Developing a Group B Streptococcus vaccine for maternal immunisation: challenges for clinical development in a low-incidence, high impact infectious disease setting

10 December 2025

Lidia Oostvogels, CMO MinervaX

2nd IABS Real World Evidence Workshop : The Role of Alternative Approaches to Phase 3 Clinical Trials for Vaccine Efficacy and Licensure

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Group B Streptococcus background and medical need

GBS IS A PREVALENT HUMAN COMMENSAL PUTTING PREGNANT WOMEN AND NEWBORNS AT RISK

GBS colonizes

- Gastrointestinal & Urogenital tracts
- Skin, respiratory tract, and breast milk

~20% carry GBS at any one time

- Colonization last from 1 mth to > 1yr
- Most have carried GBS at some point

GBS colonization is acquired from

- Touch, airways, and sexual transmission
- Food, breast feeding, and pets!

Colonization is mostly non-symptomatic

GBS colonization in pregnant women can lead to:

Adverse pregnancy outcomes

- In utero GBS infections of unborn infant
- Resulting in Preterm Delivery & Stillbirth
- Birth of a very sick infant

Neonatal infections

- Early Onset Disease 0-6 days of age (EOD)
- Late Onset Disease 7-89 days of age (LOD)
- Sepsis, pneumonia, meningitis
- 80% of meningitis <3 months of age
- Neurodevelopmental outcomes in meningitis survivors: up to 18% have moderate to severe impairment**

5%
Placentas colonized

>3.5%
of Preterm births

1-4%
Of all Stillbirths

0.5-2.5
in 1.000 live births

1.530
Cases in US annually

8%
Fatality rate*
- EOD: 10% (5% in HIC, 27% in Africa)
- LOD: 7% (4% in HIC, 12% in Africa)

50%
Hospitali

* Madrid L, et al. 2017 ** Kohli-Lynch M, et al. 2017

CURRENT PROPHYLACTIC MEASURES IN PREGNANT WOMEN AND NEWBORN BABIES ARE INSUFFICIENT

High-income countries

>90% Pregnant women routinely screened for presence or risk of GBS colonization*

Intrapartum antibiotic prophylaxis (IAP) administered to GBS-positive women

Despite IAP prophylaxis, 0.5 in 1.000 live births still fall sick to invasive GBS disease

IAP **only** effective against **Early Onset Disease** (but still ~50% EOD disease in newborns)

IAP has **no effect** on **adverse pregnancy outcomes** and **Late-Onset Disease**

IAP has **resulted in** **antimicrobial resistance** ultimately threatening current use of IAP

Middle & low-income countries

Mostly no GBS screening or IAP

Full impact of GBS infections

A maternal vaccines could address shortfalls of current prophylaxis, prote
mother directly and infant via placental transfer of antibodies

*) Screening may be culture- or risk-based.

STRONG SUPPORT FROM GLOBAL HEALTH ORGANIZATIONS FOR MATERNAL VACCINE

World Health Organization

- Preferred Product Characteristics developed
- Heatlh Economics developed with LSHTM (London School of Hygiene & Tropical Medicine)
- SAGE (Strategic Advisory Group of Experts on Immunization) mapping landscape and prepping African regulators on Phase III and post-licensure commitments
- TAG (Technical Advisory Group) on GBS formed

Global Alliance for Vaccine & Immunization, GAVI

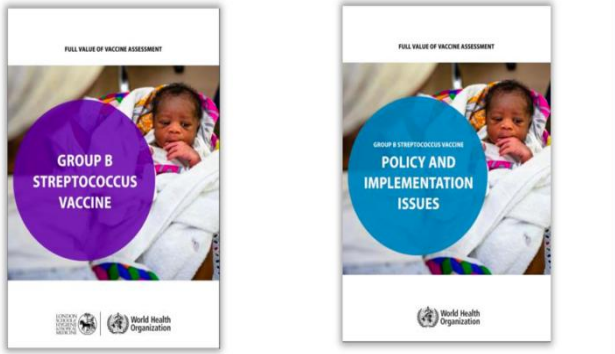
- Next five-year strategy; outlines plans to support access to Group B Strep vaccines, June 7, 2024

Joint Committee on Vaccination and Immunization, UK

- Monitoring landscape and committed to implement GBS vaccine based on Accelerated Licensure

