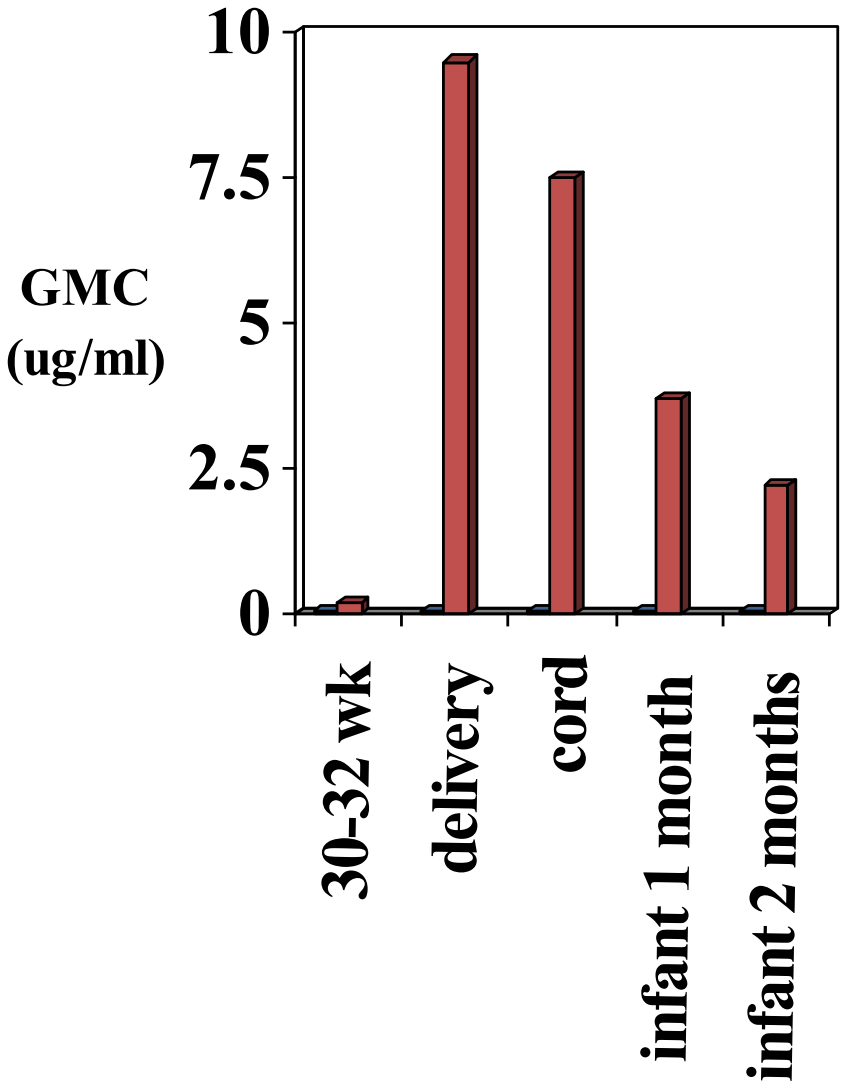
The Group B Streptococcal Vaccine pipeline

Prof. Kirsty Le Doare

PDVAC 7th October 2025

City St George's University of London, Makerere University Johns Hopkins University, Uganda

First trials in pregnant women



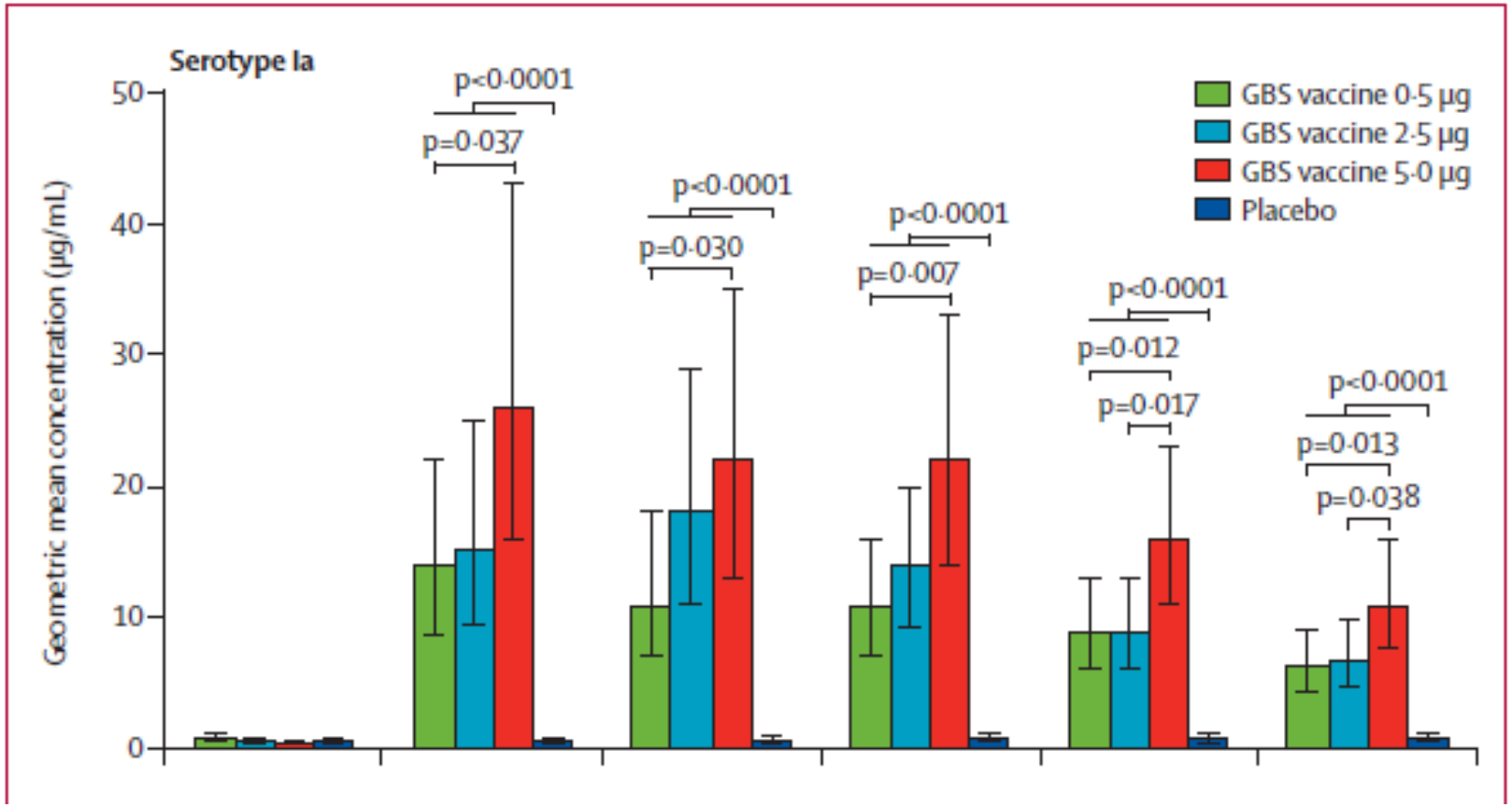
Pregnant women vaccinated with a TT-CPS serotype III vaccine

Safe and immunogenic

Immunity lasting in the infant to at least 2 months

Baker 1988

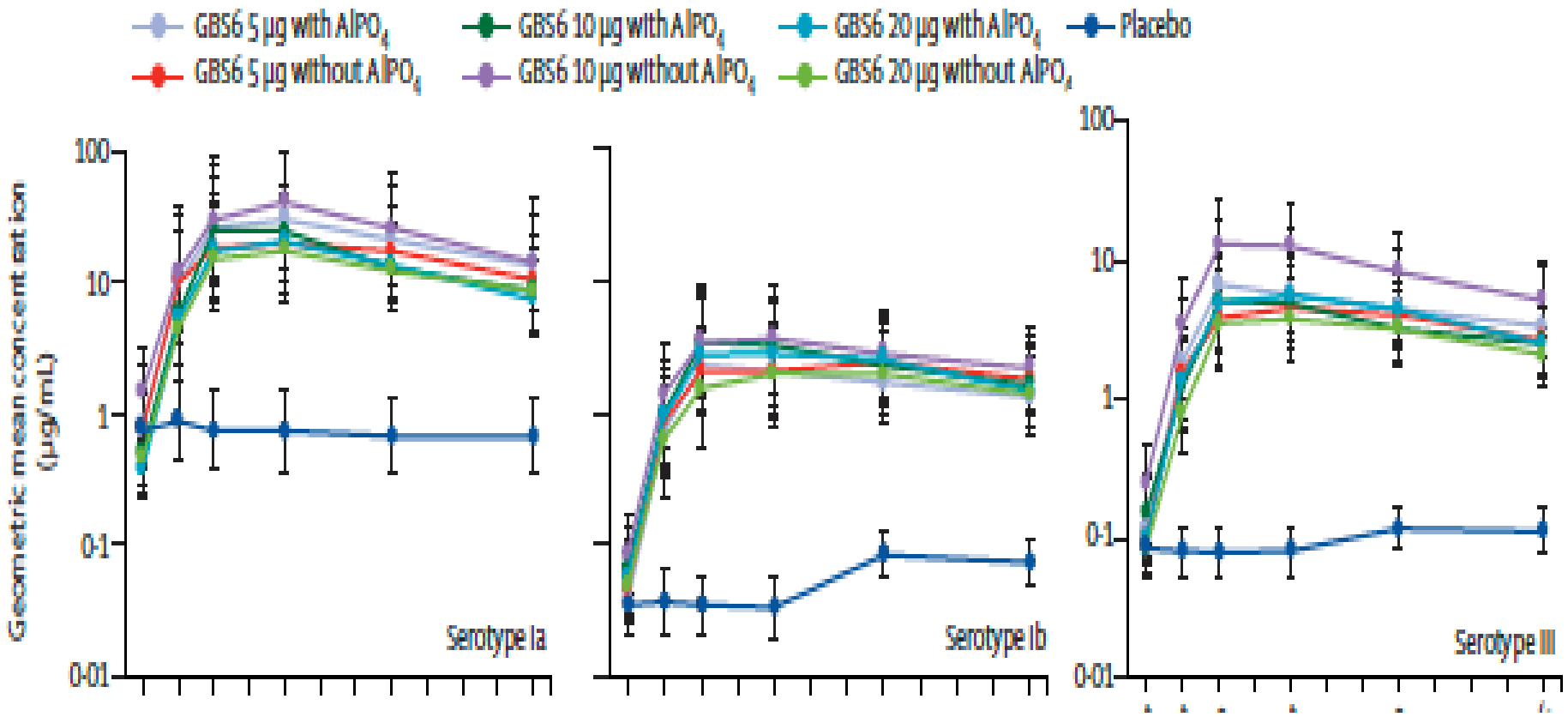
The Second Generation: Application of Scientific Advances to GBS Vaccine Design



