Group B streptococcal vaccines

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Disclaimer

I serve as Chair of influenza vaccine DSMBs for BioCSL/Sequiris for which my institution receives compensation

Investigator on passive and active vaccine studies for MedImmune, Novotech, Gilead, and Alios for which my institution receives compensation
Microbiology

- 1st described 1935
  - Maternal fatalities described by 1938
- Encapsulated bacteria ....
  - 10 serotypes defined by CPS
  - 4 cause most disease worldwide
    - Ia, II, III and V
    - Type III most a/w meningitis (LOS)
  - Colonises 10-30% pregnant women
Global impact

Causes disease in:

- Newborns: EOS (day0-6) & LOS
- Pregnant women
- Elderly
- Immunosuppressed

High and low income settings
GROUP B STREPTOCOCCUS (GBS) IS A NORMAL BACTERIUM WHICH COLONISES BETWEEN 20-30% OF ADULTS IN THE UK USUALLY WITHOUT SYMPTOMS OR SIDE-EFFECTS BUT CAN BE DEADLY TO NEWBORNS*
Mother to Infant Transmission of GBS

- **GBS colonized mother**
  - 50% chance of colonized newborn
  - 50% chance of non-colonized newborn

- **Non-colonized newborn**
  - 98% asymptomatic

- **Colonized newborn**
  - 1-2% chance of early-onset sepsis, pneumonia, meningitis
Newborn sepsis epidemiology

EOS
- Acquired during or just prior to birth
- Sepsis or pneumonia
- Rates HIC per 1000 births: (post 2000)
  - Europe 0.53 (0.44–0.62)
  - Americas 0.67 (range 0.54–0.80)
  - Australasia 0.15 (range –0.03 to 0.07)
- LMIC:
  - mean incidence 0.43 (95% CI 0.37–0.49)

CFR 4.6%
CFR 12.6%

Lancet 2012; 379: pp. 547-556
Young infant age at onset, Soweto, South Africa

Cutland, C et al. 2015. EID 21:638-45
Newborn sepsis epidemiology

LOS

- 50% present with meningitis
- Approx half rate of EOS
- Acquired from mother or others

Lancet 2012; 379: pp. 547-556
Prevention: Risk factors EOS

Preterm labour.
Rupture of membrane ≥ 18 hours.
Maternal fever ≥ 38°C.
A previous infant with EOGBS.
GBS bacteruria during the current pregnancy.
Known carriage of GBS in current pregnancy.
Clinical diagnosis of chorioamnionitis
Other twin with current EOGBS.
<table>
<thead>
<tr>
<th>Recommendation 1</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>All maternity services should have an established plan for prevention of EOGBS.</td>
<td>Consensus – based recommendation</td>
</tr>
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<table>
<thead>
<tr>
<th>Recommendation 2</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Universal culture-based screening, using combined low vaginal plus or minus anorectal swab at 35-37 weeks gestation, or a clinical-risk factor based approach are both acceptable strategies for reducing EOGBS.</td>
<td>Consensus – based recommendation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Good Practice Point</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>If a woman’s GBS carriage status is unknown at the time of labour onset, then treatment according to clinical risk factors is appropriate.</td>
<td>Good Practice Point</td>
</tr>
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<thead>
<tr>
<th>Recommendation 3</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low vaginal and anorectal swabs for GBS screening should be incubated in enriched media to achieve acceptable sensitivities.</td>
<td>Consensus – based recommendation</td>
</tr>
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<table>
<thead>
<tr>
<th>Recommendation 4</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Intrapartum antibiotic prophylaxis with IV penicillin-G or ampicillin should be offered to all women at increased risk of EOGBS.</td>
<td>Consensus – based recommendation</td>
</tr>
</tbody>
</table>
CURRENTLY THE BEST WAY OF KNOWING WHICH WOMEN CARRY GBS IN LABOUR IS THROUGH TESTING FOR GBS AT 35-37 WEEKS OF PREGNANCY*
Prevention: antibiotic prophylaxis

Screening based vs Risk factor based

Culture-based screening compared with risk factor-based screening
  – OR 0.45, 95% CI 0.37 - 0.53)
Antenatal vaccination

Healthy normal state

Like all normal states - not risk free
Foundation of Maternal Immunization: Maternal antibody to capsular polysaccharide (CPS) reduces infant disease risk

(Maternal antibody, GBS III CPS, μg/mL)

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

Infant Disease Infants Exposed

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 Ia was >6 μg/mL and III was >3 μg/mL

1st WHO Consultation on GBS Vaccine development
27-28 April 2016

About 60 attendees, including research groups, industry, regulatory agencies, funding partners

Background, key epidemiological gaps
  - Important body of evidence missing: GBS-related stillbirth & prematurity; disease burden in LMIC; strain dynamics and risk of replacement; unmet needs in HIC. Several ongoing initiatives. Compartmental model/systematic review-based global disease burden estimates awaited towards year end (LSHTM-led).

