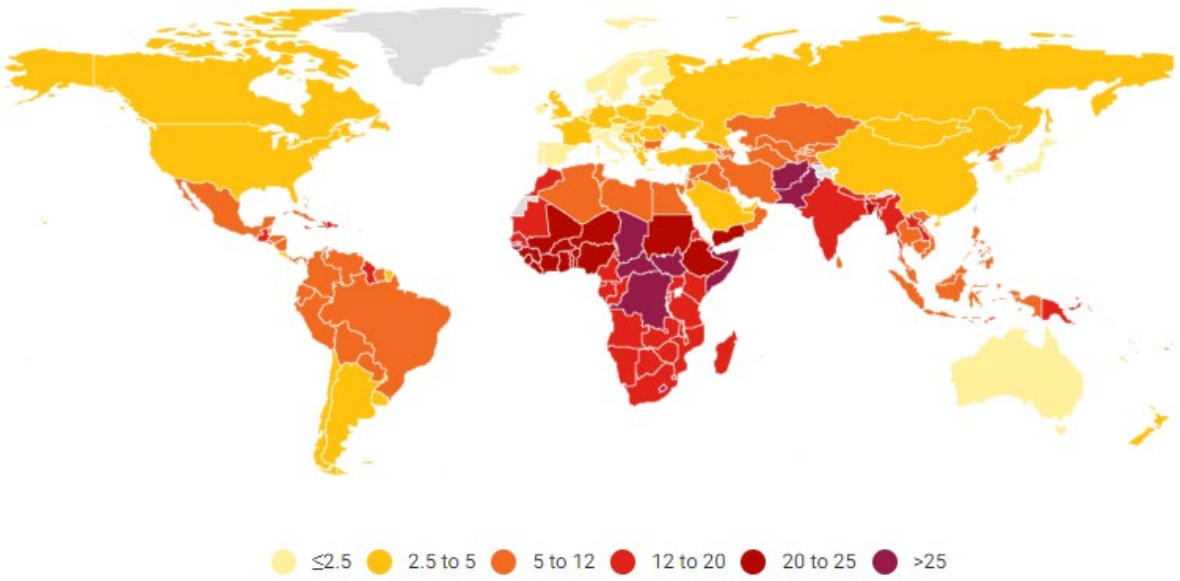
SPECIAL POPULATIONS

GROUP B STREPTOCOCCUS VACCINATION IN PREGNANT WOMEN

March 28, 2023
Incheon, Korea

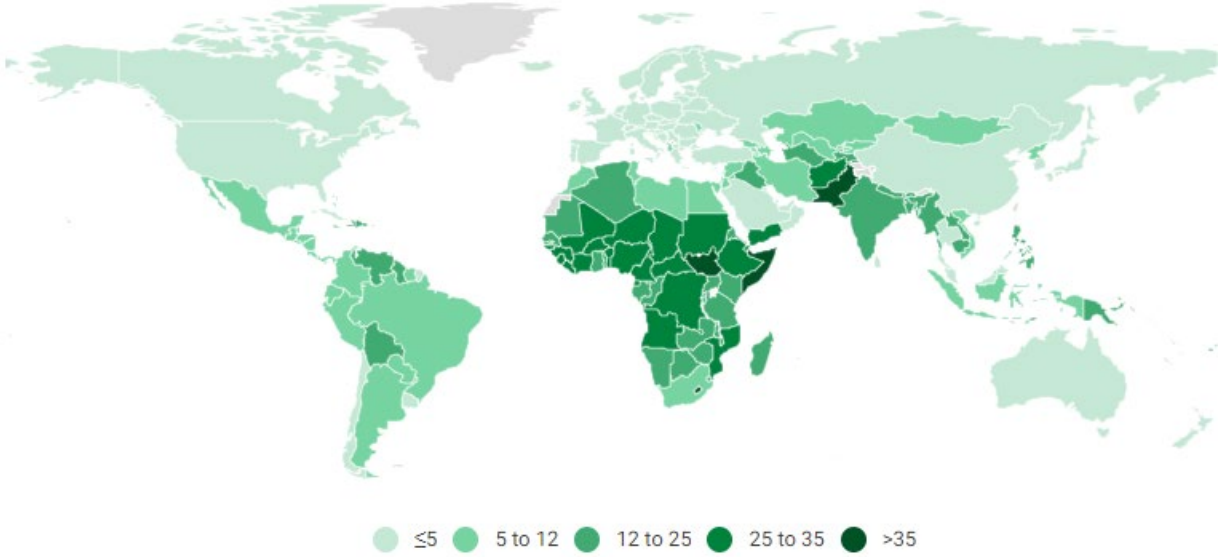
URGENT PROBLEMS TO SOLVE

Stillbirth rates (deaths per 1,000 births), by country (2021)



