Group B Streptococcus Updates for PDVAC

Kirsty Le Doare

PDVAC 12th December 2023

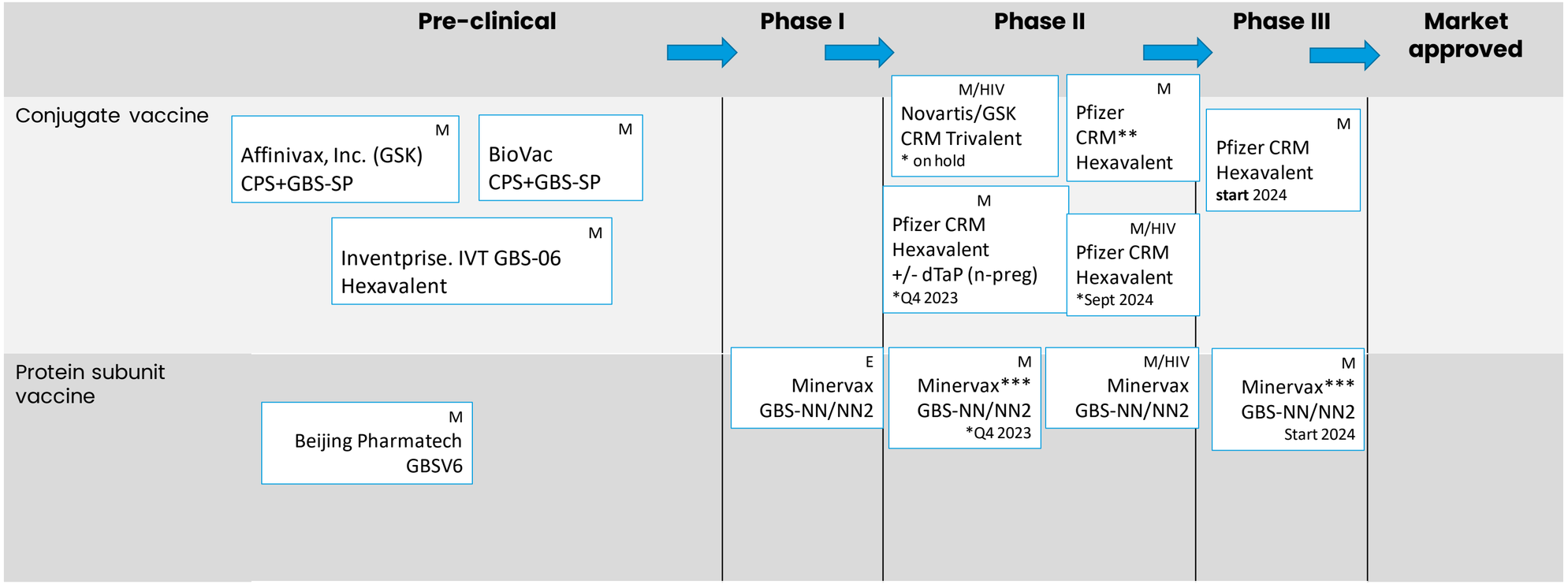
Question for PDVAC recommendation

Does PDVAC agree with the proposed approach to create regulatory consensus on the feasibility of the correlate pathway for GBS vaccines intended for use in LMICs?

GBS vaccine development pipeline

Target indications: M=maternal, E=elderly, HIV = HIV infection

Protein carrier: TT=tetanus toxoid, CRM=CRM 197, GBS-SP=GBS surface proteins



*results expected

- Clinicaltrials.gov
- EU Clinical Trials Register

Updated 3rd October 2023

**Pfizer: EMA PRIME: 22/04/2022; FDA Breakthrough Therapy Designation 7/09/2022

***Minervax EMA PRIME: 15/09/2022

Key achievements of 2023, critical issues

Key Achievements:

- Pfizer and Minervax vaccines receive EMA (Prime) and FDA (Breakthrough) designation
- Agreement on standardized assays
- First clinically validated serocorrelates of protection published

Critical Issues:

- Industry timelines regarding licensure discussions with FDA have delayed Phase III trial to 2024
- Timelines also delayed access to and development of international reference reagent
- Several issues with current correlates and sero-epidemiological studies

Disease Incidence requires prohibitively large vaccine efficacy trial

Assumptions for a 1:1 randomized controlled GBS clinical vaccine efficacy trial in a high disease incidence area						
Population disease incidence Per 1000 live births	Cases due to Vaccine serotypes	Cases eligible per protocol	Case incidence Per 1000 live births	Vaccine efficacy	Lower 95%CI bound	Sample size
2.0	75-85%	70-80%	1.05-1.35	75%	>20%	40,000 – 60,000

- Global incidence of iGBS ranges from 0.1-2.2/1000 livebirths
- **Logistical issues including:**

1. vaccination of women during pregnancy
2. follow up requirements for women in late pregnancy, for babies in the first days and weeks of life

→ **likely incidence in a trial of 0.5–1 per 1000 live births = up to 100,000 pregnant women**

↓

1. extremely rapid progression of GBS sepsis before and soon after birth
2. the need to investigate stillbirth and fatal cases
3. the needs for adequate safety oversight and efficacy monitoring requiring invasive sampling (blood and CSF) and bacteriologic analyses

