GBS: Towards licensure of a maternal vaccine

Kirsty Le Doare
Paediatric Infectious Diseases Research Group & Vaccine Institute, St George’s, University of London

WHO PDVAC meeting 26th June 2018
# Areas of focus for GBS vaccine development

<table>
<thead>
<tr>
<th>Focus area</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence Generation</td>
<td>- CHAMPS network&lt;br&gt;- Neonatal Cause-of-Death studies&lt;br&gt;- Disease burden modeling&lt;br&gt;- Whole genome sequencing</td>
</tr>
<tr>
<td>Vaccine development</td>
<td>- Assay standardization&lt;br&gt;- Validate path to licensure</td>
</tr>
<tr>
<td>Economic analysis</td>
<td>- WHO global value proposition, with LSHTM&lt;br&gt;- Cost-effectiveness modeling</td>
</tr>
<tr>
<td>Policy, guidance and norms</td>
<td>- WHO Preferred Product Characteristics and technical R&amp;D roadmap&lt;br&gt;- Support for WHO activities to facilitate GBS vaccine development, licensure, and prequalification with a focus on LMIC</td>
</tr>
<tr>
<td>Delivery/Integration in antenatal care</td>
<td>- Standardization of pregnancy vigilance&lt;br&gt;- MNCH stakeholder engagement</td>
</tr>
</tbody>
</table>
EVIDENCE GENERATION – QUANTIFYING THE BURDEN OF GBS DISEASE
Burden of Group B *Streptococcus* worldwide for pregnant women, stillbirths and children: Why? What outcomes? How to estimate?

Series in journal of Clinical Infectious Diseases, Nov 2017

**Professor Joy Lawn**
London School of Hygiene & Tropical Medicine
On behalf of the GBS Burden estimation expert group
What is new to inform interventions?

- Input data worldwide
  - Worldwide reach from almost 100 countries and all regions (translated from ~20 languages)
  - Volume of inputs at least doubled compared with previous databases
  - Investigator groups bringing important unpublished datasets – notably for stillbirths and regarding hypoxic ischaemic encephalopathy in neonates with GBS infection

- All outcomes of relevance
  - All relevant outcomes: cases, deaths and disability for pregnant women, stillbirths, and children
  - More data needed, particularly for stillbirths, preterm and disability, maternal cases
  - ‘Inverse care law’, where the most vulnerable have highest burden and least available data

- Informing vaccine impact
  - Inform vaccine design & potential
  - Better understand possible variation in virulence by region or by cases (e.g. maternal, fetal, child)

11 papers, collaboration of 103 authors from over 30 institutions coordinated by the London School of Hygiene & Tropical Medicine

Clinical Infectious Diseases

#GBSburden
#momandbaby
Modelling approach

**Estimate national, regional, worldwide burden**

- Pregnant women colonised, infants with GBS disease, deaths and disability
- Maternal GBS disease
- Stillbirths with GBS disease
- Preterm birth attributed to maternal GBS colonisation

To estimate GBS infant cases and sequelae we applied a compartmental model:

1. Exposed (maternal colonisation)
2. Cases (early and late onset)
3. Deaths (neonatal and infant)

“All models are wrong but some are useful” - Lord Box

Clinical Infectious Diseases
Cases of GBS in pregnant women, fetus, and infants worldwide

CASES: 319,000 infants; 33,000 pregnant and postpartum women; 57,000 fetus

Seale AC et al. Clinical Infectious Diseases. 2017;65(S2):S200-19
Deaths from GBS: stillbirths and infants worldwide

DEATHS: 90,000 infants (mostly neonatal); 57,000 stillbirths

Seale AC et al Clinical Infectious Diseases. 2017;65(S2):S200-19
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)
VACCINE DEVELOPMENT
Key investments for GBS vaccines

• **Product Development:**
  - Pfizer: GBS vaccine development (Phase 1)
  - Biovac/PATH: GBS vaccine development (preclinical)
  - Imperial College London: Lab assay standardization

• **Evidence Generation:**
  - LSHTM: disease burden modeling
  - Wits Health Consortium:
    - Evaluating association of anti-capsular serotype specific antibodies with maternal colonization and invasive GBS disease in infants in South Asian and African countries
    - Evaluating association of surface protein antibodies with maternal colonization and invasive GBS disease in infants
  - WHO and LSHTM: Value Proposition assessment