WHO commissioned assessment of global impact of GBS

Published in Nov-21, report describes i) global public health rationale for GBS vaccines for maternal immunization and ii) inform decision making across the continuum of vaccine development and uptake with a line of sight to sustainable public health impact

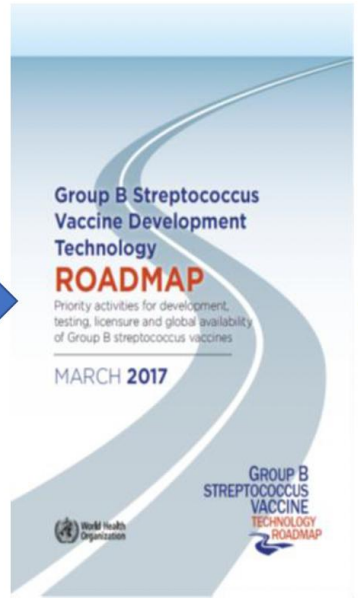


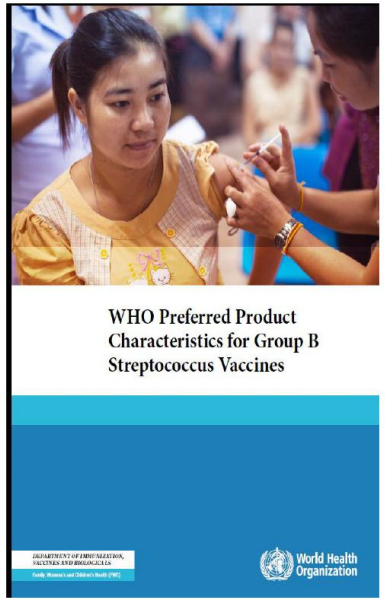
This new research shows that Group B str
appreciated threat to newborn survivo
devastating impacts for so many famil
in calling for urgent development of
***would have profound benefits** in cou*

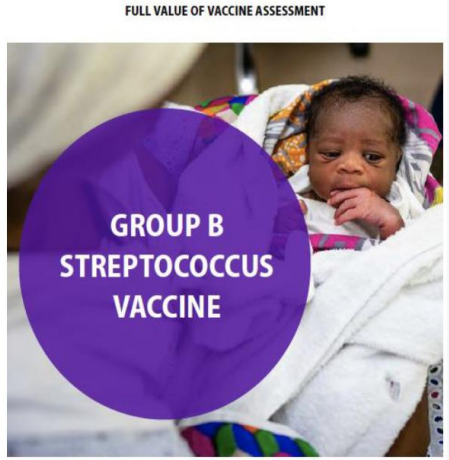
Medical Officer, WHO Immu

TOWARDS A GBS VACCINE

2015 PDVAC identified the development of maternal GBS vaccines to prevent stillbirth and infant disease suitable for use in LMIC as a priority







London School of Hygiene & Tropical Medicine | World Health Organization

Clinical Infectious Diseases

VIEWPOINTS

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

The Path to Group A *Streptococcus* Vaccines: Organization Research and Development T… Roadmap and Preferred Product Charact…

Johan Vekemans,[1] Fernando Gouvea-Reis,[1] Jerome H. Kim,[2] Jean-Louis Excler,[2] Pierre R. Smeesters,[3,4,5,6] Andrew C. Steer,[5,9,10] Jonathan R. Carapetis,[11] and David C. Kaslow[12]

[1]Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland; [2]International Vaccine Institute, Seoul, Republic of Kore… de Bruxelles, and [4]Department of Pediatrics, Academic Children Hospital Queen Fabiola, Brussels, Belgium; [5]Tropical Diseases Research Gro… for International Child Health, University of Melbourne, Australia; [7]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [8]… Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [9]Department of Paediatrics, University of … and [11]Telethon Kids Institute, University of Western Australia and Perth Children's Hospital, Australia; and [12]PATH, Seattle, Washington

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TARGET PRODUCT PROFILE MATERNAL (WHO)