Commercially unviable

Madhi 2017; Vekemans 2017

Correlate of protection as most likely pathway to licensure of a GBS vaccine

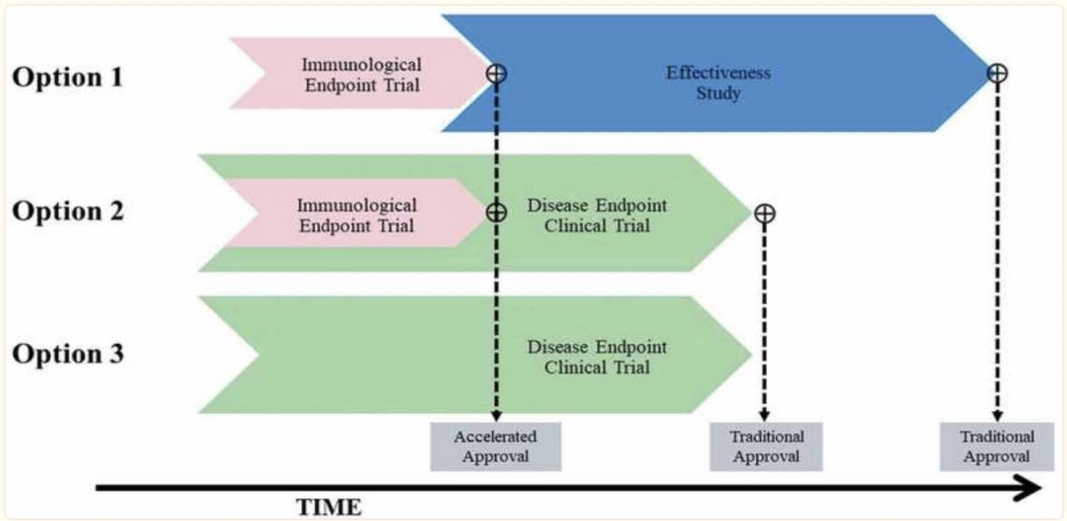


Figure 4.

Overview of potential approaches to licensure of a maternal GBS6 vaccine. Effectiveness study refers to a clinical endpoint trial that is conducted under real-world settings after vaccine licensure. Disease endpoint clinical trial refers to an efficacy trial with GBS disease as the primary study endpoint. Accelerated approval is not applicable to Option 3.

- Conditional approval
  - depends on establishing at least a putative immune correlate of protection (defined as in the CHMP and WHO guidelines).
- PRIME designation is available: known as promising innovative medicine (PIM) designation for medicines that seem promising in terms of likely ability to address an unmet need.
  - lays the path for very frequent interactions between sponsors and regulators during development
  - does not automatically lead to an accelerated assessment timetable
  - Does not predict the type of approval (i.e. conditional or full

Vaccine available at lower price:
Smaller sample size and lower cost of immunogenicity study and effectiveness study compared to an efficacy trial

HUMAN VACCINES & IMMUNOTHERAPEUTICS 2022, VOL. 18, NO. 1, e2037350
https://doi.org/10.1080/21645515.2022.2037350

Hence: could a vaccine for pregnant women against GBS be licensed based on a correlate of protection?

Quick definition

A correlate of protection is an immune response that is **statistically associated with a low risk of disease/infection**, even if it is not the actual mechanism of protection.

Absolute: a threshold- yes/no

Relative: level of response variably correlated with protection

In the context of vaccination in pregnancy this would most likely be a threshold concentration of antibody transferred via the placenta to the fetus that significantly reduces the risk of infection

How can correlates of protection be determined?

Human "challenge" studies

Epi studies

Experimental settings

Antibody administered passively e.g.

vZIG, Palivizumab

Epidemiological studies are required to identify the biomarker and threshold for a surrogate reasonably likely to predict clinical benefit

protection by (maternal) Ab

(e.g., tetanus)

responses in protected and susceptible individuals from vaccine efficacy trials

“vaccine failures”,

Immunocompromised individuals

Extrapolation from animal studies

Basis for licensure based on thresholds most likely to predict protection

ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 3816–3826

Vaccine
www.elsevier.com/locate/vaccine

Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies

George R. Siber[a,*], Ih Chang[b], Sherryl Baker[a], Philip Fernsten[a], Katherine L. O'Brien[c], Mathuram Santosham[c], Keith P. Klugman[d,e], Shabir A. Madhi[e], Peter Paradiso[a], Robert Kohberger[f]

HUMAN IMMUNITY TO THE MENINGOCOCCUS

I. The Role of Humoral Antibodies

By IRVING GOLDSCHNEIDER, M.D., EMIL C. GOTSCHLICH, M.D., and MALCOLM S. ARTENSTEIN, M.D.