• **Policy, guidance and norms**
  - Support of WHO activities to facilitate GBS vaccine development, licensure, and prequalification with a focus on LMICs
<table>
<thead>
<tr>
<th>Candidate</th>
<th>Manufacturer</th>
<th>Vaccines construct</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>NA</td>
<td>Pfizer</td>
<td>Multivalent CPS – CRM\textsubscript{197} conjugate</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>Clinical programme commenced</td>
</tr>
<tr>
<td>GBS vaccine</td>
<td>Novartis/GSK</td>
<td>Trivalent (Ia, Ib, III) CPS-CRM\textsubscript{197} conjugate</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>Safety and immunogenicity study completed. Formulation updated</td>
</tr>
<tr>
<td>NA</td>
<td>GSK</td>
<td>Multivalent formulation</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Reformulation and return to pre-clinical phase</td>
</tr>
<tr>
<td>NA</td>
<td>GSK</td>
<td>Pilus proteins</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>Biovac</td>
<td>Polyvalent CPS TT-conjugate</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>Cell banks developed with local isolates CT manufacturing 2019 CT registered for 2020</td>
</tr>
<tr>
<td>GBS-NN vaccine MVX13211</td>
<td>Minervax</td>
<td>Rib/AlpC</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>Single component vaccine completed Phase 1 trial of 240 non-pregnant women complete</td>
</tr>
</tbody>
</table>
VACCINE DEVELOPMENT – ASSAY STANDARDISATION AND CORRELATES OF PROTECTION
Anti-Capsular and anti-surface-protein assays

Mono-plex and multi-plex, approximately 34 different assays used

- RABA (Total Ig la,III,V)
- RI (Total Ig III)
- Luminex binding assay (IgG all)
- Antigen-binding assay (IgG all)
- Anti-pili antibody
- Competitive binding ELISA (IgG la,III,V)
- Anti-protein antibody
- RPA (IgG la,lb,II,III)
- Direct ELISA (IgG all)
- IF (IgG la,lb,lc,II,III)
- Indirect ELISA (IgG la,lb,II,III)

GBS Capsule

Le Doare et al Lancet ID 2018
Functional and semi-functional antibody assays

Killing or uptake, with or without standards 9 different assays in circulation

PMN

Baby Rabbit Complement

GBS

C' (NOT Fluorescent)

GBS

7.5 min at 37°C

Anti-human C3c FITC

Flow Cytometry

= C3b/iC3b on bacteria surface

10% 20%

C'

HL60 cells

Baby Rabbit Complement

Flow Cytometry

Human Complement

GBS

Flow Cytometry

Flow Cytometry

HL60 cells

Baby Rabbit Complement

Baby Rabbit Complement
Low incidence means efficacy studies are difficult

- GBS disease in infants represents an important unmet medical need
- Low incidence rates of GBS disease makes vaccine efficacy studies long and complex

### Sample Size Based on Assumptions (1:1 randomization ratio)

<table>
<thead>
<tr>
<th>Disease Rate</th>
<th>Efficacy</th>
<th>Power</th>
<th>Lower Bound</th>
<th>Per Protocol Cases</th>
<th>Sample size* (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1%</td>
<td>75%</td>
<td>90%</td>
<td>&gt;20%</td>
<td>43</td>
<td>~ 90,000</td>
</tr>
<tr>
<td>0.1%</td>
<td>75%</td>
<td>90%</td>
<td>&gt;30%</td>
<td>55</td>
<td>~ 115,000</td>
</tr>
</tbody>
</table>

* Total sample size is adjusted to account for 10% prematurity loss and 15% early withdrawals.

A serological correlate of protection is needed

*Risk factor rate for combined early and late onset GBS in S. Africa (Dangor et al. 2016 PLoS One 10, e0123014)
Precedent for Serological Correlates of Protection for Encapsulated Pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>MOA</th>
<th>Correlate Natural</th>
<th>Correlate Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. influenzae</em> type B</td>
<td>IgG(^1)</td>
<td>0.15 µg/mL(^2)</td>
<td>≥ 0.15 µg/ml (conjugate)(^3)</td>
</tr>
<tr>
<td><em>N. meningitidis</em></td>
<td>hSBA(^4)</td>
<td>≥ 4(^4)</td>
<td>≥ 4(^5)-7</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>IgG</td>
<td>N/A</td>
<td>≥ 0.35 µg/ml in infants(^8)</td>
</tr>
</tbody>
</table>

- Sero-epidemiology studies provided the mechanism of action and proposed correlate
- Vaccine efficacy studies confirmed the correlate
- For PCVs in infants an IgG threshold to license new expanded serotype PCVs was developed based on efficacy
  - Not serotype specific
  - Does not predict protection against disease in an individual

---

Serocorrelates of protection differ depending on source of serum and assay.

Table 1. Frequency and odds ratios (OR) for Ia antibodies and early-onset disease (EOD) caused by GBS Ia in neonates born at ≥34 weeks gestation.