- Dose ranging trial in South African and Malawi
- Pregnant women without HIV
- Antibody persistence for up to 1 year post delivery

Heyderman 2016

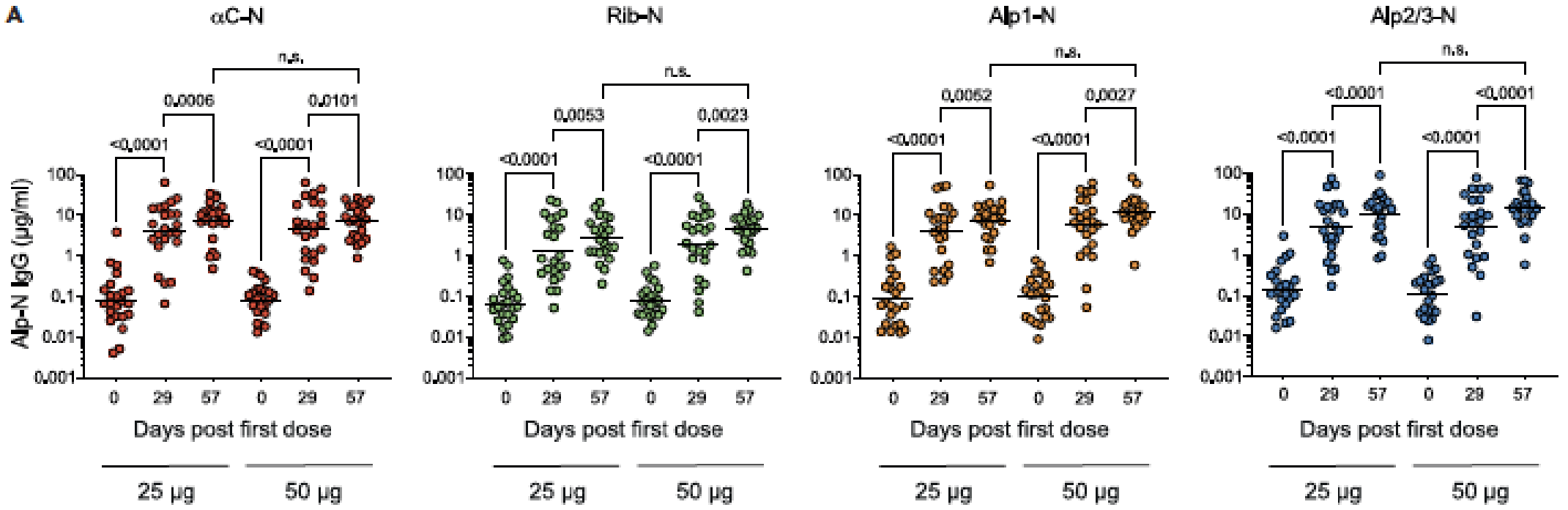
Phase 1/2 novel hexavalent group B streptococcus conjugate vaccine



- Dose ranging study in non-HIV infected healthy adults
- Safe and immunogenic to 6 months compared to placebo
- Vaccine also safe in pregnancy
- Some variability in placental transfer ratio

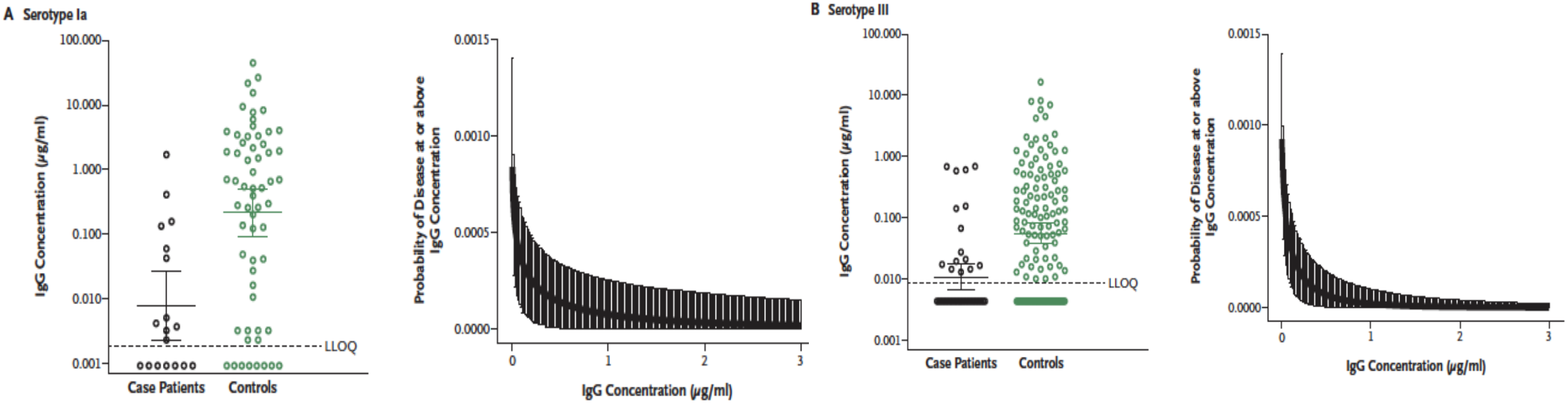
Absolon et al LID 2021; Madhi 2023

Antibody concentrations increase after multivalent protein adjuvanted vaccine



Gonzalez-Miro, Cell 2023

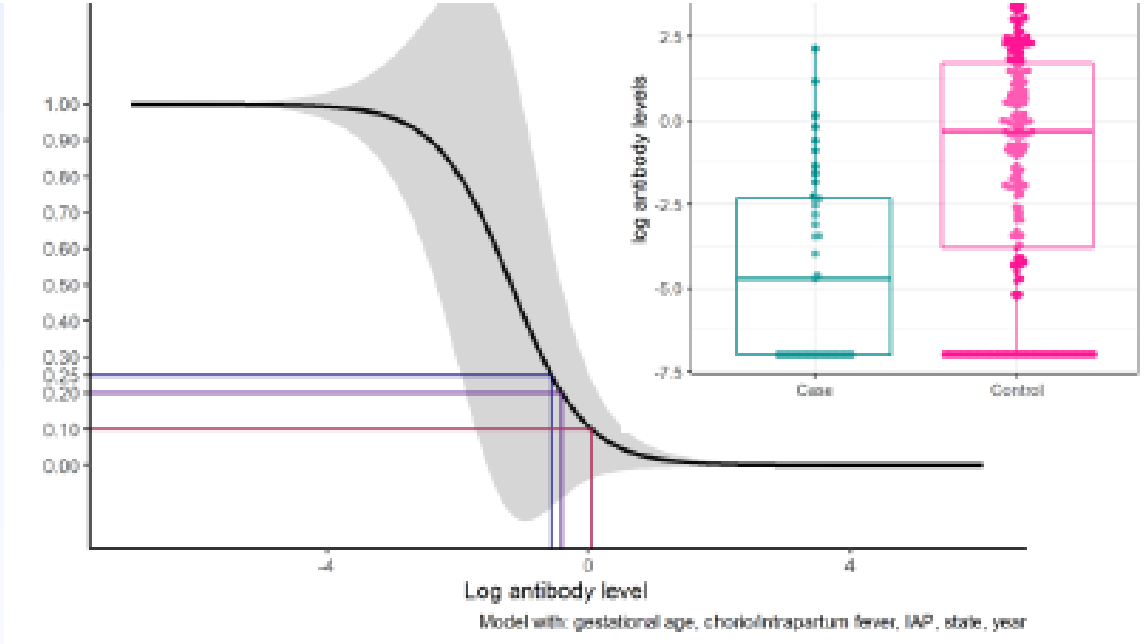
First estimate of an immunological threshold of protection from natural immune sera



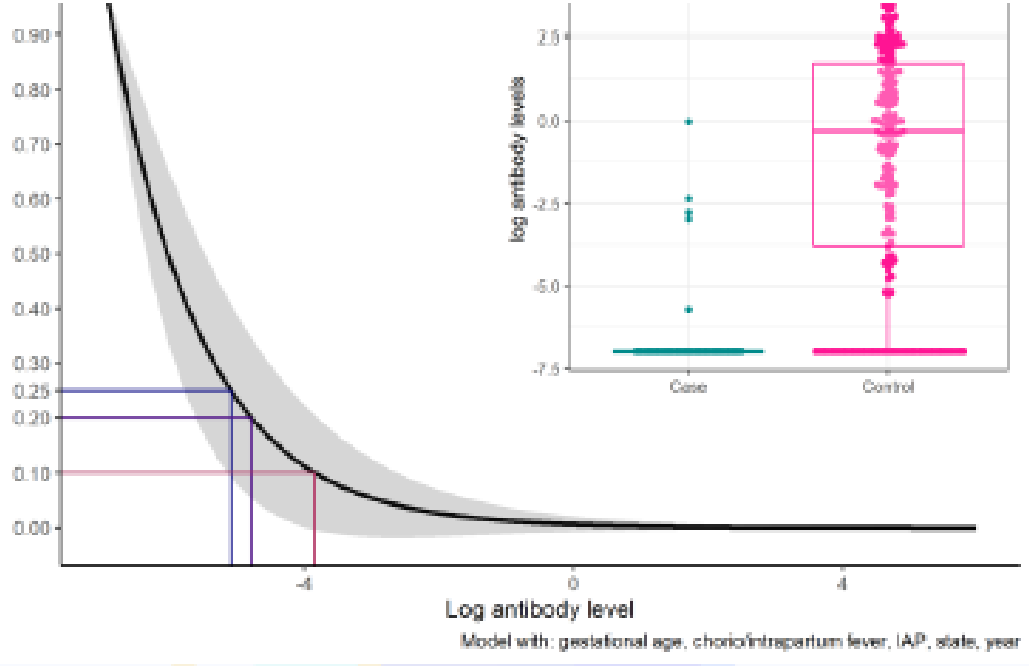
75-95% risk reduction with IgG concentrations of between 0.184-0.827 ug/mL