(*From The Department of Bacteriology, Walter Reed Army Institute of Research, Washington, D. C. 20012*)

(Received for publication 20 February 1969)

Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study

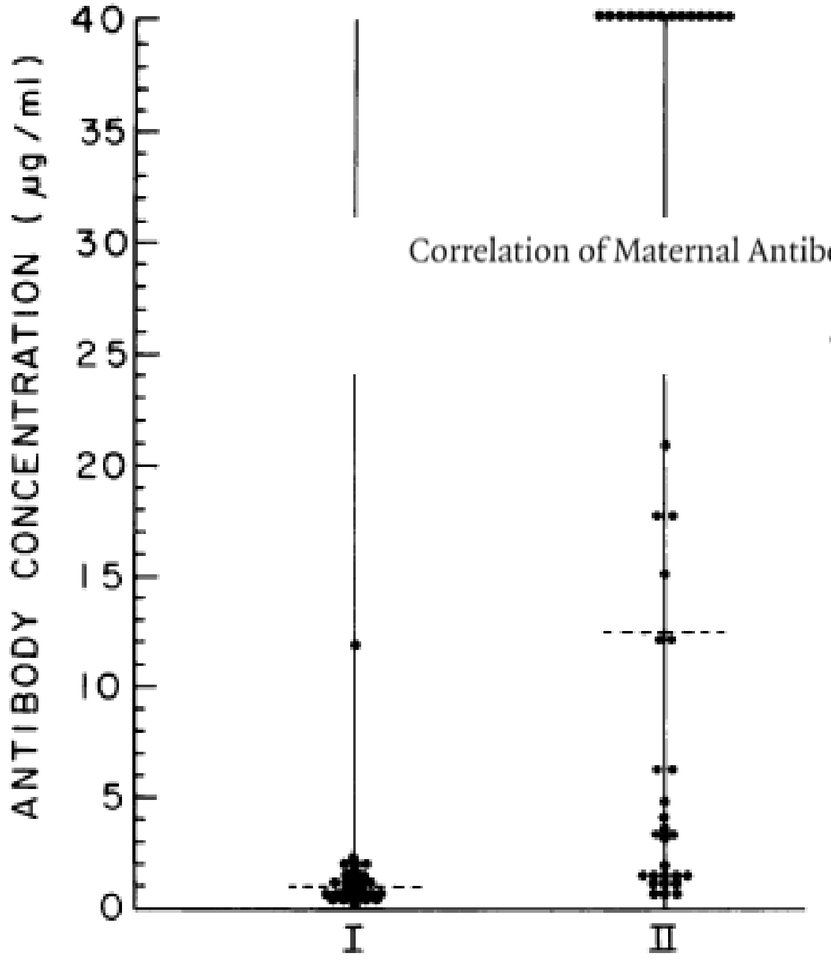
Sydel R Parikh, Nick J Andrews, Kazim Beebeejaun, Helen Campbell, Sonia Ribeiro, Charlotte Ward, Joanne M White, Ray Borrow, Mary E Ramsay, Shamez N Ladhani

A RANDOMIZED, PROSPECTIVE FIELD TRIAL OF A CONJUGATE VACCINE IN THE PROTECTION OF INFANTS AND YOUNG CHILDREN AGAINST INVASIVE *HAEMOPHILUS INFLUENZAE* TYPE b DISEASE

Juhani Eskola, M.D., Helena Käyhty, Ph.D., Aino K. Takala, M.D., Heikki Peltola, M.D., Pirjo-Riitta Rönnberg, R.N., Eija Kela, R.N., Eeva Pekkanen, R.N., Patrick H. McVerry, Ph.D., and P. Helena Mäkelä, M.D.

- For pneumococcus an aggregate IgG serocorrelate value based on results from three clinical efficacy trials was agreed by consensus to be 0·35 µg/mL.
- Importantly, a common assay was needed to support this work in order to combine data from the different trials and laboratories.

