Maternal Immunization to Prevent Group B Streptococcal Disease in LMIC: Considerations for PDVAC

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Brief refresher: Perinatal GBS disease syndromes

- **Young infant invasive disease**
  - Highest incidence syndrome (up to 3 cases/1000 live births)
  - Early-onset (<7 d of age): Vertical transmission from maternal colonization
  - Late-onset (7-89 d of age): Vertical or horizontal transmission

- **Stillbirths**
  - GBS can cross intact membranes
  - 0-12% of stillbirths may be associated; incidence 0.04 to 0.9 per 1,000 births\(^1\)
  - Pathophysiology for stillbirth likely the same as for infant disease
    - Adherence to mucosal or lung epithelium followed by bloodstream invasion

- **Maternal invasive disease\(^2\)**
  - Overall low incidence compared to infants or adults with underlying conditions
    - Pregnancy-associated disease: 2 times more common than non-pregnant
    - Post-partum infections: 10 times more common than non-pregnant

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Young infant age at onset, Soweto, South Africa
Non-vaccine prevention: intrapartum antibiotic prophylaxis (IAP)

- High efficacy against early-onset disease in clinical trials, 1980s
  - Controversy over how to identify women at risk: culture-based screening or intrapartum clinical risk factors
  - No impact on late-onset disease
- WHO conditional recommendation: IAP for GBS colonized women
  - Acknowledges must be in context of local policy
  - IAP challenging to implement in many LMIC (and even HIC)
- Concerns about unintended consequences of antibiotic exposure
  - Emerging resistance
  - Newborn microbiome
Foundation of Maternal Immunization: Maternal antibody to capsular polysaccharide (CPS) reduces infant disease risk

Maternal antibody, GBS III CPS, µg/mL

Infant Disease

Infants Exposed

(P < .001, Mann-Whitney U test)

Looking back to PDVAC 2015: GBS highlights

- Presentation on GBS epidemiology, burden, conjugate vaccine development, licensure pathways
  - 2 major companies were pursuing vaccine development
  - Interest in potential to license based on correlates of protection

- PDVAC recommendations for WHO
  - Develop preferred product characteristics
  - Develop guidance for GBS vaccine development pathway, including:
    - Strategic goals
    - Phase III design considerations
    - Ethical considerations for conduct of trial in LMIC—particularly standards of care concerns with regards to intrapartum prophylaxis

Momentum since PDVAC on key gaps /needs

1. WHO/IVR expanded activities on GBS vaccine
2. New disease burden and cost-effectiveness assessments in LMIC
3. Correlates of protection and immunogenicity assay progress
4. CPS conjugate vaccine development program accomplishments
5. Common protein vaccine development progress
1. WHO/IVR expanded activities on GBS vaccine

- Received grant* from BMGF to accelerate GBS vaccine development
- Convened first WHO GBS Vaccine Consultation, April, 2016
  - Strong representation of stakeholders (approximately 60 participants)
    - Regional diversity; Academia, public health, regulators, pharma
  - Main discussion topics
    - Pathophysiology of GBS disease
    - Global disease burden
    - Vaccine products under development
    - Phase III trial considerations
    - Licensure and implementation pathways/regulatory aspects

*WHO Activities to Facilitate GBS, Vaccine Development, Licensure, and Prequalification with a focus on LMIC
Key meeting outcomes: Areas of consensus

- **Dual product development for HIC and LMIC optimal**
  - Initial LMIC target region: sub-Saharan Africa; need more data from SEARO
  - Need more/updated cost-effectiveness data (HIC and LMIC)

- **CPS conjugate products: promising** (based on phase II trivalent; past conjugates)
  - Five-valent or higher optimal
  - Potential concerns: Women w/o pre-existing CPS antibody; HIV-infected women

- **Common protein: promising to date**
  - The territory is more uncharted; data over the next year will be helpful

- **Optimal phase III design: Disease endpoint trial with nested immunogenicity**
  - Potential for composite endpoint (GBS-confirmed stillbirth, invasive young infant disease)
  - Extent to which correlates of protection can support licensure depends on evidence generated
  - Immunogenicity assay standardization: top priority
  - IAP: efficacy trial care as per local standards and recommendations will be acceptable
2. New (and in progress) disease burden evidence, LMIC

- Africa region
  - Sub-Saharan Africa meta-analysis of disease burden\(^1\)
    - Young infant disease burden estimate twice as high as prior Africa estimate
  - Kenya young infant disease incidence, serotype and whole genome sequencing\(^2\)
  - Stillbirth burden data: Similar incidence to early-onset disease
    - Kenya\(^2\): 0.91(0.25-2.3)/1000 births
    - South Africa\(^3\): Incidence >1/1000 live births

- S Asia region
  - New data from Bangladesh on maternal and newborn colonization and serotype\(^4\)
  - Aetiology of Newborn Infections in South Asia (ANISA)\(^5\) data from India, Bangladesh, Pakistan

- Multi-country colonization, transmission and antibody study launched (BMGF-funded)

Updated global GBS disease burden estimates expected by early 2017 (led by LSTMH, funded by BMGF)

Systematic reviews and meta-analyses of published data and data from investigator group