Madhi 2023

Large study from the US CDC demonstrates thresholds for both EOD and LOD



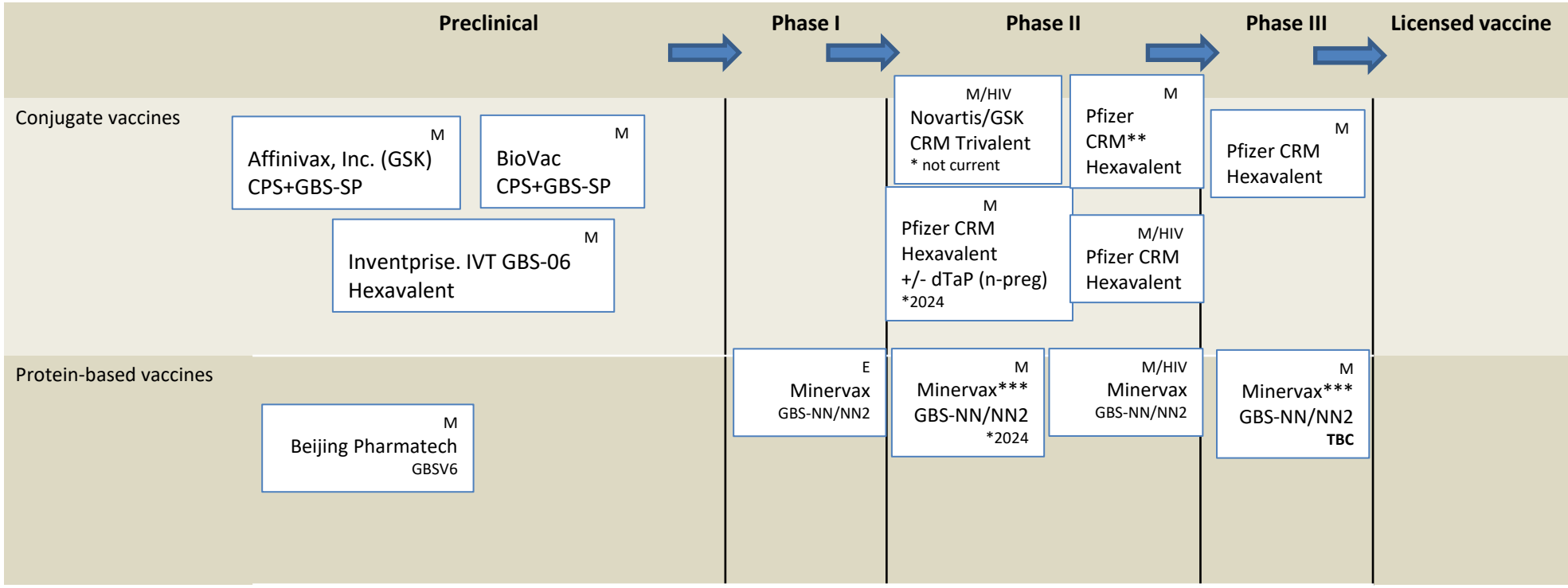
EOD IA
80% threshold (mcg/mL)
0.67 (0.24, 1.85)



LOD IA
80% threshold (mcg/mL)
0.01 (0, 0.02)

Rhodes, INMIS 2024

Group B Streptococcus Vaccine pipeline



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

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

Abbreviations: M=maternal, E=elderly, conjugates: TT = tetanus toxoid, CRM = CRM 197

Summary

- 50 year vaccine pipeline finally unblocked thanks to global efforts to standardize assays and regents that enabled serocorrelates of risk reduction (SToRR) studies
- Several SToRR studies suggest that thresholds of risk reduction are similar across populations for the major serotypes
- The pathway has enabled several novel vaccines to enter the market

Proposed Approach to Streptococcus agalactiae (GBS) Surveillance Standards

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PDVAC, October 2025

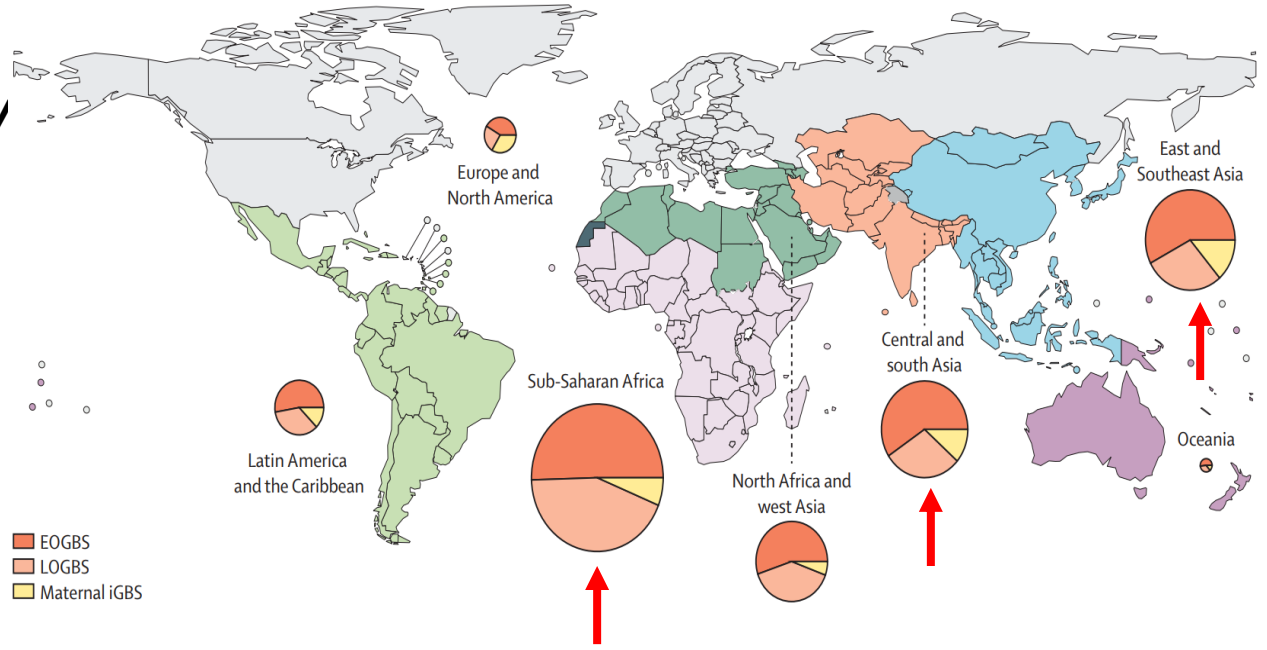
World Health Organization | IVB

The purpose of GBS disease surveillance

	Pre-licensure	Post-Licensure
	Quantify disease burden in neonates, stillbirths, and mothers	Evaluate real-world vaccine effectiveness
	Generate evidence for WHO, Gavi, and national policy	Monitor safety and rare adverse events
	Provide baseline rates for later impact measurement	Track serotype replacement or shifts
	Monitor serotypes and antimicrobial resistance	Assess equity of vaccine impact across LMICs
	Support clinical trial design and licensure pathways	Measure contribution to reducing AMR

Streptococcus agalactiae (GBS) Surveillance

- **Globally, in 2020:**
  - **20 million pregnant women were colonized with GBS**
    - 231,800 cases of EOGBS
      - ***0.5 to 1.0 per 1,000 live births globally***
    - 162,200 cases of LOGBS
  - **Skilled birth attendance**
    - 58,300 infant deaths with
  - **Without a skilled birth attendant**
    - 91,000 infant deaths
- **Disease burden mainly in**
  - Sub-Saharan Africa and Asia



Bronner P Gonçalves et al, The Lancet Global Health, 2020; "Group B streptococcus infection during pregnancy and infancy: estimates of regional and global burden"

What are the current challenges in GBS Surveillance?

Challenge 1: Need for an adequate catchment size of births/infants in first 3 months of life

- **In settings implementing intrapartum antibiotic prophylaxis (IAP) to prevent EOGBS**
  - **Large catchments will be required**
    - Invasive disease incidence may be 0.5/1000 live births or even lower
- **In settings without GBS prevention**
  - **Smaller catchments may be viable but they still need to be fairly large**
    - Ex: A hospital that serves 10,000 births a year may be anticipated to have only 10 GBS cases

