Neonatal meningitis and sepsis: what happens to survivors?

Meningitis & septicaemia | November 5th - 6th 2019
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@joylawn
#MRFConf2019
Thanks to many exceptional women!

- Uduak Okomo
- Anna Seale
- Kate Milner
- Maya Kohli-Lynch
- Cally Tann
- Proma Paul
- Jaya Chandna

Prof Kim Mullholand according to online programme!!
World you are born into determines your survival... and of disability

High income countries
~12 million births

Upper middle income countries
~39 million births

Low and middle income countries

140 million births per year

~44 million births at home

~45 million facility births

And the chance of being counted correctly - highest risk, least data ("Inverse data law")
Data waterfall ...

Cascade affecting case ascertainment for GBS or any invasive bacterial disease

- True cases of invasive disease (mother, stillbirth, newborn)
- Cases seeking care
- Cases accessing care and have clinical assessment
- Cases with microbiological sample taken correctly
- Samples where lab correctly detects GBS


WHY do children die?
Global causes of child deaths under 5 years of age in 2017

1. Preterm birth top cause of child deaths + important cause of disability and loss of human capital

2. Birth complications

3. Neonatal infections:
   “Black box” for aetiological data regarding 600,000 deaths due to neonatal infections.
Possible Severe Bacterial Infections (pSBI)

WHO definition for Possible Severe Bacterial Infection (pSBI):

The presence of any one of the following six signs:

1. a history of difficulty feeding,
2. history of convulsions,
3. movement only when stimulated,
4. respiratory rate of 60 breaths per minute or more,
5. severe chest in-drawing,
6. temperature $>37.5^\circ C$, or $<35.5^\circ C$*


Figure adapted from Seale ... Lawn Lancet ID 2013
Neonatal pSBI estimates

Geographic distribution of data included

Estimated total cases of pSBI
6.9 million per year (5.5-8.3)
Overall incidence risk 7.6% (95%CI 6.1-9.2%)

Input data 259,944 neonates, 20,196 pSBI cases

Source: Lancet ID, Seale ... Lawn JE, 2014
Meningitis and Neonatal Sepsis in Children Under 5

Estimates suggest that meningitis and neonatal sepsis combined are the second largest infectious killers of children aged under five. There has been some success in reducing cases and deaths over time, but progress still lags behind other infectious diseases.

- Estimated Total Deaths: 210,090
- Estimated Total Cases: 1,477,260
- Neonatal meningitis deaths: 19,530 (13%)
- Neonatal meningitis cases: 153,240

“All models are wrong but some are useful!!” Lord Box
Data waterfall …
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- Cases with microbiological sample taken correctly
- Samples where lab correctly detects GBS


#GBSburden
Mismatch of investigation vs antibiotics use in a Gambian Teaching Hospital (N=4999)

2% Investigation results available

- 43 LP
- 26 Blood cultures

Not investigated 91%

Uncertain 7%

Investigated 2%

94% inpatient neonates given antibiotics

- Ceftri/Fluclox: 0.4
- Amp/Gent/Ceftri/Cipro: 0.5
- Co-amoxiclav/Gent: 0.6
- Ceftri/Gent: 0.9
- Fluclox/Gent: 0.9
- Amika/Amp: 1.1
- Amp/Gent/Ceftri/Fluclox: 3.5
- Amp/Gent/Ceftri: 13.1
- Amp/Gent/Flucloc: 13.3
- Amp/Gent: 62.4

Uduak Okomo et al Paediatrics and International Child Health 2015
Data waterfall ...

Cascade affecting case ascertainment for GBS or any invasive bacterial disease

1. True cases of invasive disease (mother, stillbirth, newborn)
2. Cases seeking care
3. Cases accessing care and have clinical assessment
4. Cases with microbiological sample taken correctly

Samples where lab correctly detects GBS

Care and measurement GAP

Long term follow-up


Clinical Infectious Diseases #GBSburden
Beyond Neonatal Survival

Long term disability after neonatal conditions

NATURE PEDIATRIC RESEARCH

5 papers with first global estimates of incidence/prevalence & impairment:

• Preterm birth
• Retinopathy of Prematurity (ROP)
• Intrapartum-related neonatal encephalopathy
• Neonatal infections
• Neonatal jaundice