Placentally transferred antibodies are associated with disease protection

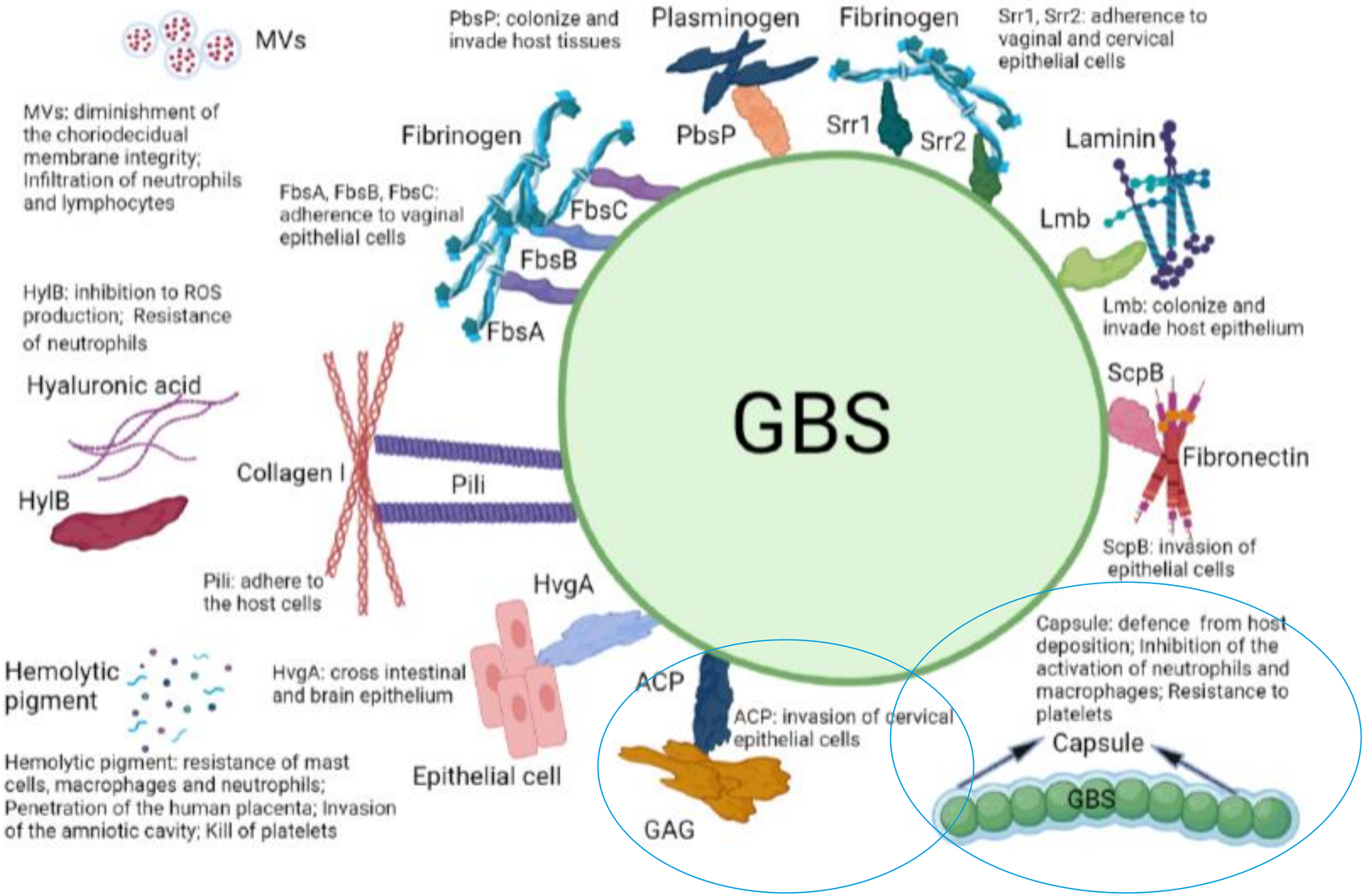


Correlation of Maternal Antibody Deficiency with Susceptibility to Neonatal Group B Streptococcal Infection

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

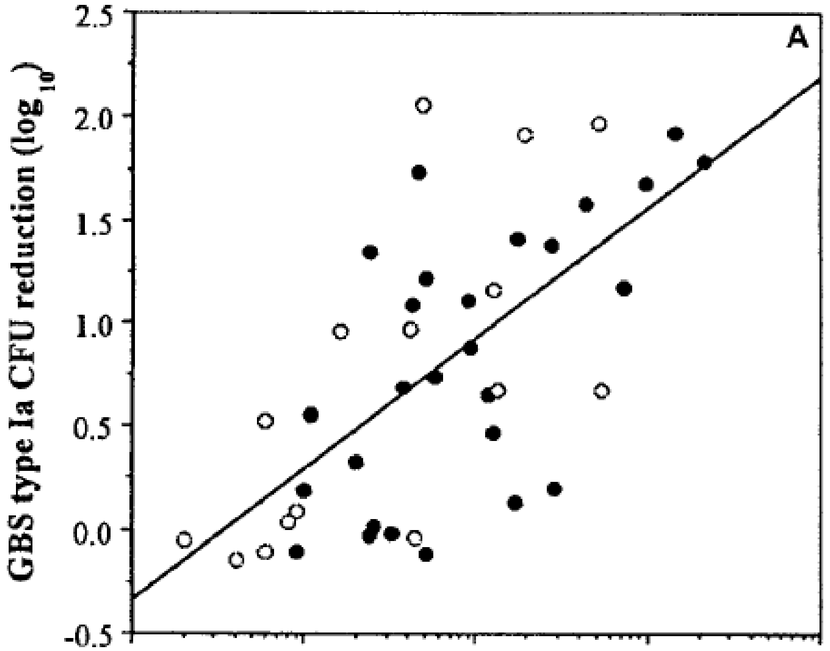
Baker 1976

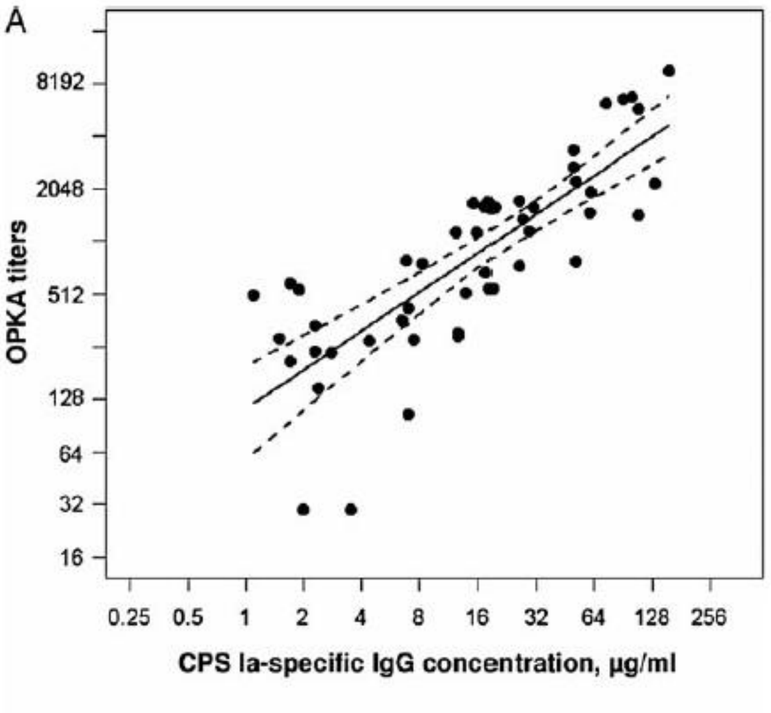
Target antigens for vaccines include capsular polysaccharide and surface proteins