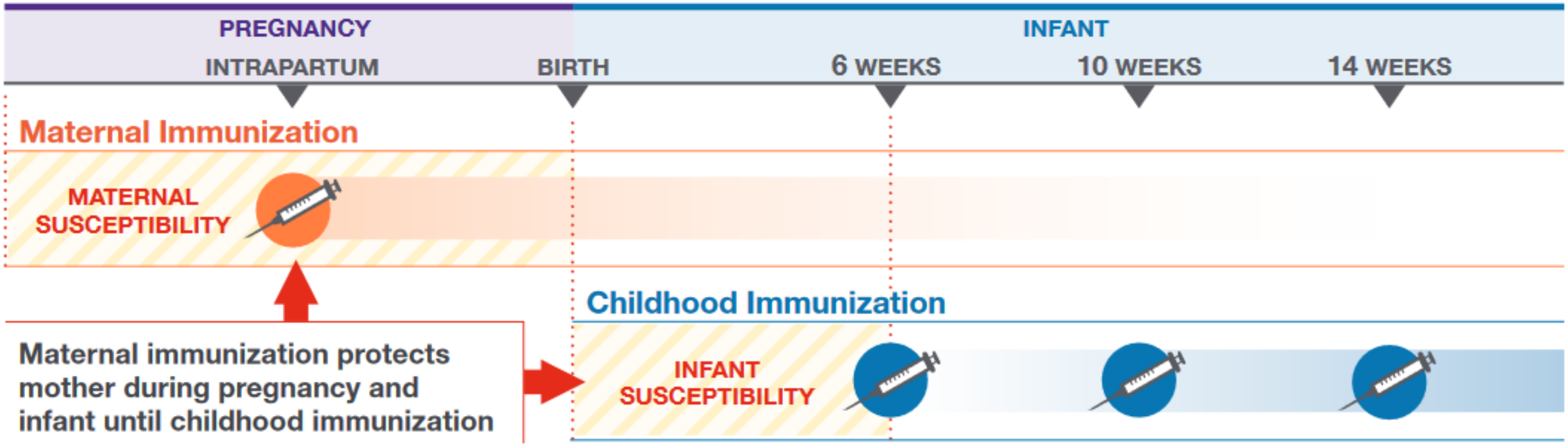
https://data.unicef.org/topic/child-survival/stillbirths/

Neonatal mortality rate (deaths per 1,000 live births) by country, 2021



https://data.unicef.org/topic/child-survival/neonatal-mortality/

MATERNAL IMMUNIZATION

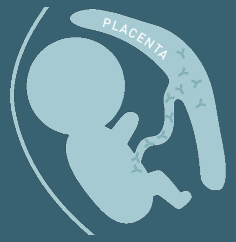


Lackritz EM, Stepanchak M, Stergachis A. Maternal immunization safety monitoring in low- and middle-income countries: a roadmap for program development. Bill & Melinda Gates Foundation and Global Alliance to Prevent Prematurity and Stillbirth (GAPPS), 2017. Modified from: Sobanjo-Ter Meulen A, Abramson J, Mason E, et al. Path to impact: a report from the Bill and Melinda Gates Foundation convening on maternal immunization in resource-limited settings; Berlin - January 29-30, 2015. Vaccine 2015;33:1873-2518.

MATERNAL IMMUNIZATION IS A PROMISING SOLUTION TO REDUCE MATERNAL AND INFANT MORTALITY AND MORBIDITY GLOBALLY

Maternal immunization is the vaccination of women during pregnancy to protect young children, fetuses, and mothers against common infectious diseases.

Vaccinating pregnant women generates antibodies that can be transferred across the placenta to the developing fetus.



Maternal immunization has already helped address serious infectious diseases…

- Contributed to **a 96% reduction** in the global number of tetanus-related neonatal deaths
- Significantly **reduced illness and deaths** of young infants during pertussis outbreaks in countries such as the U.S. and U.K.

…But there is still progress to be made in reducing maternal and child mortality and morbidity

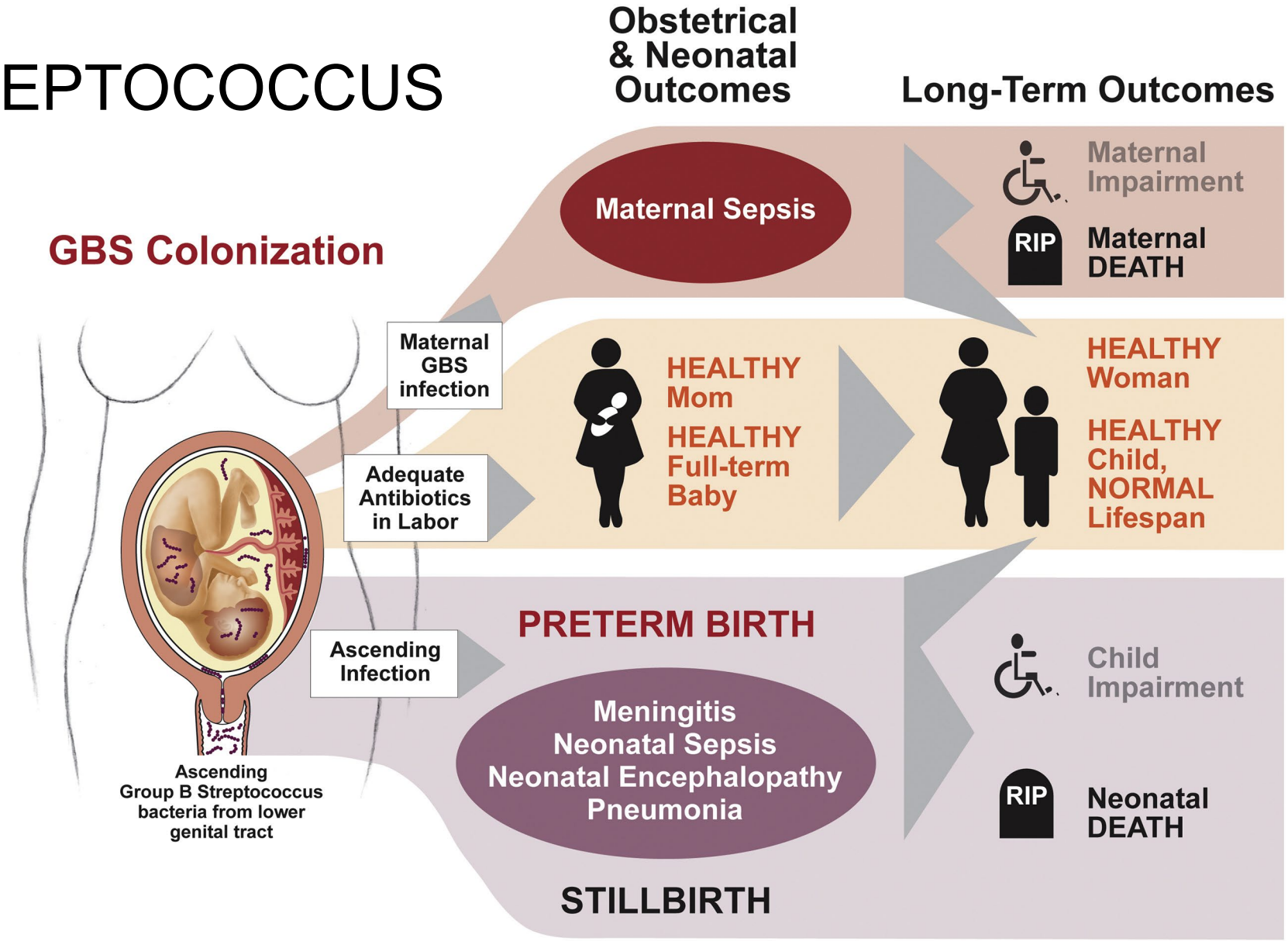
- **46%** of deaths of children under 5 occur during the neonatal period (first 28 days after birth)
- Nearly a **quarter of all neonatal deaths** globally are caused by infectious diseases