Review of current standards of maternal/infant infection prevention and care in LMIC

Current vaccine development status: GSK, Pfizer, Minervax
GBS Vaccines - Pathway to licensure

Safety requirements: build on ongoing MI initiatives
Correlate of protection working group
Phase 3 design considerations
  - Importance of clinical endpoints to support policy decisions. Standardization of data collection according to pre-defined case definitions. Composite endpoint?
  - Acceptability of trial under local standards of care, considering national/WHO recommendations. Role of local authorities
  - Study site requirements. Importance of baseline data
Schedule, timing, co-administration data, impact on selected EPI vaccines TBD
GBS vaccines - Forward view

Documented consensus-based flexible clinical development pathway and Preferred Product Characteristics

Protein based approach: need to bridge historical status of CPS-based strategy

From evidence to policy and implementation

- Ongoing modelling and health economical evaluations: value proposition, cost-effectiveness analyses. Prepare long term financing pathways
- Role in high income countries? Contribution to reduce antibiotic use
- Health system mindset for coordinated maternal and infant care; understand health provider, community, parental perspectives and acceptability. Communication and advocacy needs

Need to build stakeholder commitment, a GBS vaccine community
# Current status

Table 1
Development status of current vaccine candidates (POC, proof of concept trial).

<table>
<thead>
<tr>
<th>Developer</th>
<th>Candidate name/identifier</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>POC</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>Tetanus toxoid-CPS conjugates: monovalent (multiple studies), bivalent (one study); CRM197-CPS conjugate: monovalent (one study)</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x (trial in pregnant women)</td>
<td></td>
</tr>
<tr>
<td>Novartis/GSK</td>
<td>CRM197-CPS conjugates: monovalent (multiple), trivalent (several)</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x (trial in pregnant women)</td>
<td></td>
</tr>
<tr>
<td>Minervax</td>
<td>N-terminal domains of the Rib and AlphaC surface proteins</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis/GSK</td>
<td>Pilius proteins</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Various academic groups</td>
<td>Other protein(s) and/or protein-CPS conjugates</td>
<td>x</td>
<td></td>
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</tr>
</tbody>
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Vaccine introductions and campaigns in 2014

2014


Bangladesh  Mali  Togo  Mauritania

United Republic of Tanzania  Pakistan  Chad  Mozambique

Congo  Haiti  Angola  Rwanda  Sierra Leone  Cameroon

Pentavalent vaccine  Pneumococcal vaccine  Rotavirus vaccine  Measles 2nd dose vaccine  Measles campaign  Measles-rubella vaccine  HPV demonstration project  HPV national introduction  Meningitis A campaign  IPV

* Refers to annual birth cohort (for vaccine introductions) or target population (for vaccine campaigns)
VIS occurs every five years, aligned with strategic cycle and replenishment.

2008

2011-2015 Strategic period

2011 2012 2013

2015 2016 2017 2018

2011-2015 Strategic period

2011-2015 Strategic period

2020 2021

2021-2025

VIS #1
HPV
Rubella
JE
Typhoid
conj.
MenA

VIS #2
YF mass campaigns
Cholera stockpile
Rabies/cholera
studies
Malaria – deferred

VIS #3

RTS,S pilots?

Gavi
The Vaccine Alliance
Looking forward to VIS #3

Scope: licensure <5 years

Expected candidates for consideration

Returning candidates / incremental investments:
- Dengue
- (maternal) influenza
- rabies PEP
- Hepatitis E
- RTS,S
- meningococcal multivalent
- Cholera
- DTP booster
- Hepatitis B birth dose
- Typhoid
- PCV catch-up

New:
- RSV
- Group B Streptococcus
- Norovirus?
- ETEC?

Data gathering to begin in 2017
Thank you