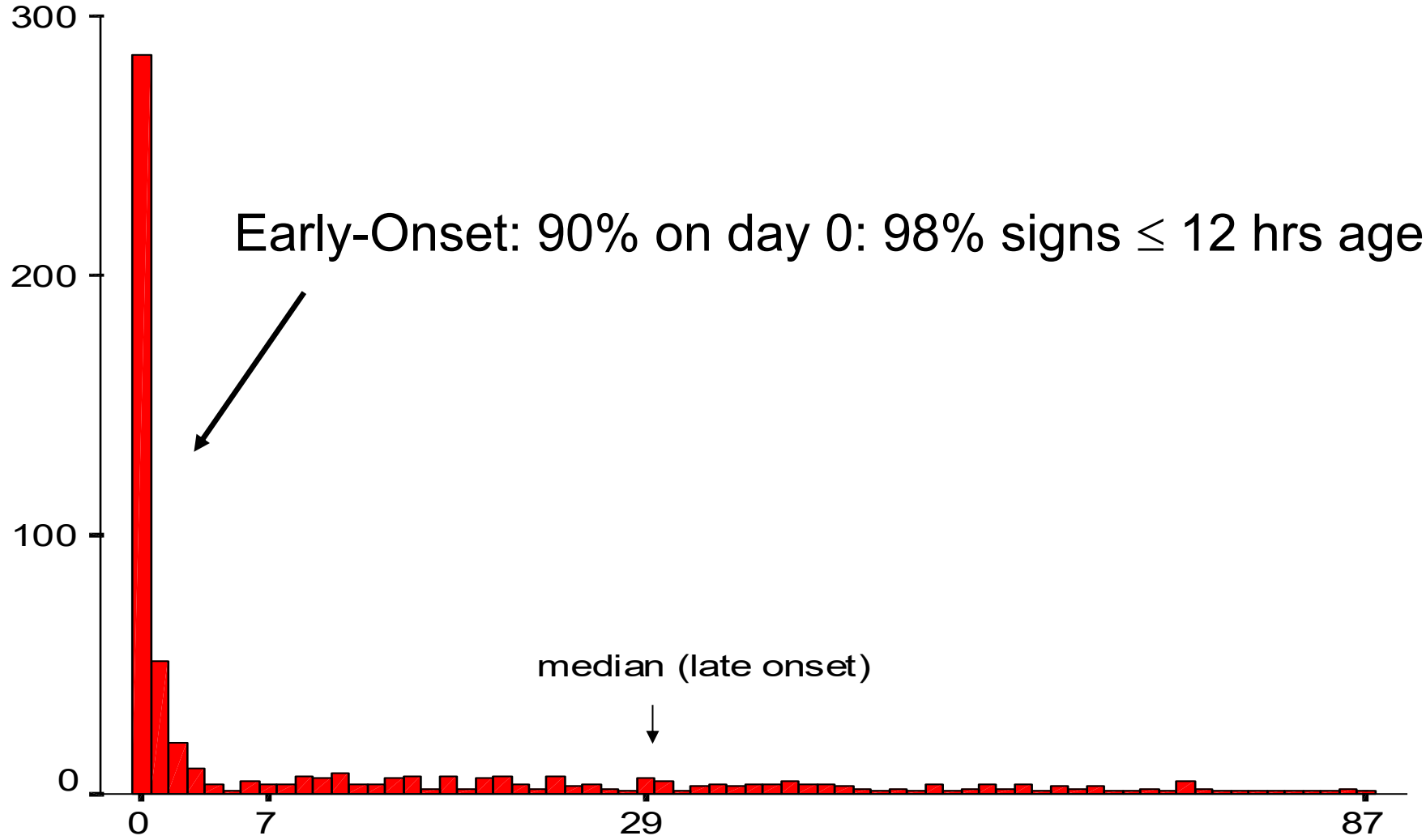
Challenge 2: Need for a live birth denominator

- **To document presence of disease and GBS strain types, a denominator may not be necessary**
  - However, to estimate incidence rate (burden), and to track changes over time a denominator is necessary
    - This does not lend well to sentinel surveillance designs unless hospital catchments and care seeking are very stable over time
      - Catchments can also be challenging to estimate for referral hospitals

Challenge 3: Care seeking at the start of life

- **Ideal care-seeking features**
  - Virtually all births occur in a hospital or medical center where an ill newborn will be immediately referred for care
    - At least a 24 hour newborn stay after delivery
  - A low threshold for care seeking post-discharge in the first three months of life
    - Signs of illness in neonates and very young infants are non-specific and may be hard for families to identify
    - Infant GBS often has a fulminant course

Challenge 4: The importance of day 0 of life



Lancet 2004; **363:** 292–94

Challenge 5: Appropriate diagnostic workup of potentially ill newborns

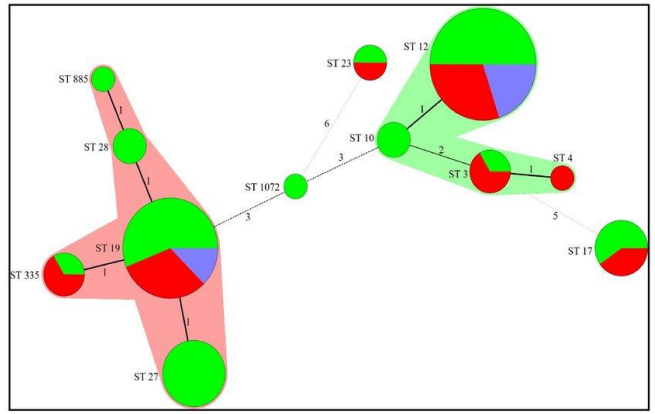
- **Hospital characteristics conducive to GBS surveillance**
  - Low threshold for blood culture-particularly on day of birth
  - Collection of blood culture before antibiotic therapy initiation
  - Collection of CSF for infants at high risk of infection
    - A meaningful portion of infants with invasive GBS disease are blood culture negative but CSF positive

Challenge 6: Strong blood & CSF culture capacity

- **How to detect invasive GBS?**
  - Blood and CSF cultures
- **Blood cultures very challenging (0.5 mL newborns to 3 mL infants)**
  - **Early onset disease (<7 days)**
    - Low bacterial load in neonates blood <1 CFU/mL
  - **Late-onset disease (7 - 89 days)**
    - 1-10 CFU/mL or higher
  - **Severe sepsis or meningitis**
    - The bacteremia level can go up to >10 CFU/mL

- **CSF cultures very challenging**
  - Low bacterial load (1-100 CFU/mL) in early onset disease
  - Higher bacterial load (10-1,000 CFU/mL) in late onset disease

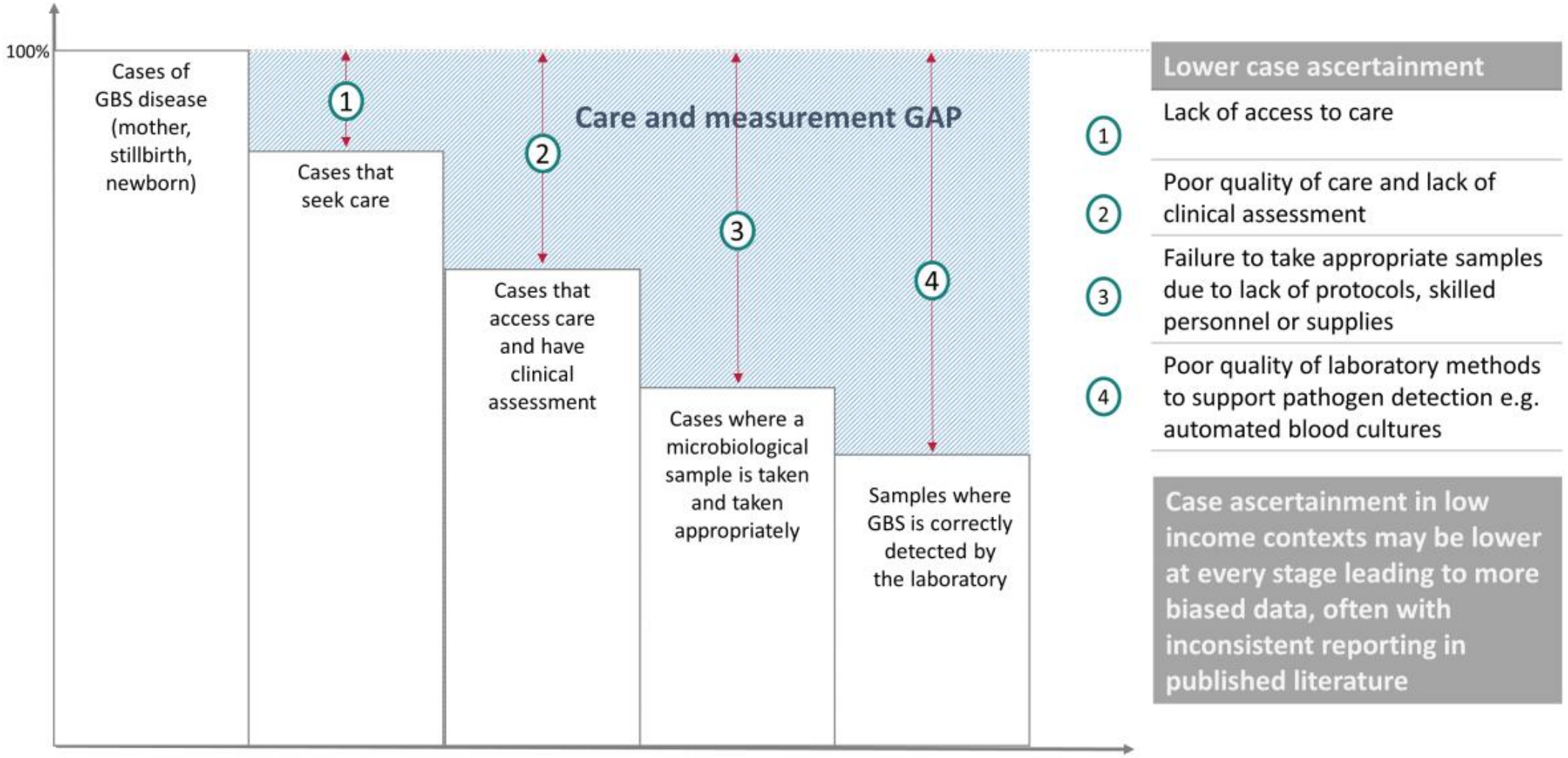
Challenge 7: Strain characterization



- **This may be the easiest challenge to overcome**
  - Isolates can be stored and shipped to a reference laboratory for any characterization that is not locally feasible
    - Serotype at a minimum will be relevant for most maternal vaccine products
    - Whole genome sequencing of strains adds further value-the JUNO project led by the Sanger institute may be able to assist