Despite the immunological changes in pregnancy, studies comparing immunogenicity of vaccines in pregnant and non-pregnant women have generally not demonstrated decreased antibody responses in pregnant women.

GROUP B STREPTOCOCCUS

GBS is a Gram-positive encapsulated bacterium

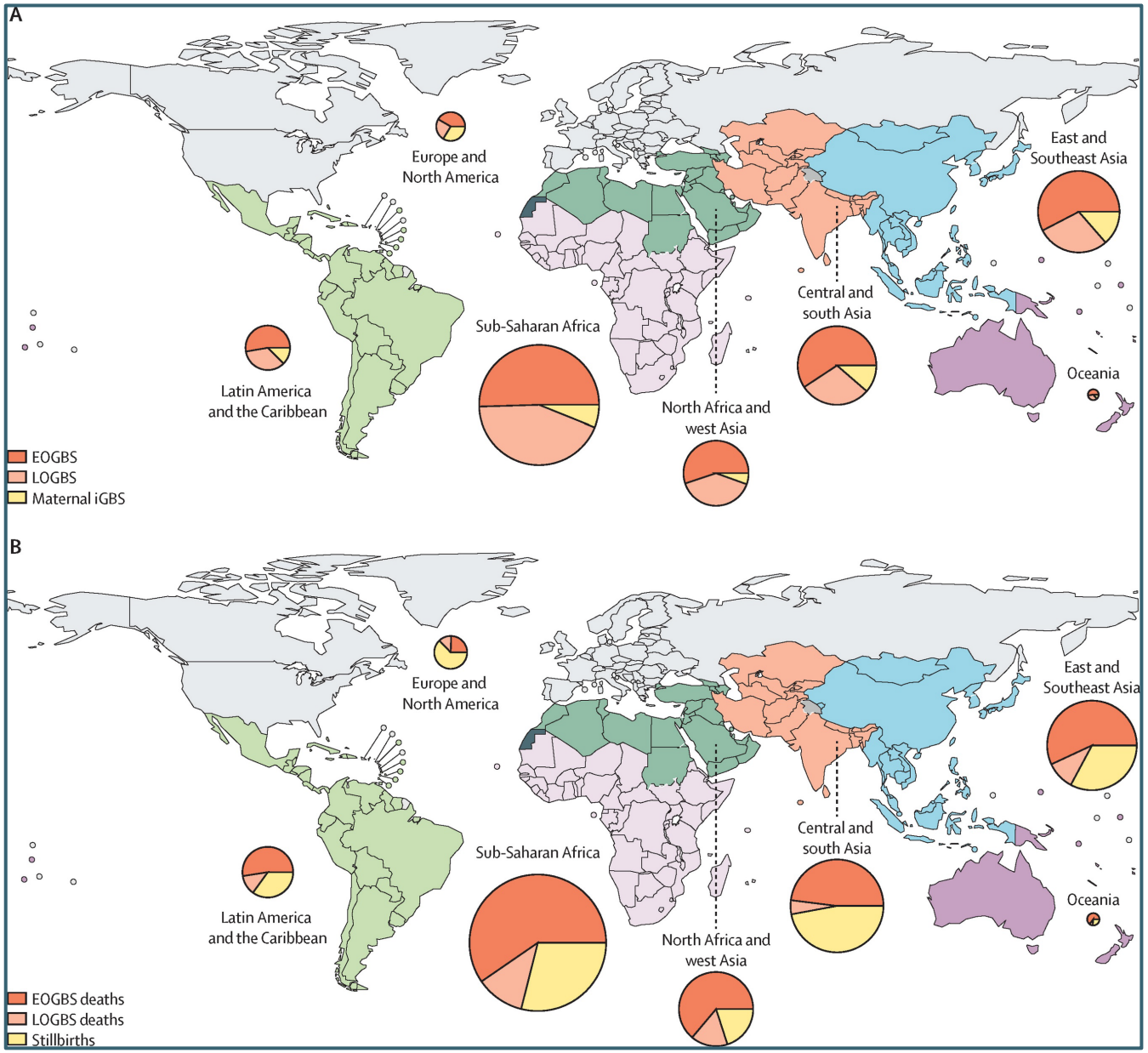
Common in gastro-intestinal tract, causes disease through ascending infection



Blair Armistead, Elizabeth Oler et al. The Double Life of Group B Streptococcus: Asymptomatic Colonizer and Potent Pathogen, Journal of Molecular Biology, Volume 431, Issue 16, 2019, Pages 2914-2931, ISSN 0022-2836, https://doi.org/10.1016/j.jmb.2019.01.035 Figure adapted from Lawn et al (2017).