Liu 2022

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





Baker 1999, Fabbrini 2016

The problem with functional thresholds of protection in maternal vaccine studies

Target Antigen	Functional Assay	Alternative Assay
Tetanus/diphtheria	Toxin neutralization assay	IgG binding assay
Hib/Meningococcus	Serum bactericidal assay	IgG binding assay
Pneumococcus	Opsonophagocytosis killing assay	IgG anti-capsular polysaccharide ELISA
Influenza	Plaque neutralization assay	Hemagglutination inhibition

For GBS:
1. Up to 40% of women will receive antibiotics in labour
2. Functional assays are extremely labour intensive in a large trial
3. Functional assays more difficult to standardize than binding assays

BUT

May help bridge the gap between natural and vaccinee immunity

Unique case for Group B Streptococcal vaccines

Unlike for Hib, meningococcal or pneumococcal vaccines:

1. No previous assessment of vaccine efficacy for any GBS vaccine formulation prior to licensure
2. A threshold for a GBS vaccine derived from natural immunity followed by demonstration of protective threshold following immunisation using standard assays and reagents.
3. Possible need for different thresholds for different vaccine platforms (polysaccharide versus protein vaccines).
4. Possible need for different biomarkers for different disease endpoints (EOD, LOD, Stillbirth)

GBS assay standardization consortium

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

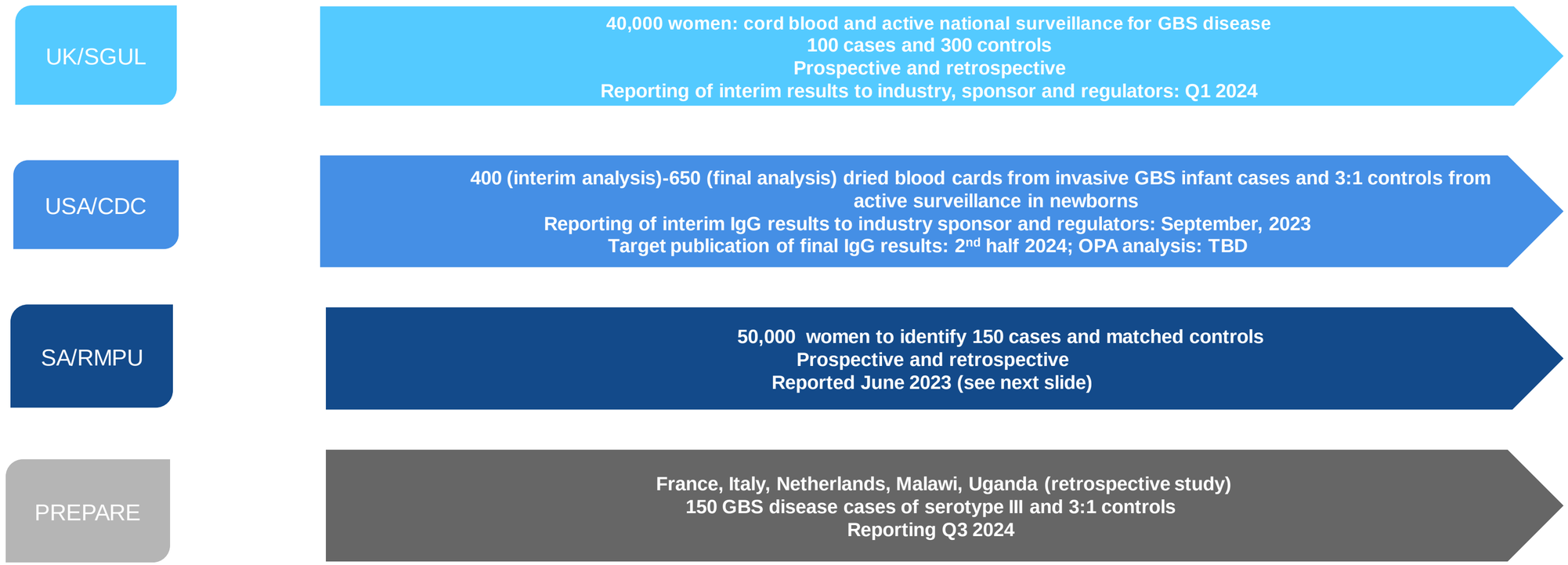
Objective 2: development of protocols for antibody quantity and function using standard reagents

Objective 3: validation of standard protocols and standard reagents across laboratories to establish a prediction of disease protection

