Serious and Life-threatening Maternal and Early Newborn Infections

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Figure 3.1. Maternal mortality ratio (MMR, maternal deaths per 100,000 live births), 2015

- 303,000 maternal deaths annually
- 99% occur in undeveloped regions
- Lifetime risk of maternal mortality 1 in 180 women
- Sustainable Development Goal 3.1 calls for reduction in MMR of < 70/100,000 by 2030
  - Current MMR 216/100,000
  - Will need to reduce MMR by 7.5%/year to achieve SDG 3 by 2030
  - This is 3X the rate of reduction from 2000-2015
Global Causes of Maternal Mortality

% of Maternal Deaths

- Hemorrhage: 27%
- Hypertensive Dis.: 14%
- Sepsis: 11%
- Abortion: 8%
- Other: 13%
- Indirect: 27%

33,000 maternal deaths directly attributed to sepsis annually

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- Puerperal Sepsis: 30%
- Septic Abortion: 26%
- Urosepsis: 10%
- Other (Malaria, AIDS): 32%
- Soft Tissue: 2%

“Puerperal Sepsis” and the Neonate

- **Chorioamnionitis**
  - 10-20% all preterm births

- **Short-term**
  - 7-fold PMR without intrapartum antibiotics
  - ↑ Sepsis, RDS, IVH, PVL

- **Long-term**
  - ↑ 2-fold increase cerebral palsy
Systematic review of Serious and Life–threatening Maternal Infections

Malaria and HIV/AIDS represent significant co-morbidities for other infectious complications in pregnancy.
Peak Occurrence of Priority Maternal Infections

- **1st Trimester**
  - Pyelonephritis/Urosepsis

- **2nd Trimester**
  - Septic Abortion
    - Chorioamnionitis/Puerperal Sepsis
    - Skin & Soft Tissue Infection
    - STIs

- **3rd Trimester**
- **L&D**
- **PP**

<table>
<thead>
<tr>
<th>Disease Occurrence</th>
<th>Low</th>
<th>High</th>
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- **Pyelonephritis/Urosepsis**
- **Septic Abortion**
- **Chorioamnionitis/Puerperal Sepsis**
- **Skin & Soft Tissue Infection**
- **STIs**
Actionable Targets
Opportunities for Bundled Interventions

1st Trimester  2nd Trimester  3rd Trimester  L&D  PP

- Urosepsis
- Septic Abortion
- Chorio/Puerperal Sepsis
- Skin & Soft Tissue Infection
- STIs

Initiation of ANC
- Bacteruria
- STI

Likely to be cost effective
Summary

- Serious infections during pregnancy are an important preventable cause of maternal and neonatal mortality and morbidity.
- Five life-threatening clinical syndromes account for the majority of maternal deaths and adverse maternal and neonatal outcomes.
- Distinct time points during pregnancy offer specific opportunities for "bundled interventions".
- Point-of-care screening and validation of context-specific diagnostic and treatment algorithms suitable for both community and facility.
- There are significant gaps in the understanding of the microbiology of life-threatening maternal infections in low-resource settings.
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Why GBS?

• Among the leading causes of neonatal infections in HIC with high case fatality rate:

• No previous systematic estimates in LMIC
  • Geographic distribution of GBS – is this real epidemiological variation in incidence, virulence or data gaps?

• Global public health policy - candidate for maternal vaccine development
Determining the Global Burden of GBS Disease

- Systematic searches, multiple databases, all languages (more than 20,000 abstracts screened)
- Investigator groups to access unpublished data for the outcomes (colonisation, stillbirths, infant disease and GBS associated Neonatal Encephalopathy)
- Meta-analyses by country or regional if enough data
- Relevant population at risk per country for all 195 UN member states
- Relevant GBS risk estimate applied for
  - Pregnant women
  - Stillbirths
  - Preterm births
  - Neonates & Infants

Landscape Review of Maternal, Fetal, and Neonatal GBS Disease

- **Case definition**
  - Pregnant women
  - Neonates
  - Culture isolation

- **Published and unpublished material**
  - (investigators)
  - Including Chinese and Russian searches

- **Inclusion & exclusion criteria**
  - Culture method described
  - Not if bias in population selection

- **Data quality assessment**
  - Time of GBS screening (during pregnancy, at delivery, or from neonate)
  - Sampling site
  - Laboratory culture techniques (selective enrichment broth?)