- Indication: Prevention of lab confirmed GBS stillbirth and invasive GBS disease in neonates and young infants
- Target Population: Pregnant Women, 2nd/3rd trimester
- Schedule: Single dose preferred, but two may be required
- Safety: At par with other WHO recommended vaccines for pregnant women
- Efficacy: 80% against still birth and invasive neonatal disease
- Immunogenicity: Established correlate/surrogate of protection based on validated assay measuring antibody levels/functionality in the mother and/or the neonate
- Coverage: >90% of invasive GBS isolates in target region
- Interference: Non-interference with other pregnancy or infant vaccines

https://iris.who.int/bitstream/handle/10665/258703/WHO-IVB-17.09-eng.pdf?sequence=1

INVASIVE DISEASE IN NON-PREGNANT OLDER ADULTS HAS INCREASED SIGNIFICANTLY OVER PAST 20 YEARS

Invasive GBS disease affects mostly older adults >65 yr

- Incidence of 20-30 per 100.000*

Affected individuals mostly have co-morbidities:

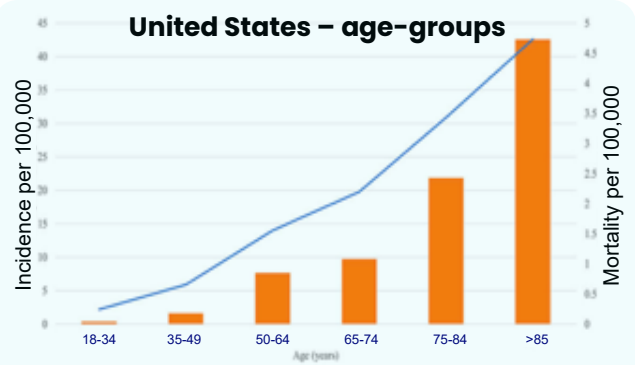
- Diabetes/Obesity
- Cardio-vascular Disease

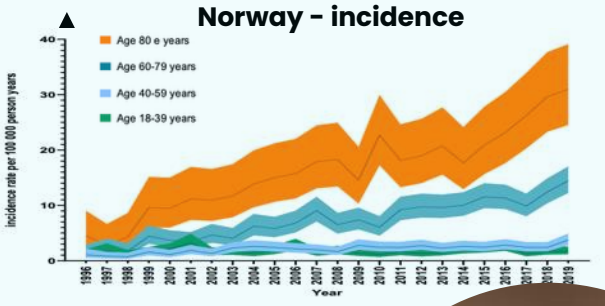
Incidence and medical need for prevention is rising

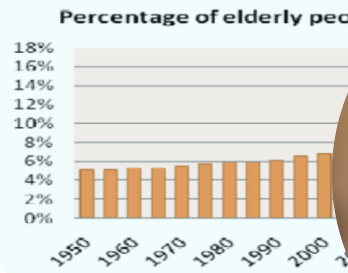
- Incidence has more than doubled over past 20 years
- General population is aging significantly

Older Adult Vaccination may be warranted

- Incidence approaching that of GBS in newborn infants
- Hospitalisation: 95%; Fatality rate 5% (3-6%)