BURDEN OF GBS

- 19·7 million (17·9–21·9) pregnant women were colonised with GBS
- 40 500 (21 500–66 200) maternal iGBS cases
- 46 200 (20 300–111 300) GBS stillbirths
- 231 800 (114 100–455 000) early-onset cases
- 162 200 (70 200–394 400) late-onset cases
- 91 900 (44 800–187 800) iGBS infant deaths
- 37 100 children (14 600–96 200) estimated to develop mod/sev NDI



Gonclaves et al. Group B streptococcus infection during pregnancy and infancy: estimates of regional and global burden (2022) Lancet Global Health

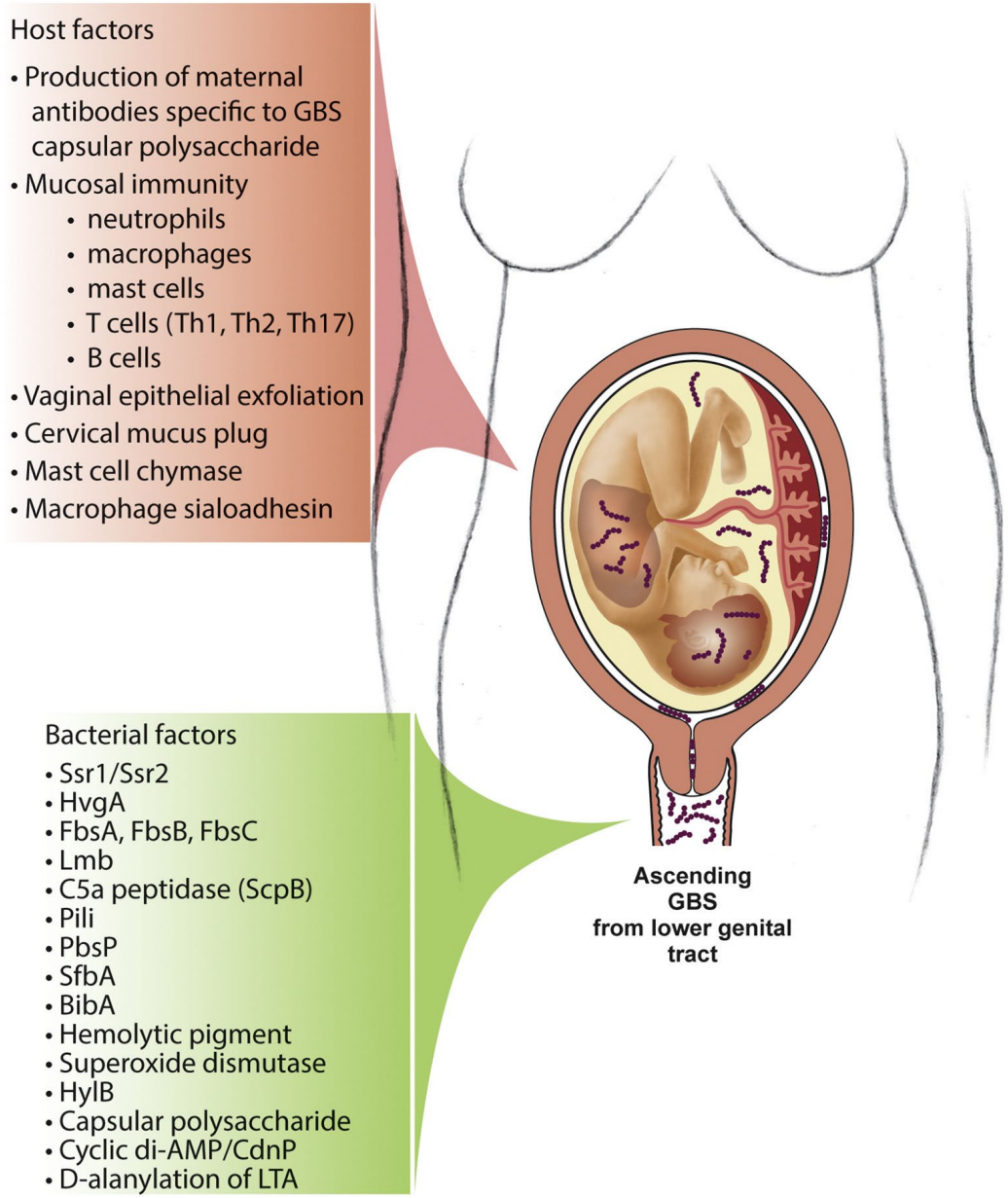
GROUP B STREPTOCOCCUS

GBS produces factors that promote asymptomatic vaginal colonization and virulence

Host defences against GBS are multifaceted

- include production of maternal antibodies specific to the GBS capsular polysaccharide

In pregnancy, IgG transfer across the placenta increases, with most of the transfer occurring in the third trimester



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GROUP B STREPTOCOCCUS

- 10 GBS capsular types
- Serotype III dominates for infant invasive disease
- Five serotypes (Ia, Ib, II, III, IV and V) account for 93–99% of GBS isolates
- Regional variation likely, but data gaps are apparent.