<table>
<thead>
<tr>
<th>Maternal antibody level, µg/mL</th>
<th>Frequency</th>
<th>OR (95% CI)</th>
<th>Reduction of risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case patients</td>
<td>Control subjects</td>
<td>Crude</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>29</td>
<td>168</td>
<td>1.00 (1.00)</td>
</tr>
<tr>
<td>≥0.5</td>
<td>16</td>
<td>151</td>
<td>0.61 (0.32–1.17)</td>
</tr>
<tr>
<td>≥1</td>
<td>11</td>
<td>117</td>
<td>0.55 (0.26–1.13)</td>
</tr>
<tr>
<td>≥2</td>
<td>7</td>
<td>88</td>
<td>0.46 (0.19–1.09)</td>
</tr>
<tr>
<td>≥3</td>
<td>4</td>
<td>75</td>
<td>0.31 (0.11–0.91)</td>
</tr>
<tr>
<td>≥4</td>
<td>3</td>
<td>62</td>
<td>0.28 (0.08–0.95)</td>
</tr>
<tr>
<td>≥5</td>
<td>1</td>
<td>55</td>
<td>0.11 (0.00–0.79)</td>
</tr>
</tbody>
</table>

Table 2. Estimated protective relations between increasing levels of maternal IgG anti–group B streptococcus (GBS) type III and early-onset disease caused by this pathogen, in neonates born at ≥34 weeks gestation.

<table>
<thead>
<tr>
<th>Antibody level, µg/mL</th>
<th>Frequency</th>
<th>OR (95% CI)</th>
<th>Percent reduction of riska (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case patients</td>
<td>Control subjects</td>
<td>Crude</td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>11</td>
<td>27</td>
<td>1.00 (1.00)</td>
</tr>
<tr>
<td>≥2.0</td>
<td>15</td>
<td>116</td>
<td>0.32 (0.13–0.77)</td>
</tr>
<tr>
<td>≥5.0</td>
<td>6</td>
<td>56</td>
<td>0.26 (0.09–0.79)</td>
</tr>
<tr>
<td>≥8.0</td>
<td>3</td>
<td>31</td>
<td>0.24 (0.06–0.94)</td>
</tr>
<tr>
<td>≥10.0</td>
<td>1d</td>
<td>26</td>
<td>0.09 (0.01–0.78)</td>
</tr>
</tbody>
</table>

Lin et al 2001, 2004
70% disease EOD risk reduction if antibody against STIa, III and V >1µg/mL in maternal serum.

90% for STIa and STIII, 70% for STV, if Ab ≥2µg/mL attack rates reduced from 1/100 livebirths to:
0.49/100 for serotype la
0/100 for serotype III

Baker 2014
75% disease EOD risk reduction if antibody >1µg/mL STIla and STIII in Europe
80% disease Combined risk reduction if antibody >6ug/mL STIa and 3ug/mL STIII in South Africa

Dangor 2016
Good correlation between antibody concentration (ELISA) and OPkA for STIa & STIII

Baker 1999
As well as in Europe for STIa, STIb and STIII....

Fabbrini 2016
Functional antibody threshold associated with absence of infant colonisation in The Gambia
Evidence limited about role of protein antibody as a CoP against invasive disease
CoP study
sample size considerations

- At 80% risk reduction the proportion of controls above the cut-off will probably vary between 30% and 70%
- 80% reduction in a case-control study means an OR of 0.2
- Precision of OR (95% CI) around 0.2 for varying case sample sizes assuming 30-70% controls > cut

<table>
<thead>
<tr>
<th>Controls &gt; cut</th>
<th>N=30 cases</th>
<th>N=90</th>
<th>N=150</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=90 c’trols</td>
<td>N=270 c’trols</td>
<td>N=450 c’trols</td>
</tr>
<tr>
<td>70%</td>
<td>0.08-0.49</td>
<td>0.12-0.33</td>
<td>0.13-0.30</td>
</tr>
<tr>
<td>50%</td>
<td>0.07-0.57</td>
<td>0.11-0.37</td>
<td>0.13-0.32</td>
</tr>
<tr>
<td>30%</td>
<td>0.05-0.81</td>
<td>0.09-0.45</td>
<td>0.11-0.37</td>
</tr>
</tbody>
</table>
European Medicines agency meeting May 24, 2017
GBS Assay Standardisation Group Meeting with Vaccine Working Party of the European Medicines Agency 24.5.17

FDA Briefing Document
Vaccines and Related Biological Products Advisory Committee Meeting
May 17, 2018
Evaluation of the Effectiveness of Vaccines Intended to Prevent Group B Streptococcal Disease in Infants
Next steps

• Prospective case/control studies of common serotypes to derive CoP from natural exposure to GBS measured in both maternal and cord/infant serum.