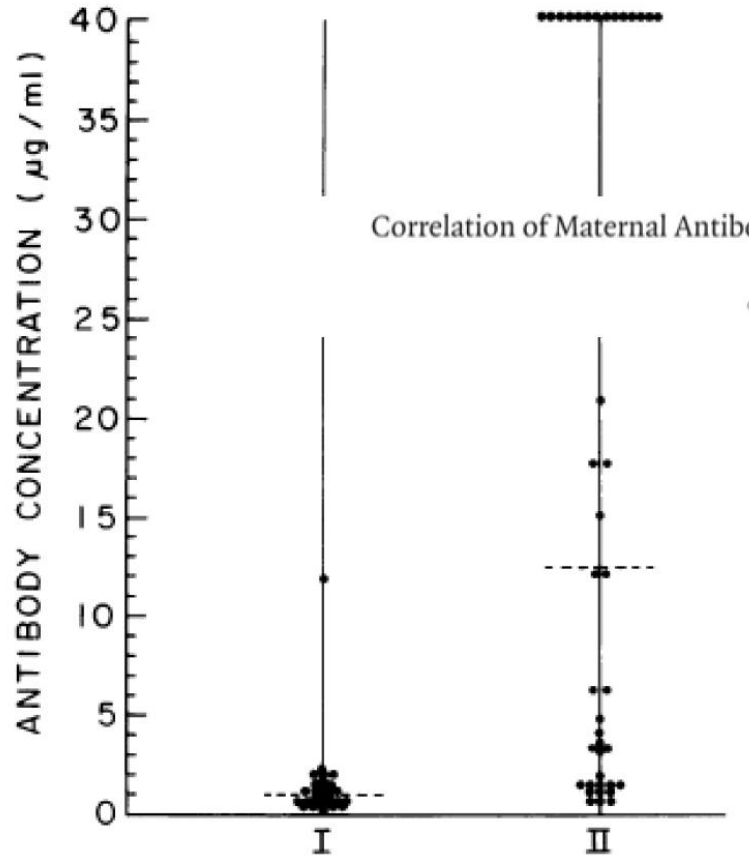




* Navaro-Torne et al (PLOS ONE 2021: 16(9): e0258030); Watkins et al, (JAMA Int Med, 2019)

