Prospect for a GBS vaccine and the pathway to licensure, including considerations for LMICs

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What problem are we trying to solve?

Slower progress in reducing neonatal mortality

Global Under-five (U5), Infant and Neonatal Mortality Rates (1990-2012)

Under-five mortality rate
Infant mortality rate
Neonatal mortality rate

Under-five: ~5% annual decline
Neonatal: ~3% annual decline

In 2016, of the **5.6 million** deaths of children under the age of five, **2.6 million** (46%) occurred in the neonatal period. **2.2 million** survivors had neurodevelopmental impairment.

1. Millennium development goal; Source: http://www.childinfo.org/mortality_underfive.php
2. IGME child mortality report 2017
What problem are we trying to solve?

Nearly half of all deaths in children under the age of five occurred in the neonatal period in 2016. And one quarter of neonatal deaths are due to infectious causes.

Global distribution of deaths among children under age 5, by cause, 2016

Why pursue a maternal Group B Streptococcus (GBS) vaccine?

- Maternal Morbidity & Mortality
- Neonatal Morbidity & Mortality
- Stillbirths
- Pre-term births

WHO and Maternal and Child Epidemiology Estimation Group (MCEE) provisional estimates 2017

Seale AC et al Clinical Infectious Diseases. 2017;65(S2):S200-19
Reducing neonatal deaths is a focus of SGD targets

By 2030 neonatal mortality reduction in ALL countries to <12:1000 livebirths
Group B Streptococcus

• Commonly found in gut or lower vaginal tract

• Leading cause of neonatal infections Early Onset and Late Onset (sepsis, meningitis) in high income countries with high case fatality rate

Source: CDC
Stages of GBS maternal and neonatal infection

Pathogenesis of late-onset disease (>72 hours) possibly through maternal transmission (including breast milk) or other environmental acquisition.
Universal intrapartum antibiotic prophylaxis (IAP) reduces early-onset disease (EOD), but does not prevent late-onset disease (LOD)

Rate of Early- and Late-Onset GBS, US 1990-2008*

- Early-onset GBS
- Late-onset GBS

Before national prevention policy
Transition

~80% reduction of early-onset disease
IAP effectiveness continues to plateau in 2016*

~30% of pregnant women receive antibiotics

*CDC Active Bacterial Core surveillance / Emerging Infections Program
Risk-based IAP is associated with increase in GBS in High income countries and difficult to implement in LMIC

Group B streptococcal disease in UK and Irish infants younger than 90 days, 2014-15: a prospective surveillance study

Catherine P O’Sullivan, Theresa Lamagni, Darshana Patel, Androulla Efstratiou, Robert Conne, Mary Meenan, Shannez Ladhani, Arlene J Reynolds, Ruth Campbell, Lorraine Doherty, Margaret Boyle, Georgia Kapata, Victoria Chalker, Diane Lindsay, Andrew Smith, Eleni Davies, Christine E Jones, Paul T Heath

Summary

Background Group B streptococcus is a leading cause of serious infection in young infants in many countries worldwide. We aimed to define the burden and clinical features of invasive group B streptococcal disease in infants younger than 90 days in the UK and Ireland, together with the characteristics of disease-causing isolates.

Methods Prospective, active national surveillance of invasive group B streptococcal disease in infants younger than 90 days in the UK and Ireland from March 2014 to March 2015."

<table>
<thead>
<tr>
<th>GBS incidence rate per 1000 live births (n=cases) UK</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>2014-15</td>
</tr>
<tr>
<td>2000-01</td>
</tr>
<tr>
<td>EOD</td>
</tr>
<tr>
<td>0.57 (517)</td>
</tr>
<tr>
<td>0.48 (377)</td>
</tr>
<tr>
<td>LOD</td>
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<tr>
<td>0.37 (339)</td>
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<tr>
<td>0.24 (191)</td>
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Cost-effectiveness analysis of maternal immunisation against group B Streptococcus (GBS) disease: A modelling study

Kyriaki Giorgakoudi a, *b, Catherine O’Sullivan b, Paul T. Heath b, Shannez Ladhani b, c, Theresa Lamagni d, Mary Ramsay e, Hareth Al-Janabi f, Caroline Trotter a

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*Corresponding author.
GBS vaccine may prevent 90,000 infant deaths and 57,000 stillbirths.