Industry expertise

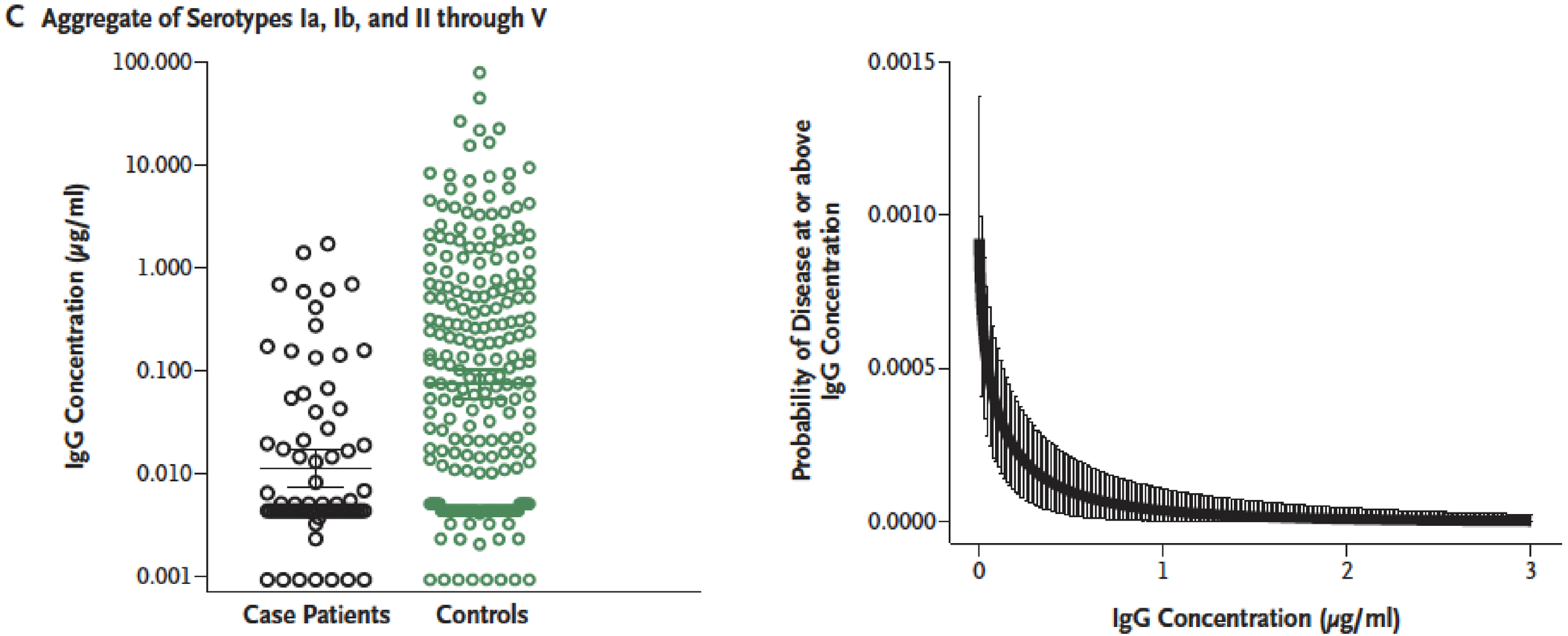
GBS vaccine path to licensure based on threshold of protection – EMA/FDA opined supportively

Sero-epidemiological studies in pregnant women and their infants
Prospective = blood (cord or infant) at birth and follow up to 3 months to investigate disease
Retrospective = infant blood taken at time of disease



*SGUL St. George's University

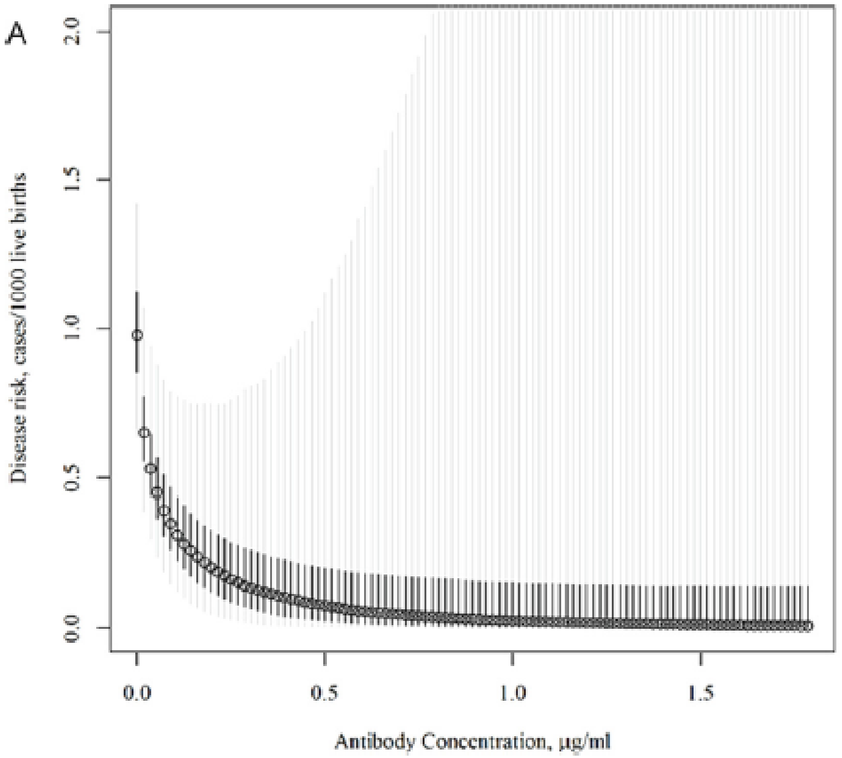
Aggregate correlate of protection recently published in natural immunity study from South Africa