Group B Streptococcus maternal vaccine development

ANTIBODIES TRANSFERRED VIA THE PLACENTA ARE ASSOCIATED WITH PROTECTION AGAINST iGBSd



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 197

MATERNAL VACCINE FOR THE PREVENTION OF INVASIVE GROUP B STREPTOCOCCUS DISEASE IN INFANTS

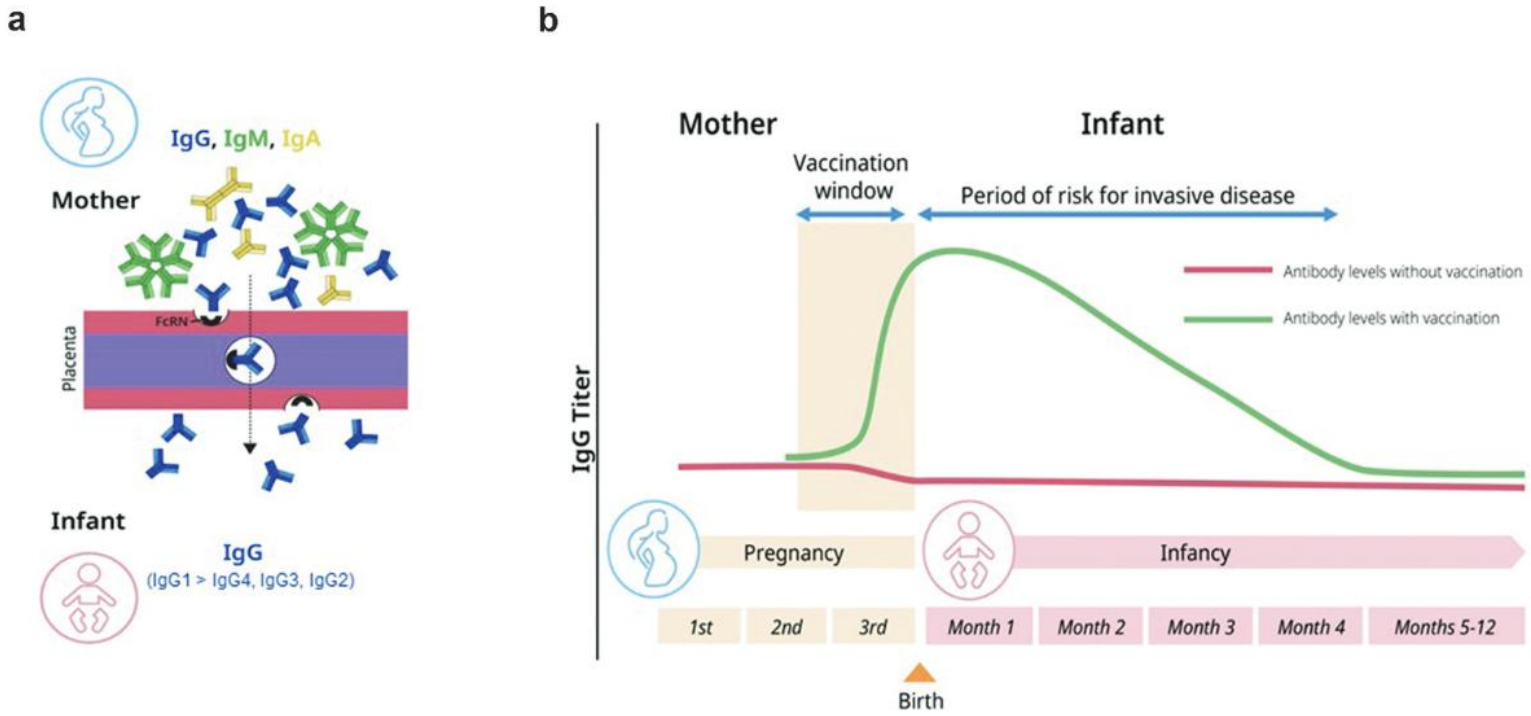


Figure 1. Schematic representation of the presence of immunoglobulins in infants due to maternal vaccination. (a) Maternal IgG is selectively transporte placenta by the neonatal Fc receptor (FcRN). (b) Maternal vaccines