Maternal Immunization to Prevent Group B Streptococcal Disease in LMIC: PDVAC 2017

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Medical Research Council: Respiratory and Meningeal Pathogens Research Unit
45% (2.7 million) of under-5 deaths occurred in first month of life
22% of neonatal deaths are associated with infections
One-third neonatal deaths related to premature birth.
MI may protect infants ≤5-mo against infection-related deaths

MI may also prevent a portion of preterm birth and infection-related stillbirths (10–50% of the overall stillbirths)

MI can have an impact on maternal morbidity and mortality

2. WHO-CHERG 2013
## Momentum since PDVAC 2016 on GBS

1. Develop preferred product characteristics (PPC) for GBS vaccine

2. Finalisation of the GBS Vaccine Development Technology Roadmap

3. 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


5. Work-in-progress on GBS assay standardisation, including reference sera.

6. Further reports on tri-valent GBS vaccine in pregnant women, including antibody kinetics in women and infants, and impact of interference to childhood vaccines.

7. Phase I study on GBS common protein (AlpC and Rib) vaccine in pregnant women, and first human studies of higher valency (>3 serotypes) polysaccharide-protein conjugate vaccine.
Strategic goal: To develop and license safe, effective and affordable GBS vaccines for maternal immunization during pregnancy to prevent GBS-related stillbirth and invasive GBS disease in neonates and young infants, appropriate for use in HIC and LMIC.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Characteristic</th>
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</thead>
<tbody>
<tr>
<td>Indication</td>
<td><strong>Prevention</strong> of laboratory confirmed GBS stillbirth and invasive GBS disease in neonates and young infants.</td>
</tr>
<tr>
<td>Target population</td>
<td>Pregnant women, in the <strong>second or third trimester</strong> of pregnancy.</td>
</tr>
<tr>
<td>Schedule</td>
<td>A <strong>one dose</strong> regimen is highly preferred.</td>
</tr>
<tr>
<td>Safety</td>
<td><strong>Safety and reactogenicity</strong> profile at least as <strong>favourable</strong> as current WHO-recommended routine vaccines for use during pregnancy (influenza, tetanus toxoid, acellular pertussis).</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Available evidence supportive of <strong>80% protection</strong> against combined risk of laboratory-confirmed GBS (all serotypes) stillbirth and invasive disease in the offspring.</td>
</tr>
<tr>
<td>Strain and serotype coverage</td>
<td>The <strong>serotypes</strong> in the vaccine formulation must cover at least <strong>90%</strong> of the current invasive disease isolates in the target region.</td>
</tr>
<tr>
<td>Adjuvant requirement</td>
<td>Preference for <strong>no adjuvant</strong>.</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Established <strong>correlate/surrogate of protection</strong> based on a <strong>validated assay</strong> measuring antibody levels/functionality in the mother and/or the neonate.</td>
</tr>
<tr>
<td>Non-interference</td>
<td>Demonstration of favourable safety and immunologic <strong>non-interference</strong> upon <strong>co-administration</strong> with other vaccines recommended for use in pregnancy. Demonstration of <strong>non-interference</strong> with immune responses to relevant vaccines from the Expanded Program of Immunization in infants of vaccinated mothers.</td>
</tr>
<tr>
<td>Route of administration</td>
<td><strong>Injectable</strong> (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery.</td>
</tr>
<tr>
<td>Registration, prequalification and programmatic suitability</td>
<td>The vaccine should be <strong>prequalified</strong> according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO defined criteria for programmatic suitability of vaccines should be met (Appendix 1).</td>
</tr>
<tr>
<td>Value proposition</td>
<td>Dosage, regimen and cost of goods amenable to <strong>affordable supply</strong>. The vaccine should be cost-effective, and price should not be a barrier to access including in low and middle income countries.</td>
</tr>
</tbody>
</table>
# Maternal GBS Vaccines in Development With Data in the Public Domain

<table>
<thead>
<tr>
<th>Vaccine candidate</th>
<th>Manufacturer</th>
<th>Vaccine construct</th>
<th>Phase</th>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Program status</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Pfizer</td>
<td>Multivalent CPS-conjugate</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>Clinical program start in 2017</td>
</tr>
<tr>
<td>GBS vaccine</td>
<td>Novartis/GSK</td>
<td>Trivalent CPS (serotypes Ia, IIb, III) conjugated to CRM\textsubscript{197}, unadjuvanted</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>Completed Safety and immunogenicity in pregnant women. Study completed and Vaccine being reformulated.</td>
</tr>
<tr>
<td>N/A</td>
<td>GSK</td>
<td>Pentavalent (Ia, Ib, II, III, V) CPS-CRM\textsubscript{197}</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>GSK</td>
<td>Pilus proteins</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>Biovac</td>
<td>Polyvalent CPS conjugate</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>Program start in 2017.</td>
</tr>
<tr>
<td>GBS-NN vaccine/ MVX13211</td>
<td>Minervax</td>
<td>N-domains of Rib and Alpha C surface proteins, unadjuvanted or Alhydrogel®-adjuvanted</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>Safety and immunogenicity in non-pregnant women. Study completed. Phase I study in pregnant women.</td>
</tr>
</tbody>
</table>
GBS Vaccine Development Technology Roadmap

1. **Research:**
   - Further quantify the unmet medical need for a GBS vaccine and its potential public health impact.
   - Pursue efforts towards the development of vaccines with the potential to overcome serotype diversity and serotype-specificity of protection.