1. Maternal GBS colonisation
2. Risk of neonatal disease with maternal colonisation
3. Neonatal disease incidence and case fatality risk
4. Risk of impairment after neonatal GBS disease
5. Stillbirth-associated GBS disease
6. Preterm birth
7. Neonatal encephalopathy
8. Pregnancy associated GBS disease

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Cost-effectiveness analyses for LMIC

- First LMIC analysis published in 2014
  - Focused on South Africa (High MIC)\(^1\)
  - Assumed: 10-30 USD/dose; VE against included types of 50-90%; coverage of 75%
  - Primary results:
    - Maternal immunization compared to do nothing: very cost-effective (range 416-3545 USD/DALY averted)
    - Maternal immunization plus risk-based approach was more effective

- In progress: Sub-Saharan Africa analysis (A. Sinha, PI, expected by 2017)
  - Groups countries into 4 clusters based on economic development, health resources, and past public health program successes
  - Assesses cost-effectiveness for each cluster

1. Kim, SY et al., Vaccine 2014. 32:1954-63
Disease burden in high income countries

- Dual pathway (HIC and LMIC) optimal for vaccine development
- US post-IAP disease burden
  - ~2000 young infant invasive cases annually; burden stable since 2010; serotype III increasing among late-onset disease cases since 2006\(^1\)
  - US cost-effectiveness analysis in progress (assessing a range of strategies including in the context of intrapartum prophylaxis) \(^2\)
- Europe: some countries are showing an increase in EOD, LOD or both \(^3\)

Invasive GBS disease surveillance in United Kingdom and Ireland: Increasing early and late-onset incidence

<table>
<thead>
<tr>
<th>Year</th>
<th>Overall incidence per 1000 live births</th>
<th>EO incidence per 1000 live births</th>
<th>LO incidence per 1000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 - 2001</td>
<td>0.72</td>
<td>0.48</td>
<td>0.24</td>
</tr>
<tr>
<td>2014 - 2015</td>
<td>0.95 *</td>
<td>0.55 *</td>
<td>0.38 *</td>
</tr>
</tbody>
</table>

*Significant increase

Incidence per 1000 live births

O’Sullivan et al., ESPID, 2016
3. Progress on correlates of protection/assays

- First data from LMIC: Observational data from South Africa

Risk reduction was 90% if maternal delivery serum to la was >6 μg/mL and III was >3 μg/mL

GBS assay standardization project launched*

- **Objective 1:** Development of standard reagents and of assays for standardisation
  - Approx. 34 different ELISA and 9 different OPA/OPKA assays published
  - Milestones (18 mos): Protocols screened for reproducibility and standard reagents prepared

- **Objective 2:** Standardised protocols for existing ELISA and functional GBS assays using standard reagents
  - Milestones (18 mos): Standardised protocols using standardised reagents acceptable for licensure application

- **Future plan:** To validate standard protocols and standard reagents across laboratories to establish a prediction of disease protection

*Kirsty LeDoare, PI; BMGF funded*
4. CPS conjugate vaccine development progress
Phase II accomplishments, GSK/NVD trivalent

- Vaccine product in humans
  - 1732 non-pregnant women
  - 610 pregnant women
- Safety: No safety flags to date
- Immunogenicity
  - >75% of recipients had >4-fold increase in serotype-specific IgG
  - Mother to infant transfer ratios of 50-81% across serotypes
  - Lower IgG response: HIV-infected mothers; women with no baseline antibody
  - No benefit from a second dose or use of alum
- Interaction with other vaccines
  - no evidence of interference with response to diphtheria vaccination among infants

Evolution of CPS-conjugate vaccine programs

- 2 major companies remain active
  - GSK; Pfizer
- Both will pursue higher-valent vaccines than trivalent
  - Both in pre-clinical phase, building on existing know-how
- Strategy: a single (unadjuvanted) dose per pregnancy in early third trimester (or maybe late 2\textsuperscript{nd} trimester); CRM\textsubscript{197} carrier protein
- PATH may launch a GBS Vaccine Program
  - Goal: accelerate development of effective and affordable vaccine for LMIC (with LMIC-based producer/trial sponsor)
    - Polyvalent CPS-conjugate vaccine
5. Progress on common protein vaccine development

- One product (Minervax GBS-NN) anticipated to enter Phase I trials for pregnant women this fall
  - Fusion protein of N-terminal domains of Alpha-like, AlpC and Rib proteins
  - Antibodies against AlpC and Rib transfer across placenta; low antibody concentrations to both may be associated with increased infant GBS disease risk
  - Pre-clinical studies, Phase Ia/b non-pregnant human studies promising

- Strategy: Two dose schedule, third trimester, alum adjuvant
- Potential strengths: high or universal strain coverage and low costs
- Immunogenicity assays for common protein vaccines need standardization
- Summer 2016: Anticipate early proof of concept data on correlates of protection
Next Steps: WHO and beyond

- Develop preferred product characteristics (PPC)
- Achieve consensus (documented roadmap) on:
  - GBS vaccine strategic objectives
  - Phase III trial design considerations
  - Flexible clinical development pathway options, depending on generated evidence
- Advance planning for WHO pre-qualification, policy making, implementation:
  - Identify key gaps and define implementation research agenda
  - Need to build stakeholder commitment, a GBS vaccine community
For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.