augment or induce maternal antibody levels to protect the infant from infectious di few months of life.

HUMAN VACCINES & IMMUNOTHERAPEUTICS 2022, V
https://doi.org/10.1080/21645515.2022.2037350

Mode of Action:

- Direct protection of immunized individual (pregnant person incl foetus)
- Transfer of antibodies across placenta protects infants for first 3 months of life

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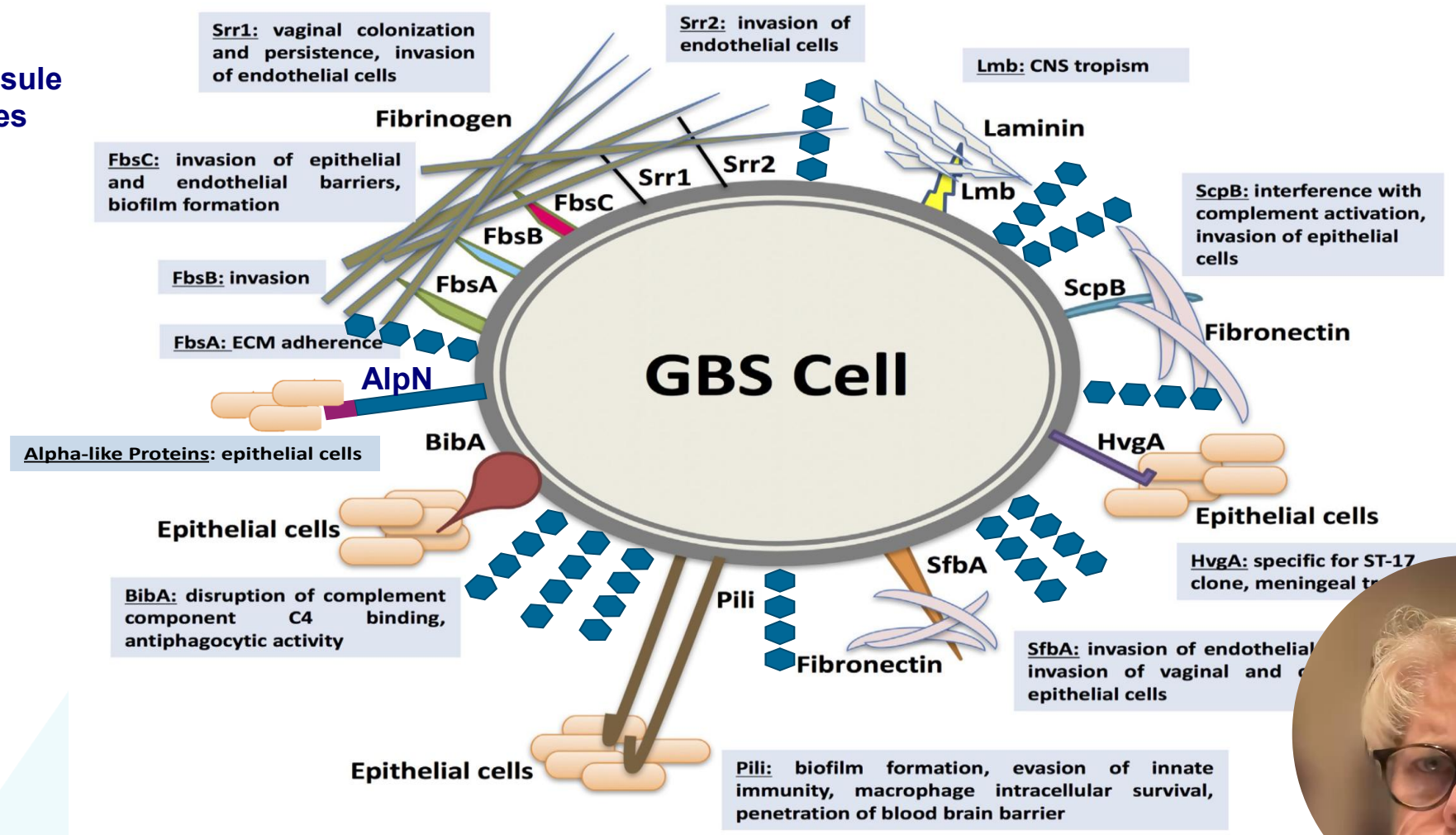
TARGET ANTIGENS FOR VACCINE INCLUDE CAPSULAR POLYSACCHARIDE AND SURFACE PROTEINS

