Group B streptococcus vaccine R&D

Update on WHO IVB activities

PDVAC

June 2019
Why pursue a maternal GBS vaccine?

Seale AC et al. Clin Infect Dis. 2017
GBS vaccine R&D: current focus of WHO action

- Role of immune correlates of protection on pathway to licensure and policy decision
- Immuno-assays: towards WHO standards
- Epidemiologic characterization: surveillance standards
- Defeating Meningitis 2030
- Full Public Value Proposition
GBS vaccine development status

Former front-runner: Phase I/II using trivalent protein conjugate polysaccharide:

- >75% of women had >4-fold rise in specific IgG; mother-infant IgG transfer rates 50-80%
- **Lower IgG response: HIV-infected mothers; women with no baseline antibody**
- No benefit from use of alum

**Back to formulation**

New front-runner: 6-valent protein conjugate polysaccharide vaccine in Phase 1/2a

- BMGF support

MINERVAX Mixture of 2 fusion proteins of the Alp-protein family, produced in E.coli, in alum.

- Phase 1, 2 dose schedule

Partnership with **PATH** aiming to produce low cost protein conjugate polysaccharide vaccine (preclinical)
Maternal antibodies to capsular polysaccharides reduces infant disease risk

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

Maternal antibody, GBS III CPS, µg/mL

Maternal antibodies to capsular polysaccharides reduces infant disease risk

High maternal IgG levels specific to the GBS capsular polysaccharide (CPS) associated to reduced risk of newborn infection in humans

Percentage of mothers of infected (cases) or non infected babies (controls) with CPS–specific IgG serum concentrations ≥ to the value shown on the horizontal axis4

Maternal immunization may protect offspring through materno-fetal antibody transfer.
Role of correlates of protection

Acknowledging the challenge of a ‘classical pathway’ including RCT demonstration of efficacy against invasive GBS bacterial disease clinical endpoint, in the context of favourable access to standards of care

Total number of pregnant women required in a placebo-controlled trial to demonstrate the efficacy of a GBS vaccine candidate against a defined disease endpoint.

<table>
<thead>
<tr>
<th>Projected VE (LL 95% CI of 25%)</th>
<th>Expected disease rate in placebo recipients (cases per 1000 livebirths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>30,000 62,000 122,000 620,000</td>
</tr>
<tr>
<td>60%</td>
<td>90,000 180,000 360,000 1,804,000</td>
</tr>
</tbody>
</table>

Assumptions: 80% power, P<0.05 for significance, 1:1 vaccine:placebo allocation, 15% loss to follow-up, 90% cases eligibility for inclusion as per primary case definition, 95% matching between vaccine and circulating types.
• GCP quality research centres, diverse geographical areas, **baseline epi data**, **high standards** procedures, standards of care defined

• High quality **standard immune assays**, measuring bactericidal activity in serum, are developed. Supportive animal model data

• **Sero-epidemiological studies** based on predefined study protocols (timepoints, endpoints, various settings) and analysis plans (threshold or continuous model) define the relationship between antibody concentrations and disease risk (natural exposure)

• Estimates of effects are produced (aggregate across serotypes/strains and when possible, serotype/strain specific). Interaction factors characterized

• **Maternal vaccination trials**: favorable safety, immunogenicity (serotype/strain specificity, bactericidal activity) characterized in details.

• **Success criteria are pre-defined**: vaccination induces antibody levels above protective thresholds in a high, predefined proportion of recipients (or alternative robust statistical estimates based on continuous models). Aggregate estimates of effects are produced, serotype/strain specificity is investigated. Antibody persistence is demonstrated, beyond the period-at-risk. Pre-defined success criteria are passed. Factors affecting immunogenicity and antibody transfer are characterized.

• **Conditional licensure** based on indirect evidence: post-licensure Phase 4 effectiveness agreement

• **Plans for confirmatory evaluation of public health impact** based on consensus study design are developed early and **financed**.