Gao J et al 2012 Research Square

Summary of Major Surveillance Challenges



Lawn et al, Clin Infect Dis. 2017 65(Suppl 2): S89-99

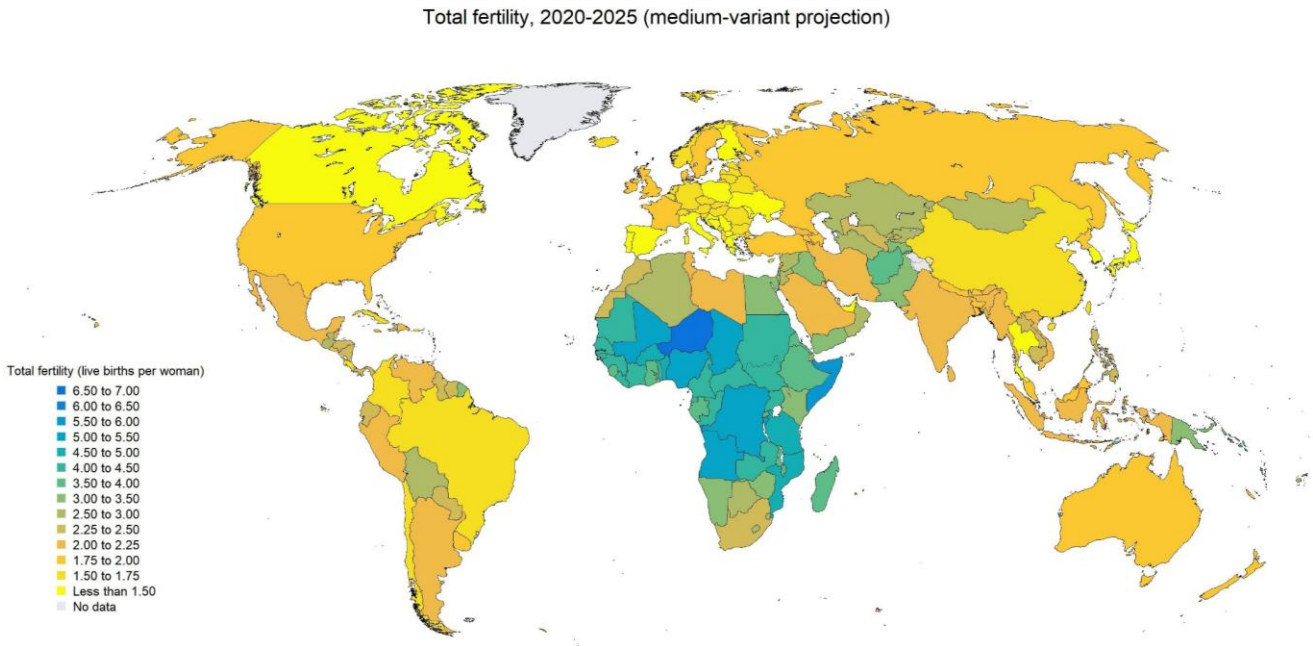
Where do we see these GBS Surveillance challenges?

- **Low and middle income countries (LMICs)**
  - Many births outside well-resourced facilities
  - Laboratory infrastructure for culture-based testing is limited or absent
    - Cultures are inherently less sensitive due to low pathogen load and small sample size
- **In high-mortality settings**
  - Particularly in sub-Saharan Africa and South Asia
    - Up to 60% of neonatal deaths occur without any laboratory-confirmed diagnosis
- **All these challenges complicate surveillance efforts**
  - Underestimate the true burden of GBS disease
    - Undermining national immunization decisions
    - Evaluating vaccine impact

Gram stain **5% Sheep Blood Aga**

Surveillance of GBS colonization in pregnant women

- **Countries with unclear GBS circulation**
  - Colonization surveillance can provide a snapshot of the prevalence of GBS in pregnancy
    - Colonization is a major risk factor for EOGBS
  - Colonization data should not be used to model burden of disease estimates at the country level
    - Colonization does not directly reflect disease incidence
      - The majority of colonized women deliver healthy neonates



Total Fertility Rate 2020-2025 / 2019 United Nations, DESA, Population division.

Next Steps

- **Current situation:**
  - WHO does not have global-level recommendations for GBS surveillance
    - Monitoring for GBS infection is dependent on the country's interest and resources
- **Next steps:**
  - How can WHO propose a framework for approaching GBS surveillance
    - **Principle:**
      - Universal routine surveillance for invasive GBS disease is not feasible or recommended for all countries
      - Is not prerequisite for maternal vaccine introduction, nor is it essential post-introduction.
    - **Preparing countries and health systems:**
      - Planning consultations with likely adopting countries to understand countries data requirements for vaccine introductions

Group B *Streptococcus* Surveillance

- **Issues to Keep in mind**
  - **Ethics**
    - Respect for patient autonomy and informed consent
    - Responsible antibiotic use to prevent resistance
    - Protection of sensitive health data
  - **Equity**
    - Uneven access to screening and treatment
    - Cultural and linguistics barriers
    - Gaps in provider and patient awareness

- **Issues to Keep in mind**
  - **Feasibility**
    - Limited infrastructure in low-resource settings
    - Integration with maternal health services
    - Mixed acceptance among stakeholders
  - **Resource Implications**
    - Investment in surveillance systems
    - Cost of diagnostics tools, trainings and medications
    - Need for ongoing public health education

Thanks

Pathway to SAGE – Group B Streptococcus

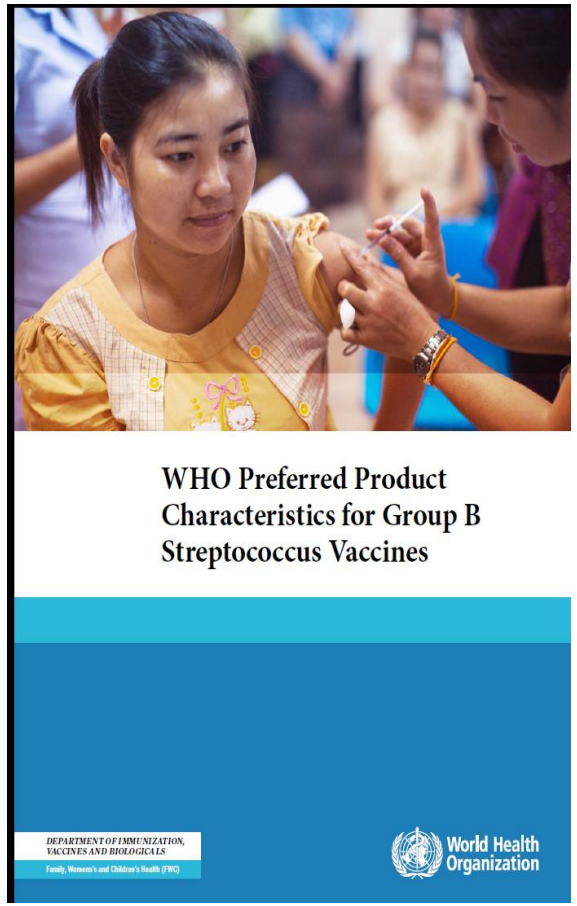
PDVAC
7th October 2025

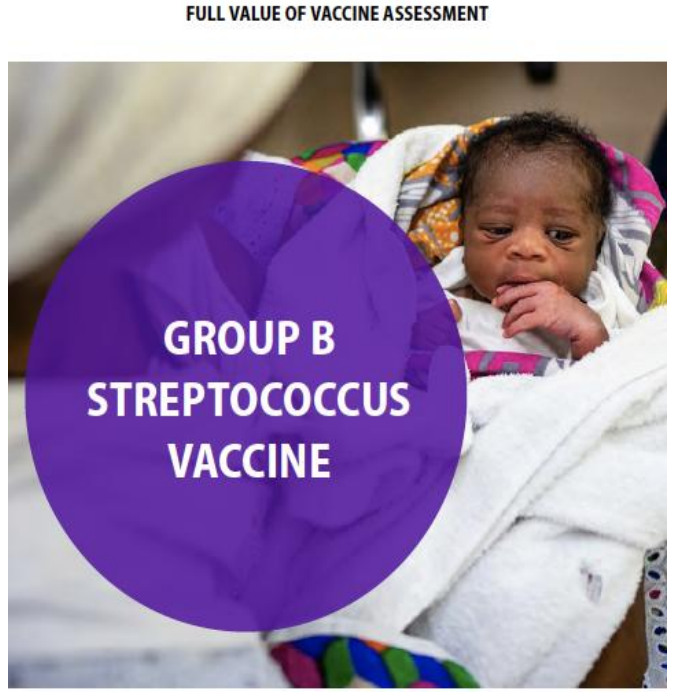
Kirsty Le Doare

WHO Consultant

Group B Streptococcus (GBS) Vaccine Advancement

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





LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE | World Health Organization

Major gaps highlighted in the Full value of vaccines assessment (FVVA) - GBS

1

GEOGRAPHIC

with more data required particularly from Asia

2

OUTCOMES

with particular gaps identified for stillbirth, impairment after infant GBS sepsis and maternal disease

3

ECONOMIC

including translation of outcomes to disability adjusted life years and assessment of vaccine cost-effectiveness