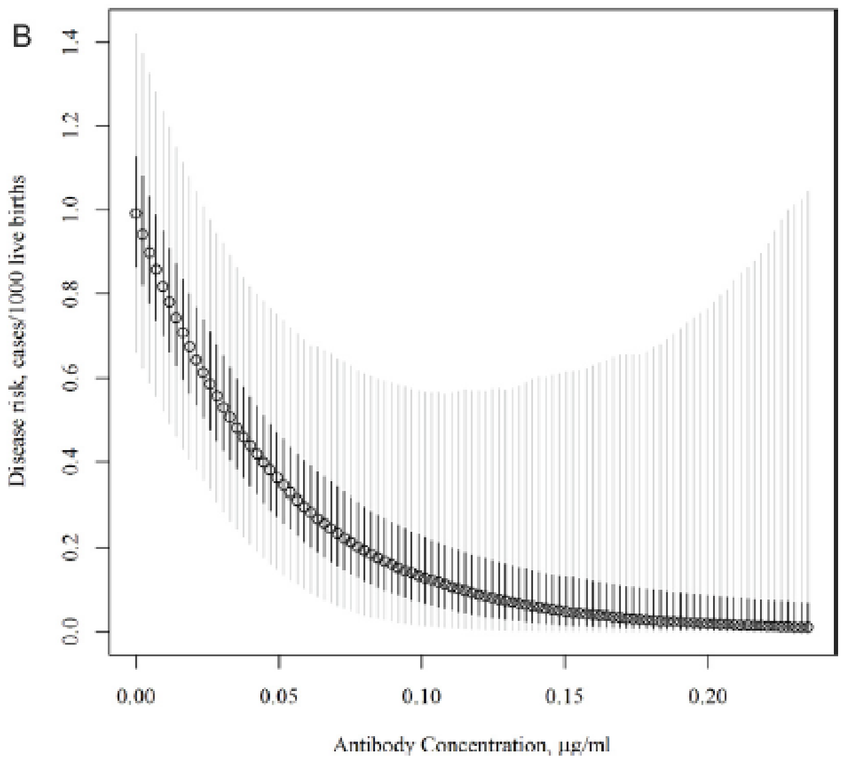
53-94% of infant blood samples reached threshold of 75% risk reduction dependent on serotype

Madhi 2023

90% risk reduction for RibN and Alp1N antibodies in natural immunity study from South Africa



Rib



Alp

Dangor 2023

Regulatory meeting updates

Virtual meeting held on 6th September attended by 34 regulators/NITAG members from South America, Africa and Asia

Purpose of the meeting was to convene regulators and policymakers to discuss Group B Streptococcal (GBS) vaccines and potential pathways to licensure and key considerations of each approach.

Three potential approaches were discussed:

- Option 1: Immunologic endpoint trial followed by a vaccine effectiveness study – most likely approach
- Option 2: immunologic endpoint trial embedded in a disease endpoint clinical trial.
- Option 3: disease endpoint clinical trial
- Both EMA and FDA have previously agreed in principle that a pre-licensure efficacy study could be waived if a sponsor proposes an acceptable putative immunologic correlate of protection (ICP)

Key issues to consider from regulatory discussions

- Key considerations for a GBS vaccine – this would be one of the first vaccines to be licenced without ANY prior data on efficacy from related vaccines or populations. Chikungunya was recently licenced in this way.
- Regulators consider approval on a threshold or an ICP. However, there are now concerns that manufacturers have moved beyond functional antibody and rely solely on antigen-specific IgG concentrations. As partial protection in natural immunity is likely to come from antibodies against both capsular polysaccharide and sub-capsular antigens, this is unlikely to be sufficient and may underestimate protection.
- For licensure based on an immunological endpoint, biomarkers should ideally be demonstrated to correlate to protection for each serotype or justification provided about why this is not possible AND a correlation between OPkA and antigen-specific IgG concentration should be demonstrated for EACH serotype in the submission package.
- If composite endpoints (e.g. disease, stillbirth, preterm birth, colonisation) are to be submitted then the immunological pathway to disease for each of the different serotypes should be more robustly demonstrated for each of the outcomes
- Discussion on composite endpoints and whether we should consider colonisation as part of the composite endpoint given that there is evidence from other polysaccharide conjugate vaccines, e.g. PCV and MenC, reduce colonisation. Difficult to correlate colonisation with serum antibody concentrations but acquisition of colonisation in the 2nd or 3rd trimester might be relevant.
- Burden estimates were requested from several countries/regions
- WHO PQ will be key to vaccine licensure in the Africa region