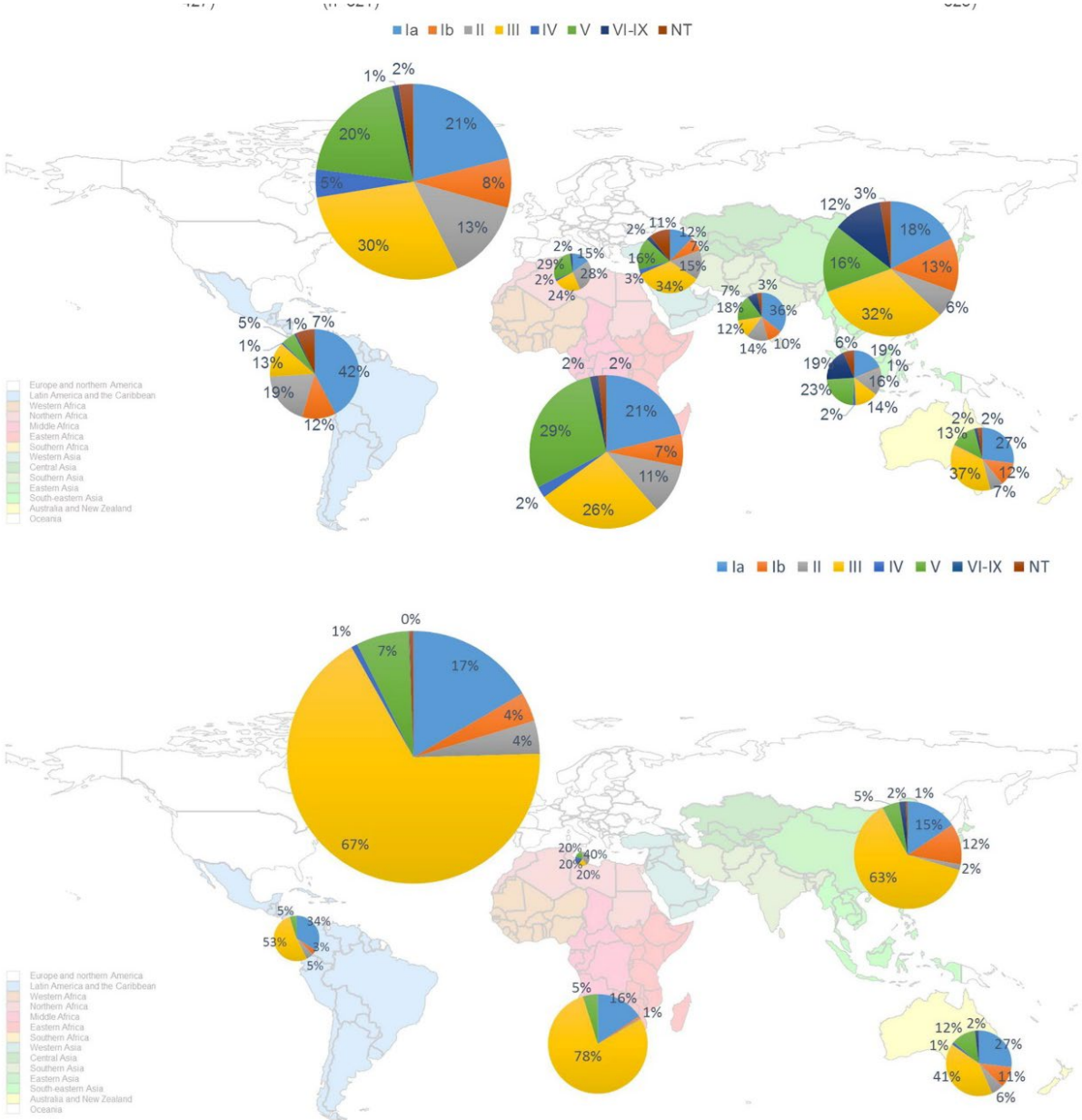


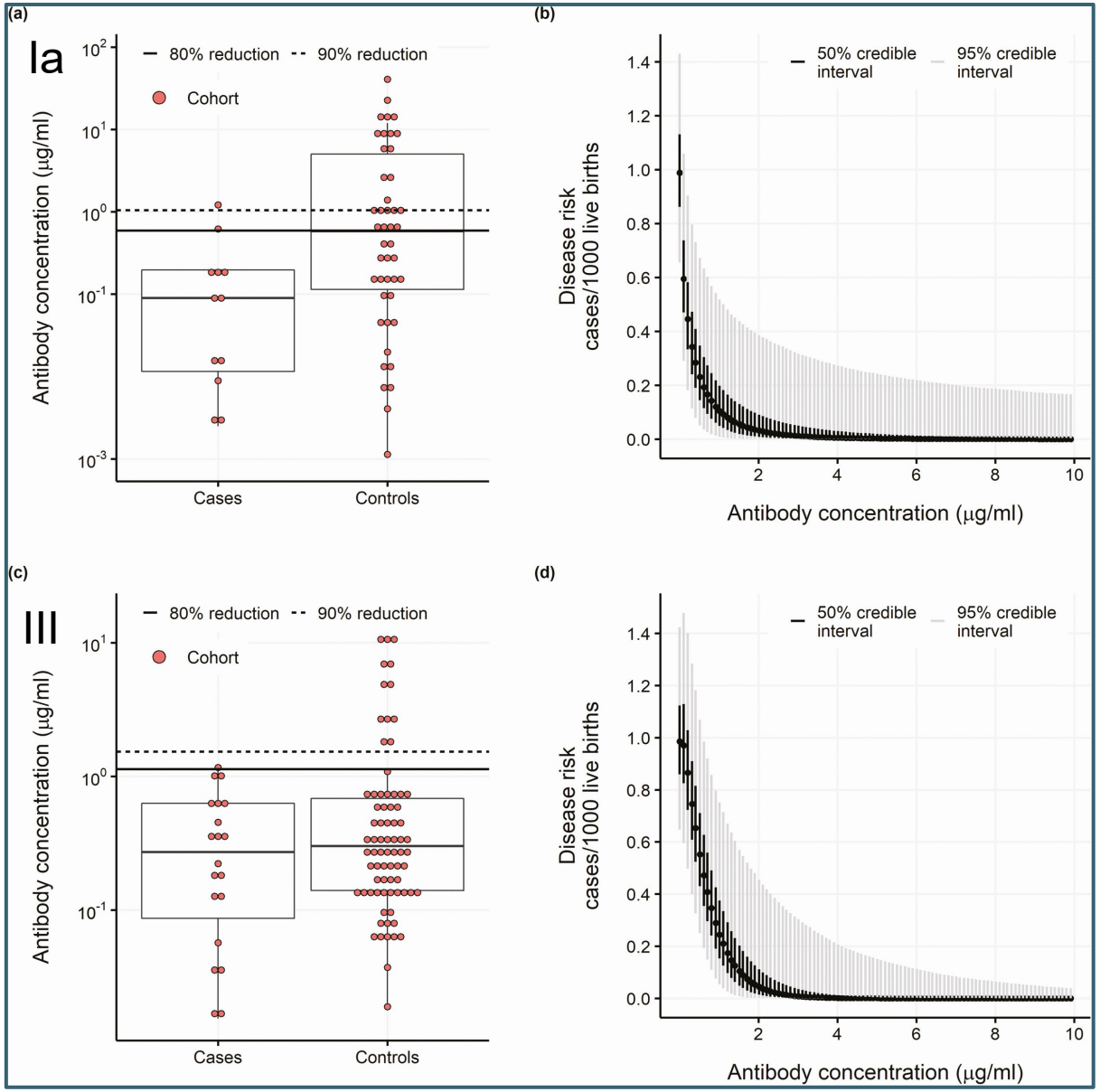
Figure : Top - Distribution of GBS serotypes by regions from maternal colonisation isolates (n = 17427); Bottom - Distribution of GBS serotypes by regions from infant invasive disease and stillbirth isolates (n = 8974). From: Bianchi-Jassir et al. Systematic review of Group B Streptococcal capsular types, sequence types and surface proteins as potential vaccine candidates, Vaccine 38 (43) 2020