4

VACCINE TRIALS

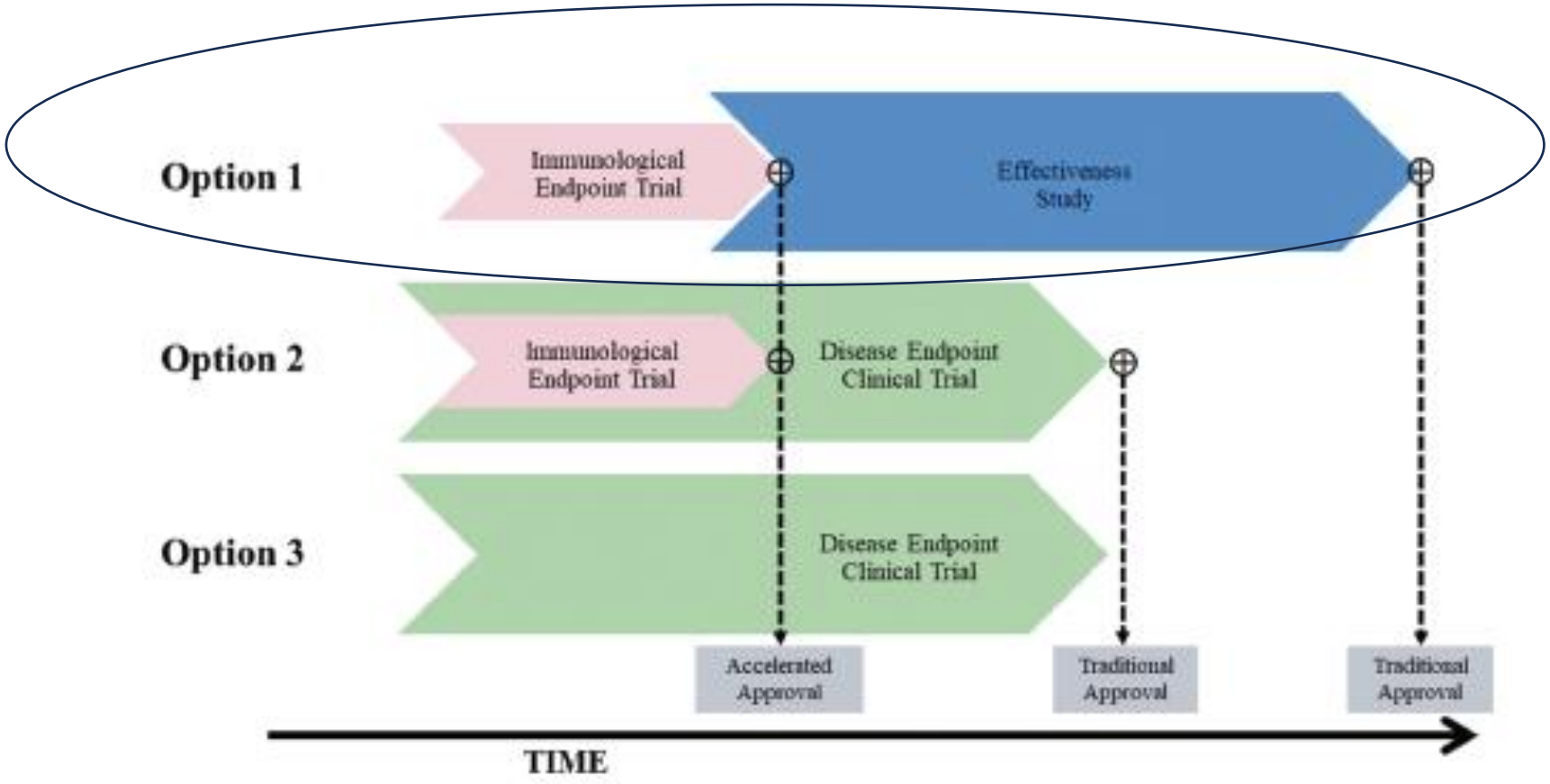
with standardized definitions of vaccine endpoints also enabling comparison of observational data and informing programme monitoring and evaluation *(24)*

WHO is continuing to lead work aimed at standardizing case definitions and vaccine endpoints *(20)*.

Uncertainty about the regulatory pathway for market approval based on serological thresholds of risk reduction (SToRR)

Group B Streptococcus Vaccine: full value vaccine assessment — WHO, 2 Novel

Regulatory strategies for a GBS vaccine for use in pregnancy in Low and Middle Income Countries (LMIC)



Absolon, Hum Vaccin Immunother 2022 Dec 31;18(1):2037350

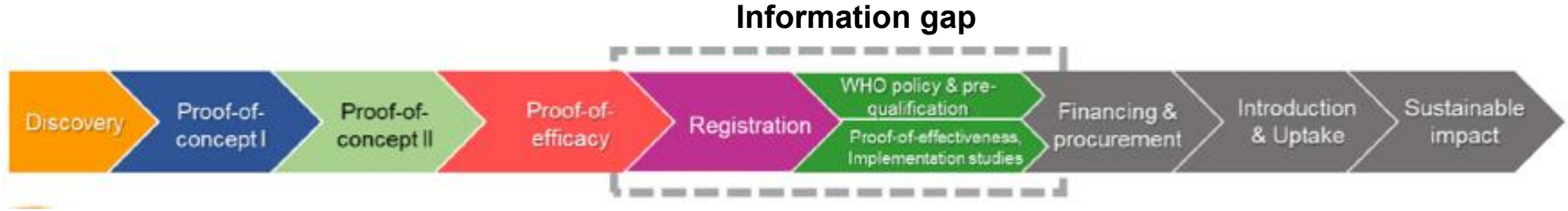
Criteria to be met for conditional market authorization regulatory pathway

European Medicines Agency (EMA) (conditional market authorization (CMA)	US Food and Drug Administration (FDA) (accelerated approval)	GBS?
The risk-benefit balance of the medicinal product is positive;	risk-benefit balance of the medicinal product is positive	✓
it is likely that the applicant will be able to provide the comprehensive clinical data;	Companies are required to conduct studies to confirm the anticipated clinical benefit. If the	
unmet medical needs;	unmet medical need based on a surrogate endpoint.	✓
the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.		✓

While an accelerated approval pathway enables early licensure, it does not guarantee its use

CMAs are valid for one year and can be renewed annually, FDA can review and remove from market if clinical benefit not shown.

Pathway to policy for traditional studies



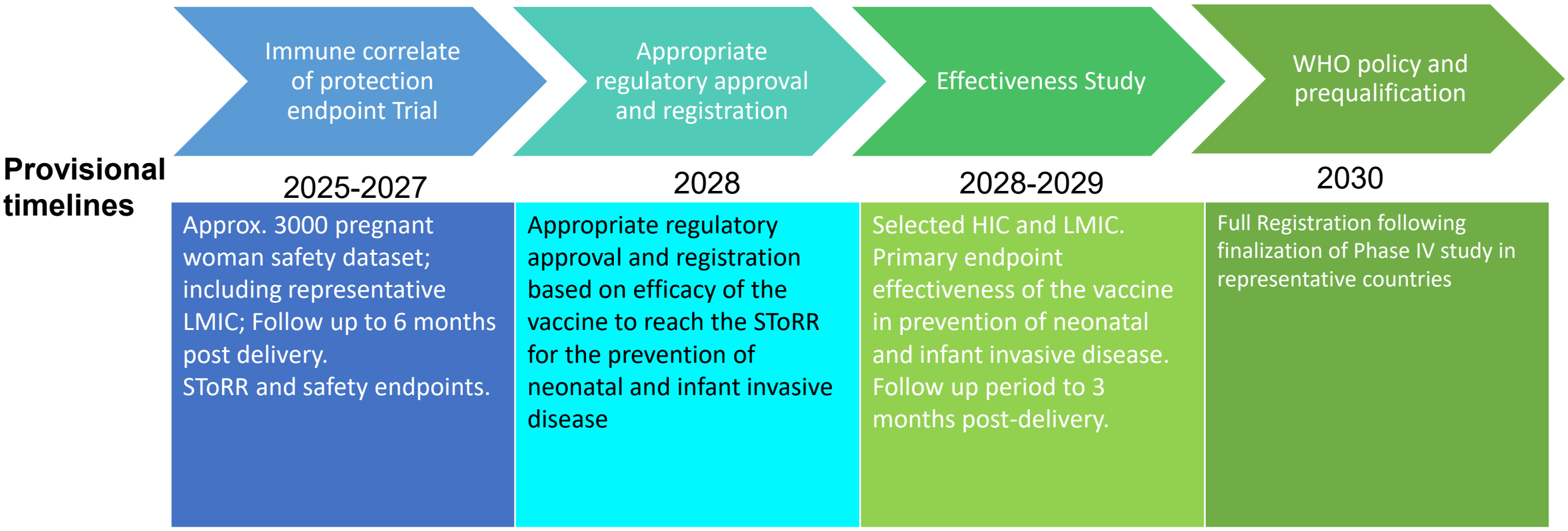
WHO policy follows registration based on proof of efficacy **FOLLOWED BY** effectiveness studies

For GBS, the definitive trial endpoint will be immunological, not clinical.

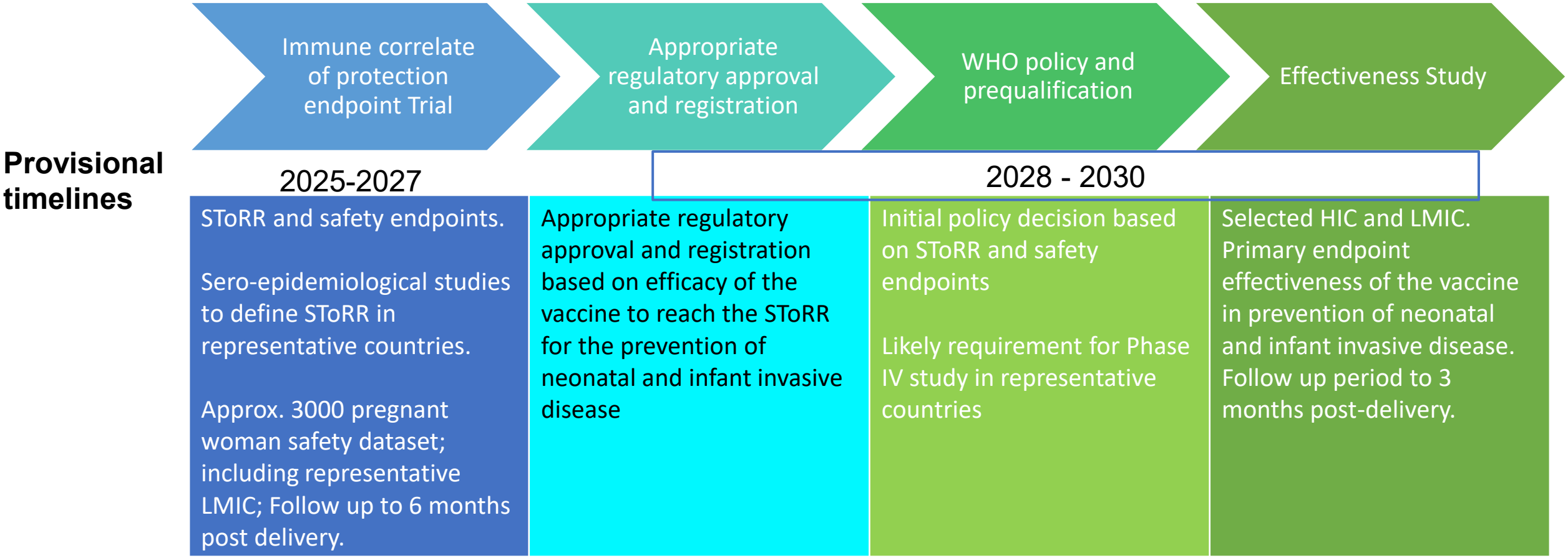
=

A broad policy recommendation may not be possible until **AFTER** the effectiveness studies