• **Post-licensure pilot implementation studies** are conducted without delays, **leading to policy decision for wide-scale use**, country processes start, and procurement is ensured by public health agencies, informed by implementation science and analyses of full public vaccine value.
Role of correlates of protection

Ongoing sero-epidemiologic studies
Derived estimates of association between antibody levels and protection, in context of natural exposure
(US, RA, UK, Uganda)

Coordination work:
- analytical methods
- Assay standardization

Assuming favorable safety
Vaccine immunogenicity studies

Next step: develop a predefined analysis and decision framework
Towards WHO assay standards: WHO Norms and Standards
Endpoints: case definitions and ascertainment

Built on a consensus building consultation process

Seale et al. Submitted to Vaccines

Projected to be of use for epidemiology studies, vaccine trials, surveillance activities

Background to surveillance standards
The Defeating Meningitis by 2030 roadmap sets out a global strategy to achieve

Our vision

Towards a world free of meningitis

Proposed visionary goals to be achieved by 2030:

- Eliminate bacterial meningitis epidemics
- Reduce cases and deaths from vaccine-preventable bacterial meningitis*
- Reduce risk of disability and improve quality of life after all causes of meningitis

* Global and regional targets to be agreed
Five pillars for the global roadmap

to achieve the overall goals of the strategy

Prevention and Epidemic Control

Through development and enhanced access to affordable vaccines, effective prophylactic measures and targeted control interventions

Diagnosis and Treatment

Achieving access to appropriate diagnostic tests at all levels of care, to enhance surveillance and ensure patients can be promptly treated through effective antibiotics and adjunctive care

Disease Surveillance

Encompassing all main causes of bacterial meningitis and their sequelae to guide meningitis control policies and accurately monitor progress toward goals

Support and Care for people & their families after meningitis

So that the heavy burden of meningitis sequelae is recognized and alleviated in every community around the world

Advocacy and Engagement

To raise public and political awareness of meningitis as a health priority and improve health-seeking behavior and access to control measures

The strategic goals, milestones and priority activities will be tailored to the context of each region
Updated WHO Vaccine Preventable Disease Surveillance Standards

- 20 VPDs based on available vaccines, current thinking in the field, and latest laboratory techniques
- Modular document with easy to use web-interface
- Last version from 2003—now regular updates without waiting 15+ years!
### Summary of updated WHO minimum recommended VPD surveillance standards

<table>
<thead>
<tr>
<th>Country commitment</th>
<th>Nationwide, case-based with laboratory confirmation of every case</th>
<th>Nationwide, aggregate with laboratory confirmation of outbreaks</th>
<th>Sentinel, case-based with laboratory confirmation of every case</th>
<th>Other (e.g. VPDs have different minimum standard of surveillance based on context)</th>
</tr>
</thead>
</table>
| Surveillance commitment in every country | • Measles  
• Poliomyelitis | - | - | • Neonatal Tetanus (no lab confirmation) |
| Surveillance commitment varies by country | • Diphtheria  
• Meningococcus  
• Rubella  
• Hepatitis A  
• Hepatitis B  
• Mumps  
• Congenital rubella syndrome  
• H. Influenzae  
• Influenza  
• Japanese encephalitis  
• Pertussis  
• Pneumococcus  
• Rotavirus  
• Typhoid  
• Cholera (event-based)  
• HPV (surveillance not recommended)  
• Non-neonatal Tetanus (no lab confirmation)  
• Varicella (no lab confirmation)  
• Yellow fever (pending) |
GBS surveillance standards

- Same format as WHO VPD surveillance standards—1st chapter for disease with vaccine in development

- Will likely have much in common with surveillance for pneumococcus, but
  - GBS causes stillbirths and disease in very young neonates
  - Consider surveillance in pregnant women
  - GBS surveillance may need large birth cohort and defined catchment area

- WHO and CDC are leading the development of these surveillance standards
  - Will create expert working group
  - Face-to-face meeting end 2019 / early 2020
WHO and LSHTM collaboration to develop a public health value proposition for GBS vaccine

PDVAC meeting
June 2019

Dr Philipp Lambach
Raymond Hutubessy
GBS value proposition - Project goals

Develop and widely disseminate a comprehensive value proposition for Group B Streptococcus (GBS) vaccination for pregnant women (LMICs and HICs as integral part of market)

The value will be expressed by articulating the preventable burden of disease, estimating expected costs/gains from vaccinating pregnant women, feasibility considerations

Data generated, tools developed and analyses shall

- Inform investments into full development of candidate vaccines
- Advance R&D and planning of public health implementation in routine programs
- Highlight major data gaps to inform future vaccine introduction in low resource countries
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
**WS 1: Burden of disease (BoD) and medical need**

**Objectives:**

- **Burden:** To assess the complete burden of GBS disease
- **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, socio-economic outcomes
- Generation of DALYs
- Will inform economic analyses
**WS 2: Economic evaluations**

**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
WS 3: Operationalization of GBS vaccination programmes

Objectives:
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 pregnancy)
- Service delivery (integration into/optimal delivery by EPI/ANC)
- Uptake (acceptance by pregnant women, HCW)
- Planning and conducting monitoring and evaluation (coverage monitoring)

Output
- Written summary of findings (report)