2. **Vaccine development:**
   - Develop quality-assured immunologic correlate(s)/surrogate(s) of protection.
   - Characterize key candidate vaccine immunogenicity parameters, including antibody kinetics.
   - Define pivotal clinical trial design, including case definition and ascertainment methodologies for colonization, invasive disease and stillbirth investigation (WHO Working Group).

3. **Key capabilities:**
   - Establish network of investigators including research centres in LMIC with GCP capacity; and also establish baseline rates of disease and common adverse obstetric and neonatal outcomes to prepare for safety and efficacy surveillance.
   - Strengthen use of adapted recommendations on safety surveillance (GAIA).
   - Access to low cost vaccine manufacturing for late stage development and commercial production.
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Regional Meta-analysis of Incidence of Invasive GBS Disease, 2000-2011

Incidence per 100,000 live births

CFR: 7%(4-10)  11%(6-16)  22%(12-32)  9%(6-13)

Care and Measurement Gap Estimating Cases From Incidence and Prevalence Data

1. Cases of GBS disease (mother, stillbirth, newborn)
   - Cases that seek care
   - Cases that access care and have clinical assessment
   - Care and measurement GAP
     - Cases where a microbiological sample is taken and taken appropriately
     - Samples where GBS is correctly detected by the laboratory

2. Lower case ascertainment
   - Lack of access to care
   - Poor quality of care and lack of clinical assessment
   - Failure to take appropriate samples due to lack of protocols, skilled personnel or supplies
   - Poor quality of laboratory methods to support pathogen detection e.g. automated blood cultures

3. Maternal disease
   - Underestimated where healthcare access low especially after delivery
   - Underestimated if clinical assessment limited
   - Underestimated if sampling limited
   - Underestimated if laboratory methods insensitive

4. Stillbirth
   - Underestimated if more antepartum, overestimated if more intrapartum
   - Underestimated if more antepartum, overestimated if more intrapartum
   - Underestimated if number of samples limited
   - Underestimated if laboratory methods insensitive

5. Infant disease
   - Underestimated where healthcare access low, esp. at birth
   - Underestimated if clinical assessment limited, most difficult early in life to take samples
   - Underestimated if sampling limited, most difficult early in life to take samples
   - Lower volumes of blood reduce laboratory sensitivity further

Case ascertainment in low income contexts may be lower at every stage leading to more biased data, often with inconsistent reporting in published literature.

Courtesy Joy Lawn et al.
» Imbalance across country of births occurring in midwife-operated units vs. hospitals with laboratory facilities.

» Empiric antibiotic treatment before referral to hospital of distressed newborns.

» Differences in threshold for investigating for sepsis.

» Home based versus facility based births, and resultant deaths prior to hospital evaluation.
Mother to Infant Transmission of GBS and Risk for Early Onset Invasive Disease (In absence of IAP)

GBS colonized mother

50%
Non-colonized newborn

50%
Colonized newborn

57% newborns colonized2

2%
Early-onset sepsis, pneumonia, meningitis

98%
Asymptomatic

Number cases EOD: 2.0 per 1000 live births (2% of colonized)1-3

Diagram source: http://www.cdc.gov/groupbstrep/clinicians/neonatal-providers.html#slidesets

Madhi SA et al. Vaccine; 2013; ; 315: D52-57
Prevalence of Maternal GBS Colonization at Birth and Observed Incidence of Invasive GBS Disease within 7 days of Birth, WHO Regions.

Disease Schema for Outcomes of Maternal GBS Colonization Showing Worldwide Estimates for 2015

Parameter | Case definitions used for estimates
--- | ---
Group B Streptococcus maternal colonization | Isolation by culture of GBS from either the vagina (high or low), rectum or peri-anal region at any time during pregnancy
Maternal GBS disease | Laboratory isolation of GBS from sterile site in pregnant or postpartum woman (up to 42 days postpartum), with clinical signs of sepsis
Stillbirth GBS invasive disease | Birth of a fetus weighting >1000g and/or ≥28 weeks’ gestation age with no signs of life and evidence of GBS invasive disease from a normally sterile site such as fetal blood, lung aspirate or cerebrospinal fluid
Neonatal and infant GBS invasive disease | Laboratory isolation of Streptococcus agalactiae from a normally sterile site in an infant aged 0 to 89 days with signs of clinical disease, including meningitis, sepsis or bacteraemic pneumonia
Neonatal encephalopathy with GBS disease | Invasive disease as above with clinical syndrome of neonatal encephalopathy
Neurodevelopment impairment in children after GBS invasive disease | Cognitive and/or motor, vision or hearing impairment in survivors of invasive infant GBS disease isolated from a normally sterile site
Preterm birth associated with GBS maternal colonization | Delivery prior to completion of 37 weeks’ gestation from mother with maternal GBS colonization isolated from vaginal, cervical and/or rectal swabs

