
</tr>
<tr>
<td>ICU beds</td>
<td>4.11</td>
<td>2.22</td>
<td>3.68</td>
<td>3.96</td>
<td>0.56</td>
<td>0.81</td>
<td>0.06</td>
</tr>
<tr>
<td>Self-defined ICU beds</td>
<td>4.11</td>
<td>5.05</td>
<td>3.68</td>
<td>5.07</td>
<td>1.25</td>
<td>2.10</td>
<td>0.11</td>
</tr>
<tr>
<td>Ambulances</td>
<td>6.06</td>
<td>1.11</td>
<td>0.50</td>
<td>1.38</td>
<td>0.15</td>
<td>0.29</td>
<td>0.06</td>
</tr>
</tbody>
</table>

(a) Hospital beds/100 acute deaths vs. Per capita GDP
(b) ICU beds/100 acute deaths vs. Per capita GDP
Treatments
Recommendations for sepsis management in resource-limited settings

Intensive Care Med
DOI 10.1007/s00134-012-2468-5

Table 9 Suggested care bundles for sepsis management in resource-poor settings

<table>
<thead>
<tr>
<th>Acute care bundle</th>
<th>Post-acute care bundle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen therapy</td>
<td>Re-evaluation of antimicrobial therapy</td>
</tr>
<tr>
<td>Fluid resuscitation</td>
<td>Deep venous thrombosis prophylaxis</td>
</tr>
<tr>
<td>Early and adequate antimicrobial therapy</td>
<td>Glucose control</td>
</tr>
<tr>
<td>Surgical source control</td>
<td>Weaning of invasive support</td>
</tr>
</tbody>
</table>

- Most recommendations had level C or D evidence
Mortality after Fluid Bolus in African Children with Severe Infection

N Engl J Med 2011;364:2483-95

Cumulative Probability of Death

Days since Randomization
RCT of 112 patients with severe sepsis in Lusaka
- Protocol: 2L bolus + 2L/4hr for JVP <3 cm ASA
- Usual care

Baseline
- Mean age 35 y
- HIV 81%
- APACHE II 18
• Mortality 62%
• Subgroup (n=18) with RR >40, SpO₂ <90%
  – Mortality 83% vs. 70%, p=0.09

<table>
<thead>
<tr>
<th></th>
<th>EGDT</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received ≥ 3 L fluid in 6 hr, n (%)</td>
<td>30 (56.6)</td>
<td>11 (20.0)</td>
</tr>
<tr>
<td>Fluids administered, L, mean (SD)h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In first 6 hr</td>
<td>2.9 (1.0)</td>
<td>1.6 (1.1)</td>
</tr>
<tr>
<td>In first 24 hr</td>
<td>3.9 (1.3)</td>
<td>3.0 (2.1)</td>
</tr>
<tr>
<td>In first 72 hr</td>
<td>5.6 (2.3)</td>
<td>4.3 (2.9)</td>
</tr>
</tbody>
</table>
How does the future look?
Urbanization – threat and opportunity

**Figure 1:** Evolution of urban and rural populations between 1950 and 2050²

<table>
<thead>
<tr>
<th>Country</th>
<th># cases</th>
<th># confirmed</th>
<th># deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea</td>
<td>3,803</td>
<td>3,347</td>
<td>2,535</td>
</tr>
<tr>
<td>Liberia</td>
<td>10,666</td>
<td>3,151</td>
<td>4,806</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>14,001</td>
<td>8,704</td>
<td>3,955</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>28,476</strong></td>
<td><strong>15,208</strong></td>
<td><strong>11,298</strong></td>
</tr>
</tbody>
</table>

*WHO Situation Report  18 October 2015*
The 2014 Ebola epidemic was unprecedented

Ebola deaths by outbreak, as of March 15, 2015

2014-2015 W. Africa outbreak

All 24 previous outbreaks combined

1976 DRC
1995 DRC
2000 Uganda
2007 DRC
1976 Sudan
2003 Congo
2001 Gabon
1996 Gabon
2001 Congo
2007 Uganda

The 10 deadliest outbreaks before 2014

SOURCE: World Health Organization
We have observed a decreasing case fatality rate among inpatients at Hastings,

- **47.7%** for the first 151 pts (Sept 20 – Oct 13)
- **31.7%** for the next 126 pts (Oct 14 - Nov 4)
- **23.4%** for the next 304 pts (Nov 5 – Dec 7)
Non-Ebola Healthcare Infrastructure Decimated

Lancet 11 April 2015
The ‘knowns’ of sepsis in Africa

• Burden almost certainly underestimated by current studies
• Tantalising suggestion of decreasing case burden as malaria control increasingly successful
• Different spectrum of pathogens
• Evidence base specific to the region is small, but growing
Turning the unknowns into knowns

• Incorporate sepsis into GBD estimates
  – Develop and validate verbal autopsy tool
• Evaluate point of care diagnostics

• Evaluate interventions
  – Fluids (in adults)
  – Earlier timing of antibiotics and fluids
  – Organised and team-based approach to supportive care – as shown by Ebola response
Thank you

neill.adhikari@sunnybrook.ca
Total expenditure on health as a percentage of the gross domestic product, 2013 *

Easy to measure