47 authors, 35 institutions led by LSHTM

Input to Global Burden of Disease with IHME

Neonatal conditions accounted for 7.5% of worldwide DALYs in 2017

Similar burden to all of Cardiovascular DALYS, 3 x HIV/AIDS

 Mostly (>95%) attributed to mortality
## Survivors of Neonatal Meningitis

### Moderate to severe neurodevelopmental impairment (8 studies, N=451)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Country</th>
<th>ES (95% CI)</th>
<th>Percentage weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell</td>
<td>1989</td>
<td>UK</td>
<td>0.38 (0.18, 0.62)</td>
<td>2.77</td>
</tr>
<tr>
<td>De Louvois</td>
<td>2005</td>
<td>UK</td>
<td>0.23 (0.17, 0.31)</td>
<td>29.06</td>
</tr>
<tr>
<td>Klinger</td>
<td>2000</td>
<td>Canada</td>
<td>0.16 (0.09, 0.25)</td>
<td>19.76</td>
</tr>
<tr>
<td>Franco</td>
<td>1992</td>
<td>USA</td>
<td>0.21 (0.05, 0.51)</td>
<td>2.46</td>
</tr>
<tr>
<td>Airede</td>
<td>2008</td>
<td>Nigeria</td>
<td>0.22 (0.11, 0.38)</td>
<td>6.86</td>
</tr>
<tr>
<td>Airede</td>
<td>1993</td>
<td>Nigeria</td>
<td>0.29 (0.13, 0.51)</td>
<td>3.53</td>
</tr>
<tr>
<td>Krebs</td>
<td>1996</td>
<td>Brazil</td>
<td>0.35 (0.22, 0.49)</td>
<td>7.54</td>
</tr>
<tr>
<td>Ali</td>
<td>1995</td>
<td>Trinidad</td>
<td>0.28 (0.15, 0.44)</td>
<td>6.51</td>
</tr>
<tr>
<td>Stevens</td>
<td>2003</td>
<td>UK</td>
<td>0.20 (0.13, 0.44)</td>
<td>21.50</td>
</tr>
<tr>
<td>Overall</td>
<td>($I^2 = 13.5%, P = 0.32$)</td>
<td></td>
<td>0.23 (0.19, 0.26)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Mod to severe impairment = 23% (95% CI: 19–26%)**

- Mild impairment 12% (95% CI: 5–19%)
- Hearing impairment 7% (95% CI: 3–12%)


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**MIND THE GAP**

- Age of follow up (aged 2 to 5 yrs)
- Less likely to detect mild impairments
- Measurement tools...

**Old, small, studies**

> >100 child development assessment tools
One study of follow up after neonatal sepsis (average 2 yrs old)

Kilifi, Kenya – only 24 cases, ~17% “cerebral palsy”
Neonatal deaths attributed to infections

120,000 babies with meningitis

27,000 with neurodevelopmental disability and/or deafness

2.2 million babies with sepsis or pneumonia

Increased risk of neurodevelopmental disability but unable to quantify

6.7 million babies with possible severe bacterial infection

Long-term higher risk of disease especially if overlap with small for gestational age

Survivors with disability

Care for disability
Group B Strepctococcus

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Editors: Joy E Lawn, Anna C Seale.


Survivors of Group B Strep Meningitis

Mod to severe neurodevelopmental impairment (15 studies, N=453, to age of 18 months)

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year of Publication</th>
<th>Number of GBS meningitis survivors</th>
<th>Number of GBS meningitis survivors with moderate-severe NDI</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Africa</td>
<td>Ben Hamouda</td>
<td>Tunisia</td>
<td>2013</td>
<td>7</td>
<td>0.43 (0.10, 0.82)</td>
<td>1.55</td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
<td>0.43 (0.07, 0.79)</td>
<td>1.55</td>
</tr>
<tr>
<td>Developed</td>
<td>Horn</td>
<td>USA</td>
<td>1974</td>
<td>7</td>
<td>0.14 (0.00, 0.58)</td>
<td>2.34</td>
</tr>
<tr>
<td></td>
<td>Haslam</td>
<td>USA</td>
<td>1977</td>
<td>15</td>
<td>0.13 (0.02, 0.40)</td>
<td>4.73</td>
</tr>
<tr>
<td></td>
<td>Chin</td>
<td>USA</td>
<td>1985</td>
<td>21</td>
<td>0.14 (0.03, 0.36)</td>
<td>6.11</td>
</tr>
<tr>
<td></td>
<td>Edwards</td>
<td>USA</td>
<td>1985</td>
<td>48</td>
<td>0.19 (0.09, 0.33)</td>
<td>10.18</td>
</tr>
<tr>
<td></td>
<td>Wald</td>
<td>USA</td>
<td>1986</td>
<td>54</td>
<td>0.17 (0.08, 0.29)</td>
<td>11.65</td>
</tr>
<tr>
<td></td>
<td>Franco</td>
<td>USA</td>
<td>1992</td>
<td>10</td>
<td>0.10 (0.00, 0.45)</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Litster</td>
<td>USA</td>
<td>2012</td>
<td>85</td>
<td>0.09 (0.04, 0.18)</td>
<td>13.83</td>
</tr>
<tr>
<td></td>
<td>Schröder</td>
<td>Germany</td>
<td>1982</td>
<td>10</td>
<td>0.40 (0.12, 0.74)</td>
<td>2.06</td>
</tr>
<tr>
<td></td>
<td>Bennhagen</td>
<td>Sweden</td>
<td>1987</td>
<td>4</td>
<td>0.25 (0.07, 0.52)</td>
<td>3.64</td>
</tr>
<tr>
<td></td>
<td>Bennhagen</td>
<td>Sweden</td>
<td>1987</td>
<td>1</td>
<td>0.11 (0.00, 0.48)</td>
<td>3.26</td>
</tr>
<tr>
<td></td>
<td>Bedford</td>
<td>UK</td>
<td>2001</td>
<td>103</td>
<td>0.29 (0.21, 0.39)</td>
<td>14.04</td>
</tr>
<tr>
<td></td>
<td>Heath</td>
<td>UK</td>
<td>2017</td>
<td>37</td>
<td>0.22 (0.10, 0.38)</td>
<td>7.84</td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
<td>0.18 (0.13, 0.23)</td>
<td>88.45</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>Zhu</td>
<td>China</td>
<td>2014</td>
<td>11</td>
<td>0.09 (0.00, 0.41)</td>
<td>4.30</td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
<td>0.09 (-0.11, 0.30)</td>
<td>4.30</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>Wee</td>
<td>Singapore</td>
<td>2016</td>
<td>20</td>
<td>0.15 (0.03, 0.38)</td>
<td>5.71</td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
<td>0.15 (-0.02, 0.32)</td>
<td>5.71</td>
</tr>
</tbody>
</table>