Courtesy: Anna Sealle & Joy Lawn
Multi-Centred Study on Maternal GBS colonization, Newborn Transmission, Serotype distribution and Serotype Specific Capsular Antibody Transfer in LMIC.

- Enrolment 6000 (760 each) mother-newborn pairs at birth in each of 8 LMIC countries (Bhutan, Ethiopia, India, Kenya, Mali, Mozambique, Nigeria, South Africa).

Colonization:
- i. Define the prevalence of GBS colonization in HIV-uninfected pregnant women at term-delivery.
- ii. Determine vertical acquisition of GBS colonization by the newborns.
- iii. Serotype distribution associated with GBS colonization in pregnant women.
- iv. Evaluation of density of GBS colonization among pregnant women.

Serology:
- v. Determine serotype specific capsular antibody levels in HIV-uninfected pregnant women.
- vii. Serotype specific capsular antibody levels at birth, and ratio of transplacental antibody transfer.

Model rates of EOD in the different settings using GBS colonization, CPS antibody, together with other population based risk-factor measures (such as premature rate, IAP exposure, prolonged rupture of membranes, maternal HIV seroprevalence and maternal malaria infection rates).
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Need for Standardized Immunology Assays to Establish Correlate of Protection Against Invasive GBS disease.

Serotype Ia: 89% reduced risk if ≥0.5 µg/mL.

Serotype III: 91% reduced in risk if ≥0.5 µg/mL.

Baker et al. (USA) J Infect Dis 2014

Serotype Ia: 90% reduced risk if ≥5 µg/mL.

Serotype III: 90% reduction in risk if ≥3 µg/mL.

Dangor Z et al. (South Africa) Vaccine 2015
Develop Quality-assured Immunologic Correlate(s)/Surrogate(s) of Protection.

» Development of standard reagents (NIBSC) and identification and review of assays for standardisation (2017/8).

» To standardised protocols for existing ELISA and functional GBS assays using standard reagents (2018)

» To validate standard protocols and standard reagents across laboratories to establish a prediction of disease protection (2019+)
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• Geometric Mean Antibody Transfer Ratio: Range 0.58-0.79 in 5.0 ug arm.

• Poorer antibody response in women with pre-vaccination antibody titers below lower limit of quantification (56-76% in Canada/Belgium vs 7.5%-32% in SA)

Madhi SA et al. Lancet Infect Dis, 2016; 16: 923-34; Donders GGG, Obs Gyencol; 2016; 172 (2) 213-221
GBS Serotype Ia antibodies in HIV-uninfected and HIV-infected mothers and their infants with one 5.0 µg dose of GBS vaccine

Similar immunogenicity trends observed for serotypes Ib and III

Increased risk of invasive GBS Disease in HIV-exposed infants:
Early-onset disease: RR: 1.69 (95%CI: 1.3-2.2)
Late-onset disease: RR: 3.18 (95%CI: 2.3-4.4)
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Sample Size Calculation for an Efficacy Trial for an Invasive Disease Outcome

<table>
<thead>
<tr>
<th>Vaccine efficacy (lower bound 20% VE)</th>
<th>Incidence (per 1000 births)</th>
<th>Approximate Sample Size N (1:1) (+10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>1</td>
<td>44,000</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>29,000</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>22,000</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>14,700</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>11,000</td>
</tr>
<tr>
<td>70%</td>
<td>1</td>
<td>70,000</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>46,500</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>35,200</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>23,000</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>17,500</td>
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</tbody>
</table>
Key Next Steps on GBS Vaccine Development Roadmap

» Completion of assay standardisation and further study on correlate of protection (capsular and protein antibody).

» Standardisation of endpoint for clinical diagnosed sepsis, invasive disease (culture and PCR diagnosed) and stillbirths (WHO Working Group).

» Possibly explore utility of molecular assay for diagnosing stillbirths, EOD and LOD in appropriate case-control studies, including sampling from deaths.

» Phase Ib/Ila studies of common protein (AlpC and Rib) and serotype-specific capsular antibody in pregnant women.

» Decision making on licensure, correlate of protection vs. randomized placebo controlled trial.
1st International Symposium on Streptococcus agalactiae Disease (ISSAD)

Cape Town, South Africa

Dates: 20th - 23rd February 2018