ANTI-CAPSULAR ANTIBODY PROTECTIVE

Immunity and GBS disease risk reduction in South Africa

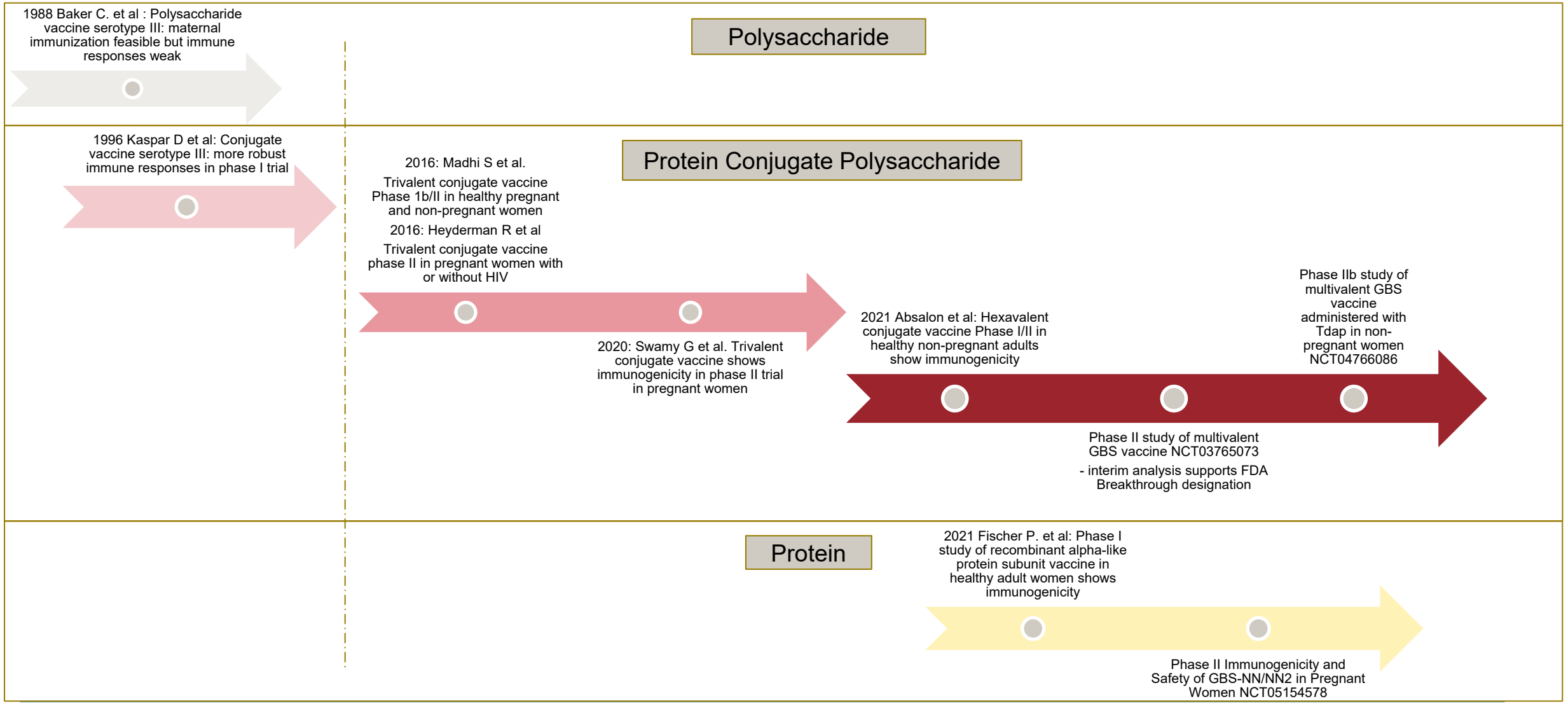
Methods
- Matched case-control study
- GBS serotype-specific anticapsular IgG
- IgG threshold associated with 90% risk reduction estimated (by absolute disease risk)

Findings
- Cord-blood IgG GMCs lower in case vs controls
- Cord-blood IgG concentrations ≥1.04 and ≥1.53 µg/mL associated with 90% risk reduction of serotype Ia and III disease respectively.
- Maternal sera IgG threshold with 90% risk reduction ≥2.31 µg/mL and ≥3.41 µg/mL for serotypes Ia and III, respectively.