Polysaccharide Capsule
10 Capsule Serotypes
CPS Ia, Ib, II-IX



Vaccine Targets:

- CPS
- AlpN
- Pilus
- BibA
- FbsA

and Spellerberg B (2018) Fr iol. 9:437

VACCINES CURRENTLY IN CLINICAL* DEVELOPMENT (FOCUS MATERNAL IMMUNISATION)

Company	Construct	Comments
Minervax	• Protein based: 4 out of 5 N-terminal domains of the Alpha-like GBS surface protein family, AlpN • AlOH adjuvant	• Maternal: 2 Ph I and 2 Ph II trials completed, LTFU Ph I and Ph II ongoing • Maternal program pivotal trial under preparation – based on Surrogate Endpoint Marker • Older/At Risk Adults: 1 Ph I trial completed
Pfizer	• 6-valent CPS • CRM_{197}-conjugate	• 2 Phase I trials completed and Phase II data available • Phase III IgG Surrogate endpoint trial – ongoing since Aug 2025
Inventprise	• 6-valent CPS • CRM_{197}-conjugate	• Phase I-II ongoing

*Further vaccines are in preclinical development

Group B Streptococcus pathway to licensure

LICENSURE APPROACHES OF MATERNAL GBS VACCINE

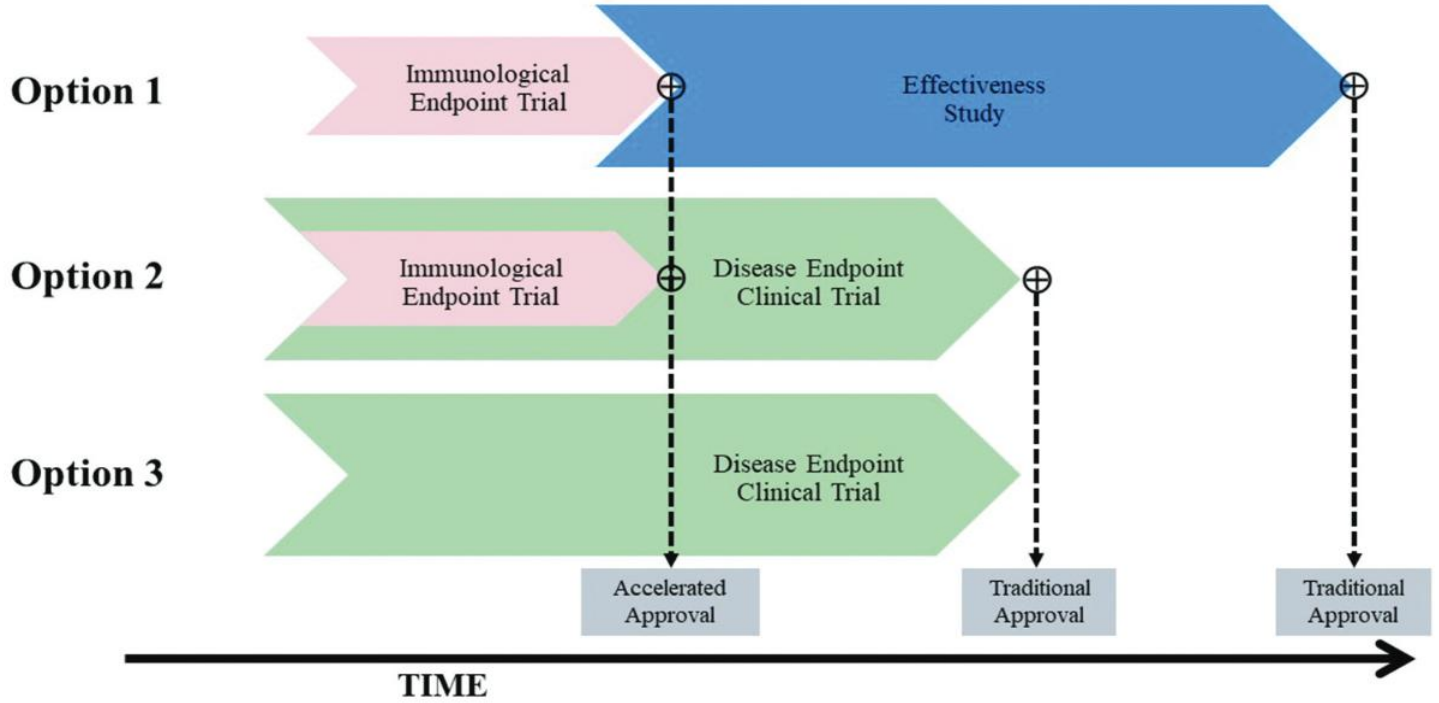


Figure 4. Overview of potential approaches to licensure of a maternal GBS6 vaccine. Effectiveness study refers to a clinical endpoint trial that is conducte world settings after vaccine licensure. Disease endpoint clinical trial refers to an efficacy trial with GBS disease as the primary study endpoint. Accelerated a applicable to Option 3.

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https://doi.org/10.1080/21645515.2022.2037350

VACCINE DEVELOPMENT STRATEGY TO PREVENT INFANT GBS: MATERNAL VACCINATION: CHALLENGES

- A GBS phase III clinical trial to demonstrate efficacy against infant iGBS disease, would require at least 60.000 woman/infant pairs in countries with an iGBS incidence >1:1000 live births* - leading to up to 120.000 trial participants.
- Challenging clinical endpoints:
  - iGBSd: potential to lose cases due to administration of Antibiotics before bloodculture is taken
  - Stillbirth, Premature Birth:
    - Difficult to demonstrate GBS is the (only/main) causal agent due to potential colonisation of mother (birth canal)
    - Autopsy on newborn/stillborn is not routinely done; and emotional burdensome
- Alternative approach for licensure of maternal GBS vaccines*:
  - Evaluation of safety
  - Insights into efficacy based on evaluation of serological thresholds of risk reduction (

*: Clinical and regulatory development strategies for GBS vaccines intended for maternal immunisation in low- and middle-income countries; Kirsty Le Doare et al in Vaccine, Volume 58 (11 June 2025) https://www.sciencedirect.com/science/article/pii/S0264410X25004281

EXAMPLE OF SAMPLE SIZE CALCULATION FOR VE RCT

Rationale for market approval based on an immune correlate of protection

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

NATURAL IMMUNITY AND 'CORRELATES OF PROTECTION'

- Naturally occurring antibodies against multiple GBS antigens exist in most individuals due to a life-time of exposure
- Maternal GBS antibodies are transferred across the placenta to the foetus
- Low levels of antibodies correlate with increased risk of invasive neonatal disease
- (Preliminary) 'correlates of protection' have been developed for natural anti-CPS and anti-AlpN antibodies
- Functional antibodies required in the newborns, so CoPs shou 
ideally be based on OPkA in cord blood

POTENTIAL TO LICENSE BASED ON SURROGATE EFFICACY MARKER

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

The role of immune correlates of protection on the pathway to licensure, policy decision and use of group B *Streptococcus* vaccines for maternal immunization: considerations from World Health Organization consultations

Johan Vekemans [a,*], Jonathan Crofts [b], Carol J. Baker [c], David Goldblatt [d], Paul T. Heath [e], Shabir A. Madhi [f], Kirsty Le Doare [e], Nick Andrews [g], Andrew J Pollard [h], Samir K. Saha [i], Stephanie J. Schrag [j], Peter G. Smith [k], David C. Kaslow [l]

'An alternate approval pathway, based on safety and an immunological endpoint thought to predict clinical benefit (commonly referred to as serological threshold of risk reduction [SToRR]), is being considered for GBS maternal vaccines.'