Mod to severe impairment = 18% (95% CI: 13-22%)

Maya Kohli-Lynch et al., CID, 2017
Step 4. Neurodevelopmental impairment after GBS

- 229,000 survivors of infant GBS disease with
  - Sepsis: 171,000
  - Meningitis: 58,000

- Risk of neurodevelopmental impairment after
  - GBS Meningitis: 18% moderate/severe NDI at 18 months
  - GBS Sepsis: not able to quantify long term outcomes
  - Mild neurodevelopmental impairment not quantified

\[\text{Moderate/severe Neurodevelopmental impairment after infant GBS meningitis and GBS sepsis}\]

\[\text{Survivors of infant GBS meningitis and GBS sepsis}\]

\[\text{Cases of infant invasive GBS disease}\]

Min est of 10,000 infants (3000-27,000) per year moderate-severe neurodevelopment impairment after GBS meningitis, and unknown after GBS sepsis


‘Iceberg’ of data on neurodevelopmental outcomes

Lack of cohorts, inconsistent case definitions, Messy tools & timing,
Finagel’s laws of information

1. The information you have is not what you want
2. The information you want is not what you need
3. The information you need is not what you can obtain
4. The information you can obtain costs more than you want to pay

Laws to improve health information

1. The information we NEED
2. The information we have that we can USE now!
3. The information that we must OBTAIN!
4. The information system that would cost less if we INTEGRATED more!
Multi-domain measurement = messy!

- Measuring neurodevelopment is multi-domain. Must include hearing and vision.
- Over 100 tools (mostly measure 6mnths-3years) but few meet accuracy and feasibility criteria
- Major challenges: cost, training requirements and adaptability
- Need for a simple, adaptable measurement that can be used across multiple LMICs

Survivors of Group B Strep Meningitis and Sepsis

New data collection in progress

Electronic cohorts:
• Denmark
• Netherlands
Age up to 30 yrs!

Cohort re-enrolment studies in 5 Low-middle income countries:
• Argentina
• India
• Kenya
• Mozambique
• South Africa
Age ~3-15!
Closing data gaps

1. Careseeking and UHC (+ active surveillance)
2. Clinical care improved quality
3. Lab investigations, LP to become the norm
4. Lab capacity strengthening (esp for GBS)
   Innovation – diagnostics, new interventions

- Follow up systems for at-risk newborns and COHORT studies to 5 years and beyond
- Improved measures/tools to detect multi-domain impairment, feasible in routine programmes

Bad data will always be with us – but we need to smell it, improve it & use it!
ADVANCE NOTICE
Group B Strep Global Conference
ISSAD 2021 in London

Children, adults families affected need care, support and voice, not just a statistic

@joylawn
Challenge 1 – exposure and definitions

STROBE – Neonatal Infections

Pregnant women (n=…)

Not assessed for eligibility (n=…)

Pregnant women assessed for eligibility (n=…)

Excluded (n=…)

Ineligible (n=…)

No consent (n=…)

Stillbirths (n=…)?

Pregnant women recruited (n=…)

Lost to follow-up (n=…)

Livebirths (n=…)? (STROBE-NI 5.2)

Lost to follow-up (n=…)

Well (n=…)

Assessed for signs of infection and/or risk factors (n=…)?

Lost to follow-up (n=…)

Died (n=…)?

Clinical case pSRI (n=…)? (STROBE-NI 4.1, 4.3)

Lost to follow-up (n=…)

Discharged (n=…)

Microbiological sampling

Blood (n=…)

CSF (n=…)

(STROBE-NI 4.5, 4.6)

Asymptomatic but peripartum risk factors (n=…)

Died (n=…)?

Microbiologically confirmed cases (n=…)?

Sepsis (n=…)

Meningitis (n=…)

Pneumonia (n=…)

(STROBE-NI 4.1)

Lost to follow-up (n=…)

Discharged (n=…)

Spring Guidance

Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI): an extension of the STROBE statement for neonatal infection research


The Lancet Infectious Diseases 2016 16, e202-e213 DOI: (10.1016/S1473-3099(16)30082-2)