Madhi S, Izu A, Kwatra G, et al. ssociation of Group B Streptococcus (GBS) Serum Serotype-Specific Anticapsular Immunoglobulin G Concentration and Risk Reduction for Invasive GBS Disease in South African Infants: An Observational Birth-Cohort, Matched Case-Control Study *Clin Infect Dis*, Volume 73, Issue 5, 1 September 2021, Pages e1170–e1180, https://doi.org/10.1093/cid/ciaa1873

GBS VACCINE DEVELOPMENT, SELECTED STUDIES



Timelines are not to scale, and do not include all vaccines or trials

MATERNAL GBS VACCINES – IMMUNE RESPONSE

Maternal GBS vaccination of pregnant women (trivalent - sIII, Ia, and Ib conjugated to CRM197) induces anti-GBS antibodies that are transferred to the newborn at delivery - South Africa (Madhi et al 2016) and US (Swamy et al 2020)

Vaccine was less immunogenic in HIV infected women (Heyderman et al 2016)

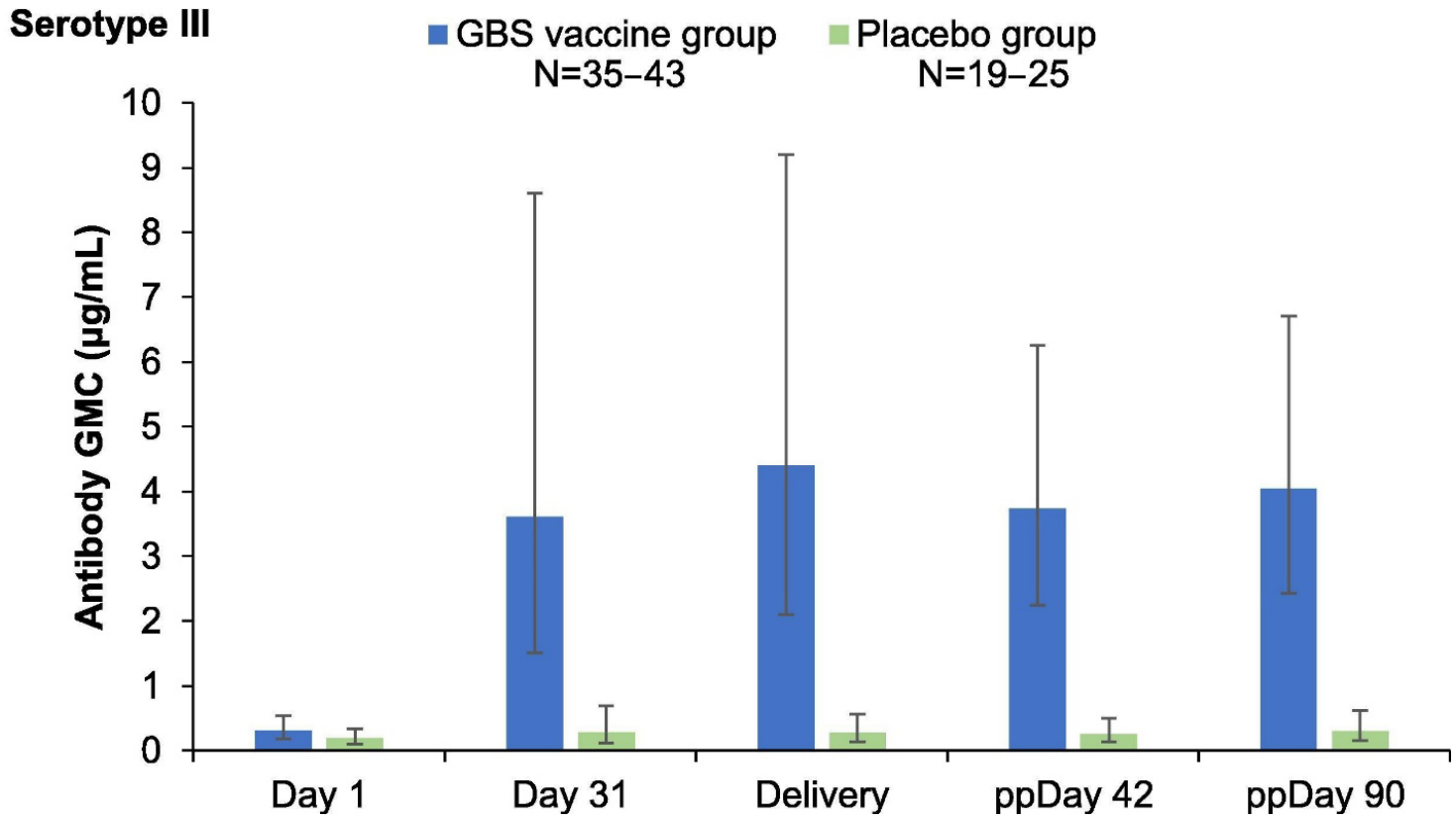


Figure: Geometric mean concentrations of GBS serotype-specific serum antibodies in women before and after vaccination (per protocol immunogenicity set). Abbreviations: GBS, group B streptococcus; N, number of women with available results in each group (range across timepoints); GMC, geometric mean concentration; pp, postpartum. Day 1 timepoint is pre-vaccination. Error bars represent 95% confidence intervals. From Geeta K. Swamy, et al Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in pregnant women and their infants: Results from a randomized placebo-controlled phase II trial, Vaccine, 38 (44) 2020, 6930-6940

PREFERRED PRODUCT CHARACTERISTICS FOR A GBS VACCINE (WHO)

