Maternal GBS vaccine
Immaculada Margarit
PD-VAC Meeting
Geneve, September 7th 2015
The Group B Streptococcus (GBS)

- *Streptococcus agalactiae* (Group B Streptococcus, GBS) is a Gram-positive beta-hemolytic microorganism that colonizes the human lower Gastro Intestinal and Genital tracts.

- GBS can cause life-threatening infections in neonates and in immuno-compromised adults.

- Mother to Infant Transmission:
  - 20-25% women are colonized (global) .............................................200/1000
  - 50% of babies born to these mothers are colonized ........................100/1000
  - 2% become infected ........................................................................2/1000

Edwards MS, Nizet V 2011, in Infectious diseases of the fetus and newborn infant. Elsevier Saunders, :419-469
Stages of GBS maternal and neonatal infection

Adapted from: Doran & Nizet Molecular Microbiology 2004 54 (1), 23–31

Maternal Colonization
- During gestation
- At delivery

Maternal Infection
- Chorioamnionitis

Fetal/Neonatal infection
- Pneumonia
- Bacteremia
- Meningitis

Commensal state
Invasive state
# GBS as major cause of neonatal invasive disease

- **2.9 Million neonatal deaths occurring world-wide annually**, 98% of which in developing countries\(^2\)\(^-\)\(^3\)
- **32% of neonatal deaths are due to infections**\(^2\),\(^4\)
- **GBS is a leading cause of neonatal sepsis and meningitis**\(^5\)

## GBS meningitis 86.1% 

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 Mo</td>
<td>201</td>
</tr>
<tr>
<td>2–23 Mo</td>
<td>212</td>
</tr>
<tr>
<td>2–10 Yr</td>
<td>113</td>
</tr>
<tr>
<td>11–17 Yr</td>
<td>61</td>
</tr>
<tr>
<td>All pediatric cases</td>
<td>587</td>
</tr>
</tbody>
</table>

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GBS neonatal infections cause significant mortality and sequelae.

<table>
<thead>
<tr>
<th></th>
<th>Early Onset Disease (EOD)</th>
<th>Late Onset Disease (LOD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>≤ 6 days</td>
<td>7-89 days</td>
</tr>
<tr>
<td><strong>Acquisition</strong></td>
<td>Mother</td>
<td>Mother or community</td>
</tr>
<tr>
<td><strong>Manifestations</strong></td>
<td>Bacteremia</td>
<td>Meningitis</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>Bacteremia</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td><strong>CFR</strong></td>
<td>5-10% in developed world up to 38% in developing world</td>
<td>3-11% in developed world up to 29% in developing world</td>
</tr>
<tr>
<td><strong>Sequelae rates</strong></td>
<td>26%</td>
<td>34-46% (post-meningitis)</td>
</tr>
<tr>
<td><strong>Typical Sequelae</strong></td>
<td>Deafness, Blindness, Seizures, long-term Neurodevelopmental defects</td>
<td></td>
</tr>
</tbody>
</table>

GBS causes peripartum morbidity

- **Maternal infection:**
  - Invasive GBS disease has declined with IAP, but still occurs in 0.04 pregnant and 0.49 post-partum women /1000 live births (US)\(^1\)
  - Chorioamnionitis occurs in 2.9% of pregnant women vaginally colonized at the time of delivery

- **Stillbirth:**
  - 2009 global estimates: ~2.6 million, corresponding to ~1.9% live births\(^2\)
  - ~20% stillbirths are due to infection, ~4-10% to GBS\(^3\)

- **Preterm birth:**
  - Accounts for 75% of perinatal mortality worldwide\(^4\)
  - 2010 estimates: ~15 mn/year (~11%, up to 18% in some African countries)\(^5-6\)
    - 25-40% may be due to infections, including GBS

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GBS toxins cause placental damage

- Preterm birth and fetal infection can be caused by GBS β-hemolysin induced damage of maternal-fetal barriers and inflammation$^{1-3}$