• Compare convalescent sera with acute illness sera to understand role of sample collection on Ab function.

• Study antibody kinetics: transfer from mother to infant; Ab decline between birth and 3 months of life.

• Establish the correlation between function and ELISA-type antibody data

• Evaluate of the role of common protein antibody in protection against colonisation and disease.
ECONOMIC EVALUATION – VALUE PROPOSITION
Project components / Workstreams (WS)

Disease burden (WS 1):
- Medical need for maternal immunization against GBS at global level
- Quantification of MI preventable burden of disease under different assumptions

Economic analyses (WS 2):
- Economic burden of disease
- Vaccine cost effectiveness
- Economic impact

Operationalization issues (WS 3):
- Vaccination schedule
- Service delivery
- Uptake
- M&E

Lambach, Capetown 2018
WS 1: Burden of disease (BoD) and medical need of GBS vaccine for use in pregnant women

- **Goal:** Assess medical need of GBS vaccine

- **Objectives:**
  - **Burden:** To assess the complete burden GBS disease in pregnancy
  - **Serotypes:** To describe GBS serotypes by region (country if enough data)
  - **Intrapartum antibiotic prophylaxis:** To estimate GBS disease burden preventable with IAP, implications for antibiotic use and potentially AMR
  - **Vaccine impact:** To estimate GBS disease burden preventable by vaccination in pregnant women
  - **Data gaps:** To synthesise data gaps regarding burden assessment and programmatic tracking

- **Outputs**
  - Revised analyses of cases, deaths, disability
  - Generation of DALYs
  - Data relevant to inform economic analyses
WS 2: Economic evaluations regarding GBS vaccine for use in pregnant women

• **Goal:** Evaluate GBS maternal-immunization preventable BoD, vaccine-preventable disease incidence and numbers needed to vaccinate

• **Objectives:**
  • Estimate cost of illness and cost of immunization programs (building on Workstream 1)
  • Estimate global impact of maternal GBS vaccination on disease, deaths, antibiotic consumption and resistance
  • Conduct economic evaluation to assess the cost-effectiveness, return on investment, budget impact, extended cost-effectiveness and producer/consumer surplus of maternal GBS vaccination

• **Outputs**
  • Estimates based on a range of health economic evaluations to understand the value of a GBS vaccine targeting pregnant women from the perspective of the research and development community, funders and countries

*Lambach, Capetown 2018*
WS 3: Operationalization of GBS vaccination programmes

• **Goal:** Evaluate the potential impact of vaccine introduction on standard medical practice based on
  • factors that may influence adoption and effectiveness of vaccination during pregnancy
  • capacity of existing service delivery models

• **Research areas/questions:**
  • Vaccination schedule (repeat dose administration and optimal vaccination timing during preg.)
  • Service delivery (integration into/optimal delivery by EPI/ANC)
  • Uptake (acceptance by pregnant women, HCW)
  • Monitoring and evaluation (adequate coverage monitoring for GBS vaccination of pregnant women)

• **Output**
  • Summary of latest "MI operationalization" evidence and application to GBS vaccine

Lambach, Capetown 2018
<table>
<thead>
<tr>
<th>Focus area</th>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence Generation</td>
<td>- Disease burden modeling</td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>- Whole genome sequencing</td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>- Ongoing evaluation of disease in Asia</td>
<td>✔️</td>
</tr>
<tr>
<td>Vaccine development</td>
<td>- Assay standardization</td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>- Validate path to licensure</td>
<td>✔️</td>
</tr>
<tr>
<td>Economic analysis</td>
<td>- Global value proposition</td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>- Cost-effectiveness modeling</td>
<td>✔️</td>
</tr>
<tr>
<td>Policy, guidance and norms</td>
<td>- Support for WHO activities to facilitate GBS vaccine development, licensure, and prequalification with a focus on LMIC</td>
<td>✔️</td>
</tr>
<tr>
<td>Delivery/Integration in antenatal care</td>
<td>- Standardization of pregnancy vigilance</td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>- MNCH stakeholder engagement</td>
<td>✔️</td>
</tr>
</tbody>
</table>
Thank you

Joy Lawn, Shabir Madhi, Johan Vekemans, Philip Lambach, Nick Andrews
Bringing together stakeholders from basic science, immunology, vaccinology, social sciences, industry, public health and national and international policy makers to tackle the key challenges related to the best use of vaccines in pregnancy and in newborns, and in the long term, to improve maternal and newborn health.

Pump priming grants  Fellowship  Network activities

Join us!

www.imprint-network.co.uk