Indication	Prevention of laboratory-confirmed GBS stillbirth and invasive GBS disease in neonates and young infants.
Target Population	Pregnant women in second or third trimester of pregnancy
Schedule	One dose schedule highly preferred (injectable IM, ID or SC or needle-free delivery)
Safety	Safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines for use during pregnancy
Efficacy	Available evidence supportive of 80% protection against combined risk of laboratory-confirmed GBS (all serotypes) stillbirth and invasive disease in the offspring
Strain and serotype coverage	Serotypes in vaccine formulation must cover at least 90% of the current invasive disease isolates in the target region
Adjuvant requirement	Preference for the absence of an adjuvant
Immunogenicity	Established correlate/surrogate of protection based on a validated assay measuring antibody levels/ functionality in mother and/or neonate. Demonstration of non-interference with other vaccines in pregnancy and EPI vaccines in infancy.
Registration, prequalification and programmatic suitability	The vaccine should be prequalified. WHO defined criteria for programmatic suitability of vaccines should be met

Full Value of Vaccine Assessment. WHO and LSHTM (2021) https://www.who.int/publications/i/item/9789240037526

PATHWAY TO LICENSURE

Review

Considerations for a phase-III trial to evaluate a group B *Streptococcus* polysaccharide-protein conjugate vaccine in pregnant women for the prevention of early- and late-onset invasive disease in young-infants

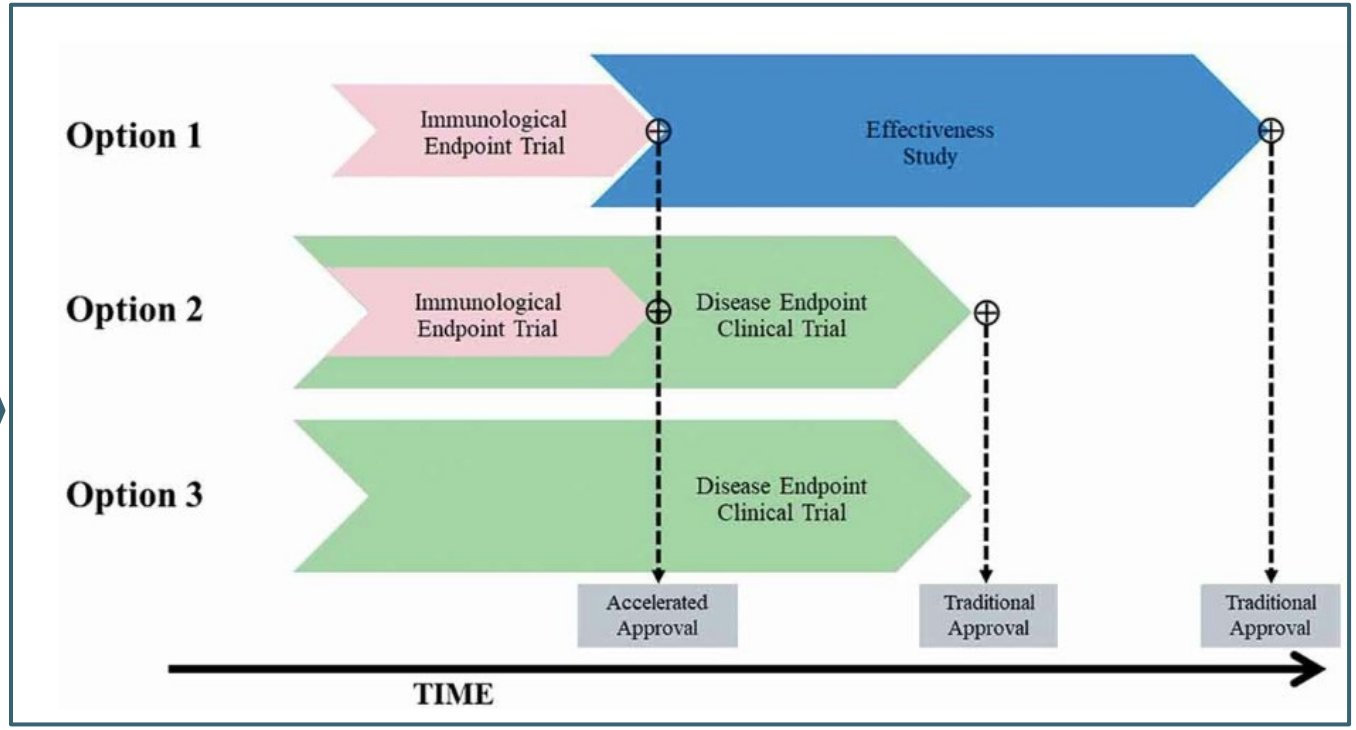
Shabir A. Madhi [a, b, c], Ziyaad Dangor [b, c], Paul T. Heath [d], Stephanie Schrag [e], Alaine Izu [b, c], Ajoke Sobanjo-ter Meulen [f], Peter M. Dull [f]

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] and David C. Kaslow[l]

Advances towards licensure of a maternal vaccine for the prevention of invasive group B streptococcus disease in infants: a discussion of different approaches

Judith Absalon [1], Raphael Simon [1], David Radley [1], Peter C Giardina [1], Kenneth Koury [1], Kathrin U Jansen [1], Annaliesa S Anderson [1]



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SUMMARY

1. There is a high burden of disease and death before, at and after birth, greatest in Africa and South Asia
2. Immunization in pregnancy is a window of opportunity to reduce this burden
3. Maternal IgG is transported across the placenta to the fetus and associated with protection against disease
4. Maternal GBS vaccines aim to reduce neonatal sepsis, meningitis and stillbirth caused by ascending infection from GBS
5. Maternal GBS conjugate vaccines induce immunity in pregnant women which is transferred to the fetus
6. Immunological response informs product development, and may ultimately facilitate licensure

Thank you