Recent discussions

1. Difficulties with regulatory packages submitted, especially with consensus on the need to demonstrate that the measured IgG concentration correlate is functional (i.e. linking between binding and functional assays)
2. Issues with combining retrospective and prospective cases
3. Difficulties in serocorrelate studies with prospective collection: recent Madhi study 28/17,752 were prospective; 90 were retrospective

WHO regulatory meeting convening – in discussion February 2024

Regulatory meeting - aims

A two day, virtual workshop with regulators and experts in correlates of protection and analyses

1. Consensus opinion about approach to a correlate of protection for licensure of a GBS vaccine

ECVP is in advanced draft but will be placed on hold until there is clarity on the pathway forward

Considerations for SAGE

- For information meeting in discussion for March 2024

- Benefits and harms plus GRADE
- (Values and Preferences)
- Resource use and cost-effectiveness
- (Equity impacts)
- Acceptability
- Feasibility

- Burden of disease, impact modelling, different clinical endpoints
- Robustness of correlates: clear threshold? Threshold different for clinical endpoints? Different correlates for different vaccine platforms? Composite endpoints?
- Is there a large effect size? Precision? Downgraded for indirectness. Results in high risk populations (obesity, diabetes). Duration of efficacy?
- Safety: bar high because of pre-term births associated with RSV maternal immunization
- Cost-effectiveness, proxy: number needed to vaccinate (present by different clinical endpoints)
- Acceptability of maternal immunization
- Co-administration with other vaccines, timing of administration (flexibility with schedules: only second-trimester, what about late presentation at 37 weeks?). One dose versus two doses
- Cold chain, multidose vials, etc

Question for PDVAC recommendation

Does PDVAC agree with the proposed approach to create regulatory consensus on the feasibility of the correlate pathway for GBS vaccines intended for use in LMICs?

Thank you

GBS Technical Advisory Group – 2023 summary

World Health Organization

1. **GBS TAG (Virtual) May 5th:**
    - prepare for regulatory convening to discuss pathways to licensure for a GBS vaccine for use in LMIC and post-licensure surveillance methods
    - Update on key issues in GBS disease and sero-epidemiology studies;
    - Update the TAG the WHO international GBS reference serum and harmonized assay methods currently under development;
    - Discussion and plan for drafting ECVP for GBS vaccine

2. **Regulatory convening September 6th:**

    Discussion focussed on:
    - Relative merits of an Immune Correlate of Protection (ICP) versus a definition of a threshold value
    - Necessity for measurement of functional antibody in addition to binding antibody for licensure
    - Composite clinical endpoints including invasive disease, stillbirth and preterm birth then pathway to disease for each of the relevant serotypes should be more robustly demonstrated

3. **GBS TAG (F2F), Rio de Janeiro following the 3rd International Symposium on 'Streptococcus agalactiae, November 19th:**
    - Gaston Consortium Updates on Assay Harmonisation and development of (international) standards.
    - Manufacturer Updates
    - Review ECVP tables
    - Review Regulatory discussions

David Goldblatt/TAG Co-chair

Status for MinervaX Maternal GBS Vaccine

- Clinical Data
  - Phase 2a (SA/UG) and Phase 2b (SA/UK/DK) completed in total of 370 HIV negative and 100 HIV positive pregnant women
  - Vaccine has acceptable safety profile warranting progression to Phase III
  - Post hoc pooling of safety data shows an approximate halving of incidences of preterm birth and stillbirth (total N in the pooled cohort, excl drop-outs: 384 active/76 placebo)
  - IgG data shows 90-100% of infant cords reaching preliminary 90% CoP threshold for two doses across Europe and Africa, as well as a single dose in Africa (EU cohort too small for meaningful assessment)
  - Induction of high OPkA killing titres also observed in infant cord
- Manufacturing
  - Phase III material manufactured to GMP – Pre-assembled liquid vaccine formulation stored at 2-8°C
  - Both single-dose and multi-dose vials will be explored for commercialization
- Phase III Planning
  - Phase III preparations ongoing – expected start in 2024
  - Efficacy likely based on surrogate functional CoP endpoint (OPkA)
  - Both two-dose and single-dose regimens to be explored

Overview of Pfizer GBS vaccine program

GBS6 vaccine

- Hexavalent polysaccharide CRM_{197} conjugate vaccine containing serotypes Ia-V, covering >98% of disease
- Maternal vaccine designed to protect infants against invasive GBS disease in first 90 days of life
- Dose/formulation: 20 µg dose per serotype without $AlPO_4$

Phase 1/2 study C1091002

- GBS6 has an acceptable safety profile in pregnant women and their infants
- GBS6 induced robust immune responses to all 6 serotypes in pregnant women
- GBS6-elicited antibodies were transferred to infants at concentrations associated with a reduced risk of invasive group B streptococcal disease based on natural immunity
- Based on safety and immunogenicity, 20 µg dose without $AlPO_4$ selected for evaluation in Phase 3

Phase 3 study C1091009

- Pivotal study for licensure, immunological endpoint trial
- Phase 3 design being discussed with regulators
- Safety database: 3000 maternal participants
- Global study in HIC and LMIC
- Timelines under discussion

Buurman E, et al. JID. 2019; 220(1):105-115; Absalon J, et al. Lancet Infect Dis. 2021; 21(2):263-74; Madhi S, et al. *N Engl J Med* 2023; 389:215-227