β-hemolytic GBS

Uterine Tissue

GBS infected

Uninfected control

Inflammatory cells, necrotic tissue

Global incidence of GBS neonatal infection

- **Estimated number of cases per 1000 live births in infants <90 days**

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases/1000 Live births</th>
<th>Estimated Cases/Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>0.56(^1)</td>
<td>&gt; 2300</td>
</tr>
<tr>
<td>UK</td>
<td>0.7(^2)</td>
<td>&gt;550</td>
</tr>
<tr>
<td>France</td>
<td>0.75(^3)</td>
<td>&gt; 600</td>
</tr>
<tr>
<td>Panama</td>
<td>1.4(^4)</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>2.5(^4)</td>
<td>&gt;540</td>
</tr>
<tr>
<td>South Africa</td>
<td>2.9(^5)</td>
<td>&gt; 2900</td>
</tr>
</tbody>
</table>

GBS neonatal infections may be under reported

- In LMIC there are a high percentage of home deliveries and deaths not reported due to limited health care access, lack of awareness, logistical hurdles

- GBS can be difficult to detect due to:
  - Poor blood collection: 1.0 mL neonatal blood volume for 90% sensitivity
  - Lack of pediatric blood culture bottles
  - Lack of proper media/supplies for GBS isolation and identification

GBS preventive and treatment measures

- **Difficult treatment:** very early, quick onset (most EOD within 48 h)

- **Intrapartum antibiotic prophylaxis (IAP)** for women at risk is the only available prevention measure.

- **Two approaches:**
  - **GBS screening** by vagino/rectal swabs at ~35-37 gestation weeks → *all* colonized women receive IAP (e.g. US, CA, FR, BE, AU, supported by key obs/gyn organizations)
  - **Clinical factors:** previous infant with GBS disease, chorioamnionitis, prematurity, PROM, fever (e.g. UK, DK)

Decline in the incidence of invasive GBS disease among infants in US prior and after IAP recommendations in 1993\(^1\):

**IAP limitations:** no effect on LOD, failures due to precipitous labor or false negative screening, allergies, concern for induction of antibiotic resistance

**Even in US, with 85% compliance for IAP, ~2500 GBS cases occur each year**

Increasing GBS antibiotic resistance

- Erythromycin resistance in invasive group B streptococcal (GBS) isolates according to patient age, England and Wales, 1991 – 2010:

A GBS Maternal Vaccine to protect neonates

- GBS infection occurs too soon for any infant vaccine
- Maternal immunization at 26-35 gestation weeks could reduce the risk of neonatal infection
- Placental IgG transfer increases >32 wks and persists for 3 mo after birth

Maternal vaccination to prevent tetanus and influenza is recommended in international guidelines¹-³

Antibodies confer protection
A vaccine is possible

Antibody to GBS III CPS in Sera from Mothers Whose Infants Had III GBS Colonization or Disease*

A vaccine for GBS is possible

Anti-CPS antibodies protect humans against neonatal infection

- High maternal IgG levels specific to the GBS capsular polysaccharide (CPS) correlate with reduced risk of newborn infection in humans\textsuperscript{1-4}

Percentage of mothers of infected (cases) or non infected babies (controls) with CPS–specific IgG serum concentrations ≥ to the value shown on the horizontal axis\textsuperscript{4}

Tools to evaluate immunogenicity of GBS vaccine candidates

1- Active & Passive maternal immunization models to assess elicitation of protective antibodies

- 6-8 weeks CD1 female mice, 1 µg CPS/dose, 3 IP injections days 1, 21 and 35
- Mating day 39
- GBS challenge (IP, 90% LD, 24-48 h)

2- ELISA (Monoplex, Multiplex) to determine anti CPS maternal IgG

3- Opsono Phagocytic Killing Assay (OPKA) to assess antibody functional activity

- Bacteria
- Heat-inactivated pre-diluted sera
- HL-60 differentiated with 0.8% DMF
- Baby rabbit complement
CPS conjugates confer protection in neonatal mice mice

<table>
<thead>
<tr>
<th>PS type</th>
<th>Challenge strain (type)</th>
<th>% survival (Alive/treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT conjugate</td>
<td>Crm conjugate</td>
</tr>
<tr>
<td>Ia</td>
<td>090 (Ia)</td>
<td>78% (52/67)</td>
</tr>
<tr>
<td>Ib</td>
<td>7357B (Ib)</td>
<td>62% (50/80)</td>
</tr>
<tr>
<td>III</td>
<td>COH1 (III)</td>
<td>97% (37/38)</td>
</tr>
<tr>
<td>V</td>
<td>CJB111 (V)</td>
<td>93% (28/30)</td>
</tr>
</tbody>
</table>