Vaccine 58 (2025) 127131

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

Clinical and regulatory development strategies for GBS vaccines intended for maternal immunisation in low- and middle-income countries

Kirsty Le Doare [a,b,c,*], Virginia Benassi [a], Marco Cavaleri [d], Godwin Enwere [e], Birgitte Giersing [a], David Goldblatt [f], Paul Heath [b], Joachim Hombach [a], Richard Isbrucker [g], Kostas Karampatsas [b], Shabir A. Madhi [h], Annelies Wilder Smith [a]

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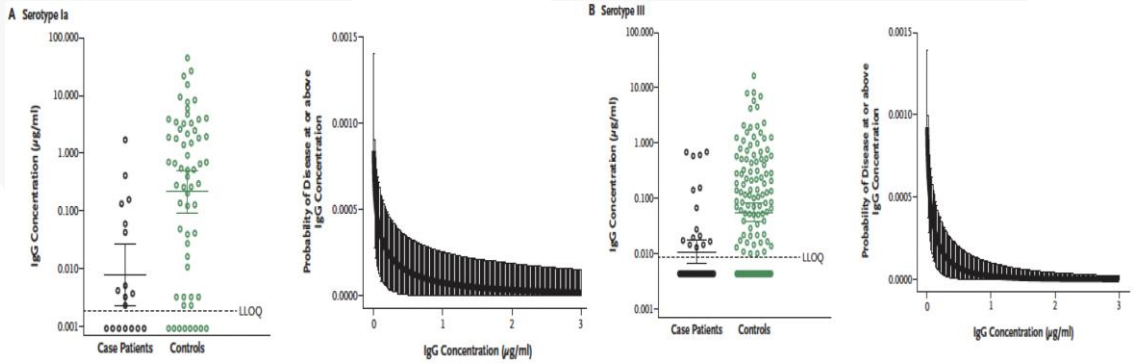
[f] Great Ormond Street Institute of Child Health, University College London, UK
[g] Biologic and Radiopharmaceutical Drugs Directorate, Health Canada, Ottowa, Canada
[h] South Africa Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Infectious Diseases and Oncol
Science, University of the Witwatersrand Johannesburg, South Africa

MATERNAL GBS VACCINES DEVELOPMENT

› GBS6 vaccine (Pfizer):

- Correlate of protection published
- Ph 3 ongoing: BEATRIX*: A Study to Learn About a Group B Streptococcus Vaccine in Healthy Pregnant Women and Their Babies
  - Relative risk reduction in proportion of infants with IgG concentration below predefined thresholds
  - Aggregate predicted VE based on IgG concentrations



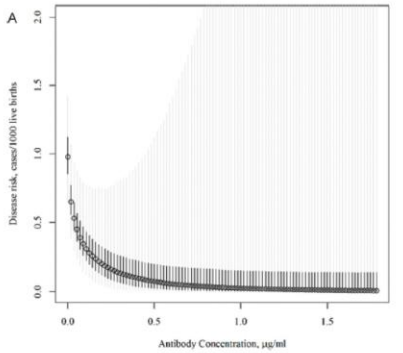
80% risk reduction with IgG concentrations of 0.198 for serotype III alone and 0.246 ug/mL all serotypes combined

Madhi 2023

› GBS-AlpN vaccine (GBS-NN/NN2) :

- Interactions with regulatory agencies on Surrogate Efficacy Marker-based licensure pathway

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



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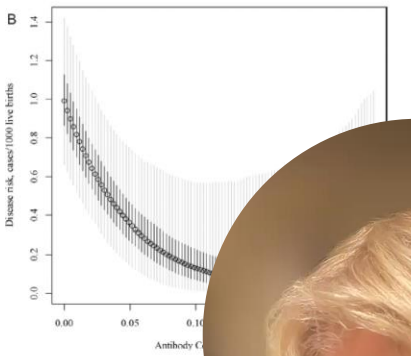

Alp

*ClinicalTrials.gov ID NCT07160244

Group B Streptococcus conclusion

SUMMARY AND CONCLUSION

- **Invasive GBS disease represents a global medical burden with potentially devastating impact during pregnancy and in infants**
  - But incidence is too low to operationalize a Randomised Clinical Efficacy Trial for licensure
- **Licensure likely based on safety and a serological threshold of risk reduction [SToRR])**
  - Followed/supported by Real World Evidence data

Thanks!

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