1. Higher impact than Intrapartum antibiotic prophylaxis (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)
# GBS vaccine development pipeline, guidelines, and norms

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Manufacturer</th>
<th>Vaccine construct</th>
<th>Phase</th>
<th>Program status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>Pfizer</td>
<td>Multivalent CPS conjugate</td>
<td>X</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&lt;sub&gt;197&lt;/sub&gt; unadjuvanted</td>
<td>X</td>
<td>Completed safety and immunogenicity in pregnant women. Study completed</td>
</tr>
<tr>
<td>NA</td>
<td>GSK</td>
<td>Pentavalent (Ia, Ib, II, III, V) CPS-CRM&lt;sub&gt;197&lt;/sub&gt;</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>GSK</td>
<td>Pilus proteins</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>Biovac</td>
<td>Polyvalent CPS conjugate</td>
<td>X</td>
<td>Program start in 2017</td>
</tr>
<tr>
<td>GBS-NN vaccine/MVX1 3211</td>
<td>Minervax</td>
<td>N-domains of Rib + Alpha C surface proteins, unadjuvanted or Alhydrogel-adjuvanted</td>
<td>X</td>
<td>Safety and immunogenicity in non-pregnant women. Study completed</td>
</tr>
</tbody>
</table>

Early-onset disease Incidence requires large Vaccine efficacy trial

Assumptions for a 1:1 randomized controlled GBS clinical vaccine efficacy trial in a high disease incidence area

<table>
<thead>
<tr>
<th>Population disease incidence Per 1000 live births</th>
<th>Cases due to Vaccine serotypes</th>
<th>Cases eligible per protocol</th>
<th>Case incidence Per 1000 live births</th>
<th>Vaccine efficacy</th>
<th>Lower 95%CI bound</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>75-85%</td>
<td>70-80%</td>
<td>1.05-1.35</td>
<td>75%</td>
<td>&gt;20%</td>
<td>40,000 – 60,000</td>
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</table>
Why a vaccine could work: Maternal anti-GBS CPS Ab appears to confer protection

CORRELATION OF MATERNAL ANTIBODY DEFICIENCY WITH SUSCEPTIBILITY TO NEONATAL GROUP B STREPTOCOCCAL INFECTION

Carol J. Baker, M.D., and Dennis L. Kasper, M.D.

Abstract  We investigated the role of maternal antibody in neonatal Group B streptococcal infection with a radioactive antigen-binding assay employing a purified polysaccharide antigen with both Type III and Group B determinants. Serums from seven women who gave birth to infants who had invasive Group B streptococcal infection with Type III strains were all deficient in antibody. In contrast, serums from 22 of 29 pregnant Type III vaginal carriers whose infants were healthy contained antibody with a prevalence significantly different from that in women delivering infants with Type III disease (P < 0.01). Three healthy neonates born to women with antibody in serums had demonstrable antibody in umbilical-cord serum. These data suggest that transplacental transfer of maternal antibody protects infants from invasive Group B streptococcal infection with Type III strains. (N Engl J Med 294:753-756, 1976)
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 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
GBS assay standardization consortium

Objective 1: development of standard reagents and identification and review of assays for standardization

Objective 2: To standardized protocols for existing ELISA and functional GBS assays using standard reagents

Objective 3: To validate standard protocols and standard reagents across laboratories to establish a prediction of disease protection
Anti-Capsular and anti-surface-protein assays

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

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

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Functional and semi-functional antibody assays

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

PMN + Baby Rabbit Complement + Baby Rabbit Complement + HL60 cells + HL60 cells + Flow Cytometry

PMN + Baby Rabbit Complement + Flow Cytometry

PMN + Baby Rabbit Complement + Flow Cytometry

PMN + Baby Rabbit Complement + Flower Cytometry

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Major regulatory authorities discuss Sero-correlate based path to GBS Vaccine licensure

European Medicines Agency (EMEA)
GBS Assay Standardization Group Meeting with the Vaccine Working Party of EMEA on May 24th, 2017

US Food and Drug Administration (FDA)
Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting on May 17th, 2018

Evaluation of the Effectiveness of Vaccine intended to Prevent Group B Streptococcal Disease in Infants
GBS vaccine path to licensure based on correlate-of-protection (CoP) – FDA opined supportively at VRBAC meeting May 2018

Sero-epidemiological CoP studies in pregnant women

<table>
<thead>
<tr>
<th>Country/Institution</th>
<th>Study Description</th>
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<tbody>
<tr>
<td>UK/SGUL</td>
<td><strong>Feasibility study</strong> 150,000 women: cord blood and active national surveillance for GBS disease</td>
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<tr>
<td>USA/CDC</td>
<td>150 dried blood cards and 3:1 controls from prospective surveillance in newborns</td>
</tr>
<tr>
<td>SA/RMPPU</td>
<td>50,000 women to identify 150 cases and matched controls</td>
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<tr>
<td>Uganda/SGUL*</td>
<td><strong>Feasibility study</strong> 70,000 women and infants: Cord blood and hospital surveillance, aiming 70-150 infant disease cases</td>
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</tbody>
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**Industry trials**

**Ph 1/2 GBS studies in South Africa and Uganda**

**SGUL***(=)-led consortium**

**GBS assay standardization**

*SGUL* St. George’s University