Female mice were immunized with **each conjugate individually** and the pups were challenged with a strain of the corresponding serotype.
A substantial challenge to GBS vaccine design is the natural diversity of GBS capsular polysaccharides (CPS):

- 10 serotypes of GBS have been characterized (Ia, Ib, II, III, IV, V, VI, VII, VIII, IX) and found to be antigenically unique
GBS Vaccine Design: Conquering Diversity

- Approaches to overcoming GBS diversity:
  1. Prepare combination of CPS-glycoconjugates
     – Combination of Ia, Ib, III, II and V may represent >90% of isolates
  2. Inclusion of GBS proteins to increase protection and breadth of responses
     – Surface-associated proteins identified mainly by genome analysis1-5

Clinical studies on CPS conjugates supporting vaccine development

- Phase I/II using **monovalent / bivalent** CPS conjugated to TT or CRM on healthy adults and pregnant women (III-TT)$^{1-4}$

- Phase I/II using **trivalent** CPS Ia, Ib, III-CRM conjugates (GSK):

  - Maternal results:
    - The vaccine was well-tolerated in pregnant women
    - >75% of women had >4-fold rise in specific IgG

  - Infant results:
    - For all serotypes, mother to infant IgG transfer rates ranged from 50-81%
    - Ab concentrations in infants remained above placebo recipients through 90 days post-partum
    - No evidence of a detrimental effect on infant Ab response to diphtheria (or pneumococcal) immunization

Possible paths to licensure

- **Efficacy PhIII study:**
  - Case-driven, including EOD and LOD
  - Possibly conducted in LMICs with high burden of disease and high uptake of TT maternal vaccine
  - Participants (≥50000) randomized to receive GBS vaccine or placebo in addition to locally available standard of care
  - Possible need of bridging studies for licensure in HIC

- **Maternal IgG concentrations as serological correlates of protection:**
  - **Rational:** a) High maternal anti-CPS IgG correlate with reduced neonatal disease risk; b) Anti-CPS IgG correlate with OPKA functional titers
  - **Approach:** Develop specific IgG thresholds based on estimation of disease risk reduction using serum samples from case-control studies
  - Lower number of participants required

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GBS vaccine cost effectiveness

- GBS is a global disease both in developing and developed world
  - High awareness in HIC countries (e.g., universal IAP, active surveillance), Ob/Gyn as responsible for GBS prevention
  - Less awareness in LMIC

- Two recent studies confirmed GBS vaccine cost effectiveness:
  - US cost-effectiveness estimates based on expected reduction in GBS cases & prevention of GBS-related deaths, Quality-Adjusted Life-Years. 
    **Results:** US cost/QALY ($91,321) for GBS trivalent vaccine comparable to ACIP-recommended vaccines
  - CDC-cost effectiveness model in S Africa. **Results:** maternal GBS vaccination very cost effective per WHO guidelines at prices up to $30/dose

GBS vaccine development hurdles

- Maternal vaccination acceptance, increased rate of adverse events during pregnancy
- Difficulty in conducting efficacy trials due to low incidence and to IAP treatment.
  - To detect a 75% reduction in EOD and LOD requires >50,000 women if incidence ~3/1000 and >1,500,000 women if lower incidence
  - Lower microbiological, clinical and analytical data quality standards in LMIC countries
- Regulatory acceptance of protection serocorrelates based on case-control studies for vaccine licencing and recommendation
- Low public awareness of GBS as a cause of vaccine-preventable illness
- Need for more reliable epidemiological data
- Co-administrations of other recommended vaccines
WHO support needed

- Raise education/awareness regarding GBS and its impact
- Initiatives to obtain more reliable epidemiological data
- Create consensus on indication for vaccine use in pregnant women
- Definition of serocorrelates of protection for vaccine licencing and recommendation
- Definition of preferred product characteristics
- Roadmap for vaccine introduction in LMIC