Pathway to policy for a GBS vaccine for use in pregnancy in LMIC



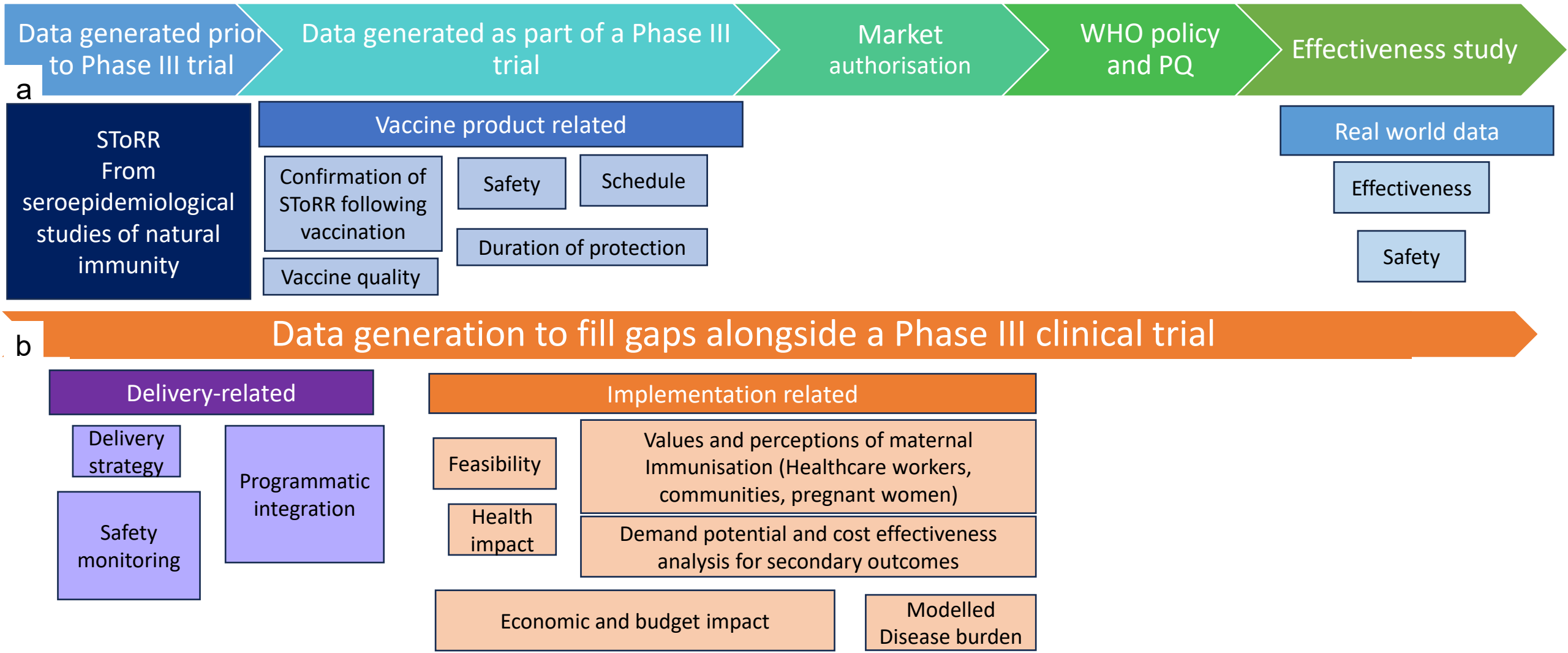
ACCELERATING the Pathway to policy for a GBS vaccine for use in pregnancy in LMIC



Data requirements for WHO policy review

Evidence Type and Quality	Considerations (high, moderate, low, or very low)	GBS
Balance of benefits and harms	Efficacy and effectiveness vs AE	Safety: bar high because of maternal immunization
Risk of Bias/Consistency	Multiple representative sites	Burden of disease lacking in many sites Few LMIC sites can undertake Phase III
Directness	vaccine's impact on relevant outcomes	Different disease endpoints (EOD/LOD)
Precision/Magnitude of effect	certainty in effect estimates/size of the vaccine's effect	Uncertain effect size Robustness of the SToRR Duration of efficacy
Values/Preferences	Acceptability/importance of the vaccine.	Acceptability of maternal immunization
Resource use and cost-effectiveness		Cold chain, multidose vials, etc Cost-effectiveness
Equity impacts	Impact on health inequalities.	
Feasibility	Practical considerations for implementation.	Embedding within existing ANC/EPI. Co-administration with other vaccines, timing of administration.

Two pathways for evidence generation for a GBS vaccine policy for use in pregnancy in LMIC for widespread use



Summary

Now that the phase III trial of the leading candidate has started, we must address the evidence gaps highlighted in the ECVP to facilitate a timely SAGE opinion post-licensure.

Work is underway to address some of these gaps with early adopter countries.

Complimentary data will be presented for PDVAC review as it becomes available

Thank you

Question to PDVAC

As GBS vaccines move towards vaccine licensure based on serocorrelates of risk reduction (SToRR) we need to prepare the groundwork for SAGE and PQ to ensure that there are no prolonged gaps between licensure of the vaccines and policy recommendations.

- **How does PDVAC view the proposed pathway to SAGE?**
- **Are there additional suggestions/considerations to ensure timely alignment between vaccine licensure, PQ, and SAGE review?**

Supplementary slides

An Immune marker suitable to infer protection has been identified in natural immune studies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Potential for Maternally Administered Vaccine for Infant Group B Streptococcus

S.A. Madhi, A.S. Anderson, J. Absalon, D. Radley, R. Simon, B. Jongihlati, R. Strehlau, A.M. van Niekerk, A. Izu, N. Naidoo, G. Kwatra, Y. Ramsamy, M. Said, S. Jones, L. Jose, L. Fairlie, S.L. Barnabas, R. Newton, S. Munson, Z. Jefferies, D. Pavliakova, N.C. Silmon de Monerri, E. Gomme, J.L. Perez, D.A. Scott, W.C. Gruber, and K.U. Jansen

Table S5 Seroepidemiology Study: Estimated Infant Cord Blood Anti-CPS IgG Thresholds for Selected Risk Reduction All Cases

	Type Ia Only (Case=18;Control=61)	Type III Only (Case=45;Control=143)	All Types (Case=77;Control=250)
IgG Thresholds for Target Risk Reductions[a]:			
50%	0.035	0.044	0.049
60%	0.072	0.072	0.083
70%	0.144	0.117	0.14
75%	0.206	0.151	0.184
80%	0.302	0.198	0.246
90%	0.755	0.381	0.494
95%	1.48	0.616	0.827
Parameter Estimates (95% credible interval) of Bayesian Posterior Disease Risk[b]			
λ_1	0.039(0.004 0.091)	0.029(0.013 0.048)	0.033(0.017 0.051)
ν_1	0.39(0.264 0.511)	0.504(0.406 0.604)	0.464(0.39 0.535)
λ_0	1.075(0.417 1.843)	0.188(0.116 0.266)	0.301(0.202 0.416)
ν_0	0.388(0.312 0.464)	0.431(0.378 0.48)	0.375(0.344 0.411)
π	0.001(0.001 0.001)	0.001(0.001 0.001)	0.001(0.001 0.001)

(a) Thresholds are derived as the IgG concentration at which the probability of disease is reduced by the stated percentage, relative to the assumed population incidence, for any participants with IgG concentration at or above the threshold.

(b) ν_1 and ν_0 are estimated shape parameter of Weibull distribution in case and control group, respectively; λ_1 and λ_0 are the corresponding scale parameters; π is the GBS disease prevalence in population.

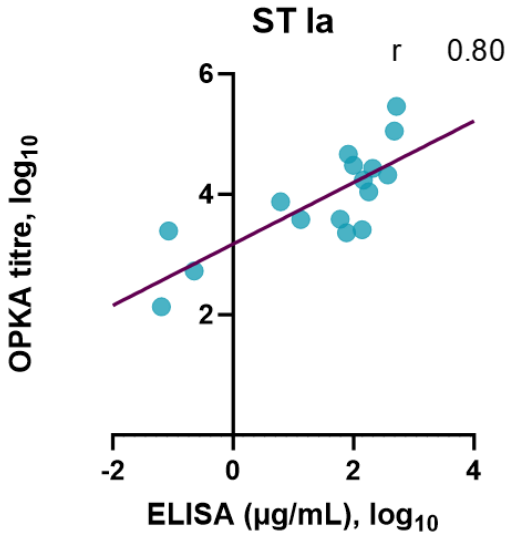
2. Comparison of immune response between candidate vaccine and a licensed vaccine for which efficacy and/or effectiveness has been shown

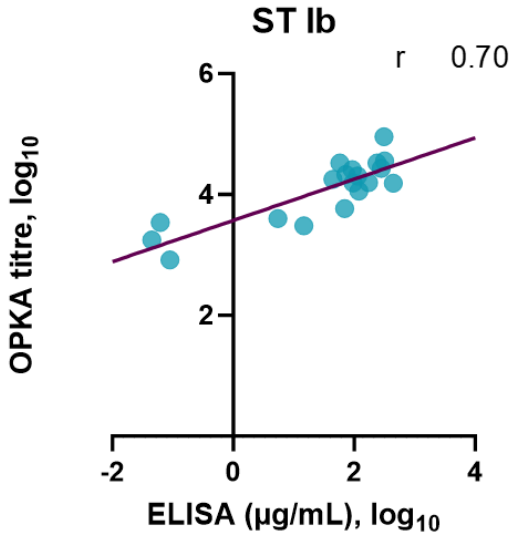
Table 2. Maternal and Infant Anti-CPS IgG Concentrations for Different GBS6 Formulations (Evaluable Immunogenicity Population).*