- **Identification**
  - Records from databases
    - MEDLINE/EMBASE/WHOLIS/SCOPUS/LILACS
    - Mat/Fet 15,842
    - IAP 1,248
    - Neonatal 33,043
    - (n=50,115)

- **Screening**
  - Records Screened
    - Mat/Fet 9,575
    - IAP 1,248
    - Neonatal 25,663
    - (n=36,486)

- **Eligibility**
  - Full-text Article Review
    - Mat/Fet 979
    - IAP 455
    - Neonatal 2,091
    - (n=3,525)

- **Included**
  - Studies Included in Meta-analysis
    - Mat/Fet 428
    - IAP 95
    - Neonatal 187
    - (n=710)

710 studies included

Clinical Infectious Diseases. 2017;65(S2)
Prevalence of GBS colonisation in pregnant women by country adjusting for sampling site & laboratory culture method

- **Worldwide:** 18% (17%-19%)
  - 21.7 million women colonised
- **Highest:** Caribbean 35% (35%-40%)
- **Lowest:** Southern and Eastern Asia (11%, 13%)

Russel N, et al Clinical Infectious Diseases. 2017;65(S2):S100-11
Maternal GBS Disease

• Input data on GBS
  - Data limited to developed countries (5 studies)
  - GBS incidence low in developed region (0.38 per 1,000 pregnancies)

• Case fatality risk with GBS
  - 0.2% for pregnant and postpartum women
  - 2.2% for newborns born to women with maternal GBS sepsis

CASES: 33,000 (UR, 13,000-52,000) pregnant and post-partum women
Preterm Birth

• Input data on GBS
  • 45 broadly distributed studies from 23 countries
  • Both cohort/cross-sectional and case-control studies

• Estimates
  • Preterm births attributable to GBS based on population attributable fraction, given prevalence of

CASES: Up to 3.5 million PTB associated with maternal GBS colonization, but insufficient evidence to quantify

• Odds ratio to be 1.85 (95% CI, 1.24–2.77) in case-control studies

Stillbirth

• Input data on GBS
  • Data limited to 14 studies (none in Asia)

• Estimates
  • 1% (95% confidence interval [CI], 0–2%) of all stillbirths in developed countries and 4% (95% CI, 2%–6%) in Africa were associated with GBS.

CASES: 57,000 (UR12,000 – 104,000) fetal infections/stillbirths
Neonatal and Infant GBS Disease

- Input data on GBS
  - 135 studies with data on incidence (n = 90), case fatality ratio (n = 64), or serotype (n = 45) from 23 countries
  - Both cohort/cross-sectional and case:control studies

- Estimates
  - Pooled incidence of invasive GBS disease 0.49 per 1000 live births (95% CI, .43–.56), and was
  - Highest in Africa (1.12) and lowest in Asia (0.30).

- Cases in 2015:
  - 205,000 (UR, 101,000–327,000) infants with early-onset disease
  - 114,000 (UR, 44,000–326,000) with late-onset disease
  - 90,000 (UR, 36,000–169,000) deaths in infants <3 months age
  - 10,000 (UR, 3,000–27,000) children with disability each year

- Serotype III (61.5%) dominated, with 97% of cases caused by serotypes Ia, Ib, II, III, and V
Risk of Early Onset GBS from maternal GBS colonisation and variation with Intrapartum Antibiotic Prophylaxis (IAP)

- Baseline risk of Early Onset GBS with maternal GBS colonisation
  - no IAP policy → 1.1% risk (95% CI, 0.7%–1.6%)

- Risk of Early Onset GBS by estimated coverage of IAP for GBS colonised mothers
  - 40% coverage → 0.9 % risk (0.4-1.5)
  - 80% coverage → 0.3 % risk (0-0.9)

- Baseline risk is likely underestimated
  - low case ascertainment/exposure misclassification/etc

- Other factors affecting risk of Early Onset GBS less well understood

Russel N, et al Clinical Infectious Diseases. 2017;65(S2):S152-S72
Why pursue a Maternal GBS Vaccine?

1. Higher impact than IAP as affects more outcomes
2. Higher coverage especially in challenging settings → more equitable than IAP
3. Leverage existing programmatic platforms (e.g. antenatal care)
4. Reduce antibiotic exposure (21.7 million women)

EXECUTIVE SUMMARY FOR GBS BURDEN

1. 21.7 million pregnant women colonized with GBS
2. At least 33,000 Maternal invasive GBS disease
3. At least 57,000 Fetal invasive GBS disease
4. At least 320,000 Infants with GBS Sepsis and Meningitis
5. Up to 3.5 million Preterm births attributable to GBS

PLUS UNQUANTIFIED CASES, DEATH AND DISABILITY FOR UNMEASURED GBS DISEASE AND UNMEASURED BURDEN IN NON-INVASIVE GBS DISEASE

Could be prevented by IAP
Could be prevented by maternal GBS vaccine
## Future Directions

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<th>Focus area</th>
<th>Activity</th>
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<td>Improved data on the burden</td>
<td>- Neonatal and stillbirth cause-of-death studies</td>
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<td>- Cohort studies for impairment outcomes</td>
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<td>Vaccine development</td>
<td>- Assay standardization</td>
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<td>- Validate path to licensure</td>
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<td>Delivery/Integration in antenatal care</td>
<td>- Improved pregnancy vigilance</td>
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<td>- MNCH stakeholder engagement</td>
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Thank You