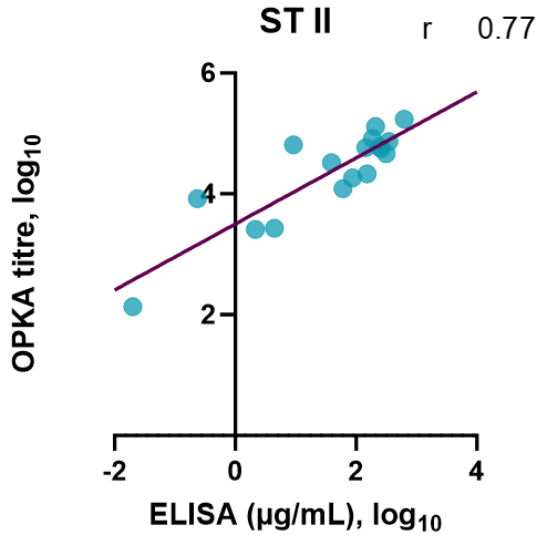
Variable	5-μg GBS6 with $AlPO_4$ (N=34–37)	5-μg GBS6 (N=29–36)	10-μg GBS6 with $AlPO_4$ (N=29–37)	10-μg GBS6 (N=29–34)	20-μg GBS6 with $AlPO_4$ (N=35–38)	20-μg GBS6 (N=34–40)	Placebo (N=91–108)
Maternal GMC at delivery — μg/ml (95% CI)							
Serotype Ia	11.94 (5.57–25.61)	14.71 (6.16–35.11)	14.26 (6.57–30.96)	18.40 (8.18–41.35)	21.99 (8.81–54.88)	40.34 (23.87–68.18)	0.11 (0.06–0.19)
Serotype Ib	0.45 (0.16–1.33)	0.28 (0.10–0.76)	0.53 (0.18–1.56)	0.89 (0.34–2.31)	0.84 (0.39–1.84)	1.28 (0.56–2.94)	0.01 (0.01–0.02)
Serotype II	8.68 (4.46–16.87)	3.26 (1.60–6.65)	9.91 (5.41–18.15)	8.38 (4.81–14.61)	15.54 (7.82–30.91)	27.64 (15.63–48.88)	0.14 (0.10–0.20)
Serotype III	2.52 (0.99–6.38)	1.67 (0.64–4.34)	3.57 (1.49–8.56)	3.77 (1.75–8.13)	2.59 (1.16–5.81)	6.38 (2.83–14.38)	0.02 (0.01–0.03)
Serotype IV	1.69 (0.92–3.12)	0.54 (0.25–1.14)	1.41 (0.79–2.52)	1.29 (0.68–2.42)	1.82 (1.70–3.10)	2.48 (1.49–4.15)	0.01 (0.10–0.02)
Serotype V	0.19 (0.10–0.36)	0.24 (0.09–0.66)	0.68 (0.31–1.52)	1.40 (0.54–3.59)	0.85 (0.41–1.76)	0.87 (0.38–1.98)	0.02 (0.01–0.02)
Infant GMC at birth — μg/ml (95% CI)							
Serotype Ia	6.56 (2.61–16.51)	15.06 (7.26–31.28)	11.89 (5.46–25.85)	12.30 (4.88–31.04)	8.26 (2.84–24.00)	29.56 (16.96–51.51)	0.08 (0.04–0.14)
Serotype Ib	0.26 (0.08–0.84)	0.27 (0.08–0.90)	0.32 (0.09–1.18)	0.45 (0.15–1.39)	0.32 (0.14–0.75)	0.71 (0.27–1.82)	0.01 (0.01–0.02)
Serotype II	6.61 (3.62–12.06)	4.37 (2.40–7.94)	7.44 (3.81–14.53)	6.95 (3.19–15.12)	7.95 (3.47–18.20)	20.77 (10.66–40.45)	0.10 (0.07–0.14)
Serotype III	1.21 (0.45–3.23)	1.41 (0.52–3.86)	2.04 (0.82–5.10)	2.26 (0.84–6.04)	1.01 (0.36–2.83)	3.15 (1.29–7.69)	0.02 (0.01–0.02)
Serotype IV	1.42 (0.74–2.74)	0.81 (0.35–1.91)	1.07 (0.64–1.82)	0.68 (0.33–1.37)	1.02 (0.55–1.90)	2.09 (1.18–3.72)	0.01 (0.01–0.01)
Serotype V	0.11 (0.05–0.24)	0.20 (0.06–0.62)	0.42 (0.16–1.09)	0.78 (0.26–2.30)	0.36 (0.15–0.87)	0.58 (0.24–1.43)	0.01 (0.01–0.02)
Infant-to-maternal GMR (95% CI)							
Serotype Ia	0.53 (0.35–0.81)	1.07 (0.45–2.53)	0.64 (0.51–0.81)	0.66 (0.52–0.83)	0.44 (0.27–0.69)	0.70 (0.57–0.86)	0.76 (0.62–0.93)
Serotype Ib	0.52 (0.36–0.75)	1.09 (0.52–2.32)	0.57 (0.41–0.80)	0.46 (0.26–0.83)	0.41 (0.32–0.54)	0.66 (0.48–0.93)	0.92 (0.69–1.22)
Serotype II	0.72 (0.52–1.00)	1.12 (0.61–2.04)	0.78 (0.60–1.03)	0.70 (0.47–1.05)	0.51 (0.34–0.76)	0.74 (0.60–0.92)	0.67 (0.54–0.83)
Serotype III	0.50 (0.36–0.69)	0.84 (0.54–1.28)	0.58 (0.44–0.77)	0.56 (0.38–0.84)	0.36 (0.25–0.50)	0.55 (0.41–0.74)	0.81 (0.69–0.95)
Serotype IV	0.81 (0.59–1.11)	1.30 (0.68–2.50)	0.85 (0.57–1.26)	0.67 (0.50–0.88)	0.50 (0.37–0.70)	0.71 (0.55–0.92)	0.66 (0.52–0.83)
Serotype V	0.58 (0.42–0.81)	0.78 (0.42–1.44)	0.52 (0.38–0.71)	0.44 (0.24–0.83)	0.40 (0.29–0.53)	0.65 (0.52–0.82)	0.28 (0.62–0.83)
Infants reaching IgG threshold — % (95% CI)							
Serotype Ia	89 (74–97)	100 (88–100)	97 (82–>99)	93 (78–99)	83 (66–93)	97 (85–>99)	40 (29–50)
Serotype Ib	49 (31–66)	62 (42–79)	57 (37–74)	57 (37–74)	63 (45–78)	71 (52–85)	14 (8–23)
Serotype II	100 (90–100)	97 (82–>99)	97 (83–>99)	97 (83–>99)	94 (81–99)	97 (85–>99)	35 (25–45)
Serotype III	72 (55–86)	77 (58–90)	77 (58–90)	83 (65–94)	69 (52–84)	83 (66–93)	13 (7–21)
Serotype IV	85 (69–95)	70 (51–85)	87 (69–96)	73 (54–88)	80 (63–92)	97 (85–>99)	4 (1–11)
Serotype V	36 (21–54)	43 (26–63)	57 (37–74)	70 (51–85)	53 (36–70)	57 (39–74)	9 (4–16)

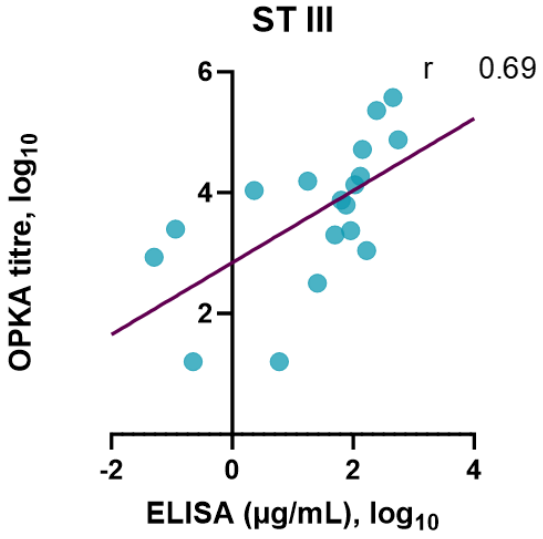
* The numbers of participants in each group are presented as ranges because of occasional missing values in assays for a particular serotype. The total GBS6 dose in the 5-μg GBS6 groups was 30 μg (5-μg CPS per serotype); in the 10-μg GBS6 groups, 60 μg (10-μg CPS per serotype); and in the 20-μg GBS6 groups, 120 μg (20-μg CPS per serotype). The standardized lower limit of quantitation (LLOQ) values for IgG are 0.002 μg per milliliter for serotype Ia, 0.005 μg per milliliter for serotype Ib, 0.022 μg per milliliter for serotype II, 0.009 μg per milliliter for serotype III, 0.004 μg per milliliter for serotype IV, and 0.01 μg per milliliter for serotype V. Assay results below the LLOQ were set to 0.5× LLOQ. The IgG threshold that was determined to be associated with a 75% reduction in the risk of disease was 0.184 μg per milliliter, as derived from a universal Bayesian model. CI denotes confidence interval, GMC geometric mean concentration, and GMR geometric mean ratio.

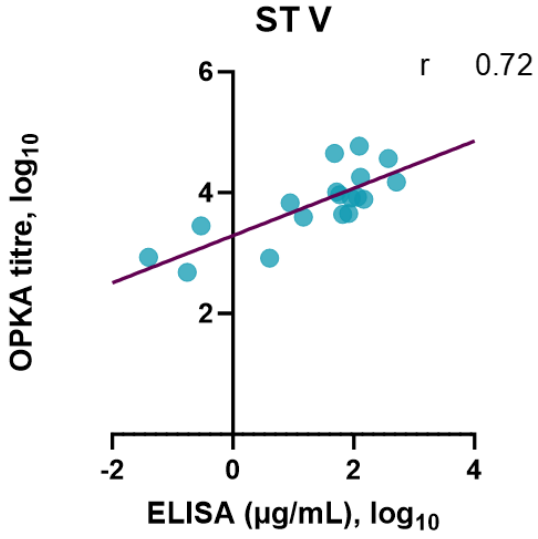
Good correlation between quantity and function











1. Measurement of functional antibody activity is more labor intensive, difficult to standardize, and not conducive to high-throughput

2. Women and babies receive antibiotics

3. Understanding the relationship between binding and functional antibodies is crucial