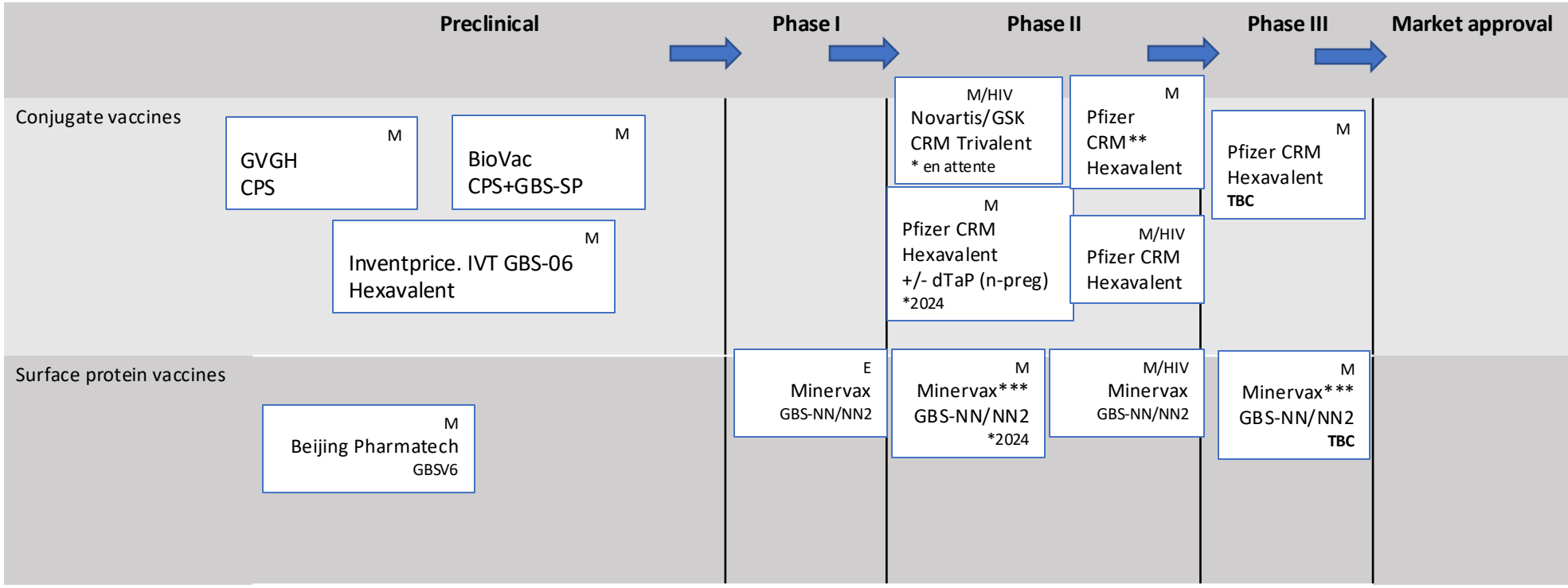
Group B Streptococcus

PDVAC
10th December 2024

Kirsty Le Doare, Annelies Wilder-Smith

Development pipeline for GBS



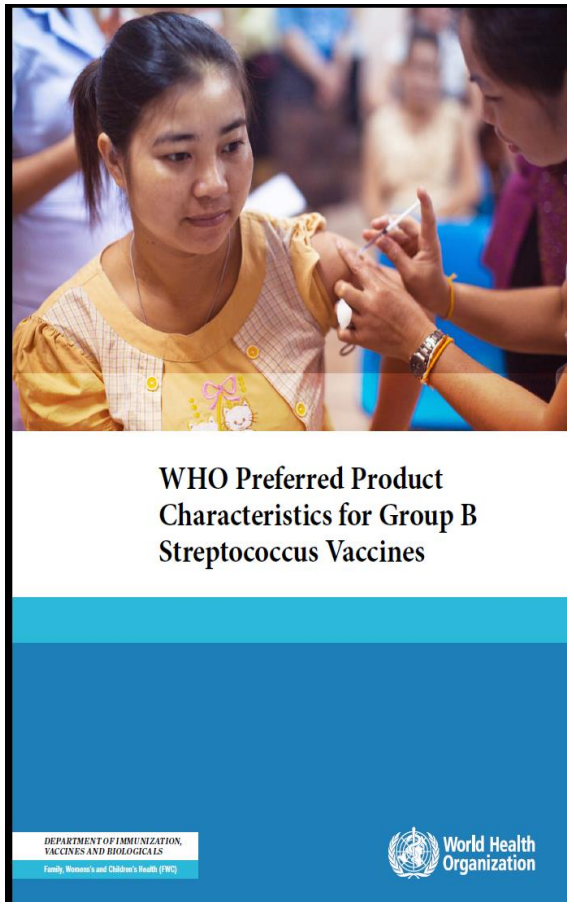
**Pfizer : EMA PRIME : 22/04/2022 ; FDA Breakthrough Therapy Designation 7/09/2022

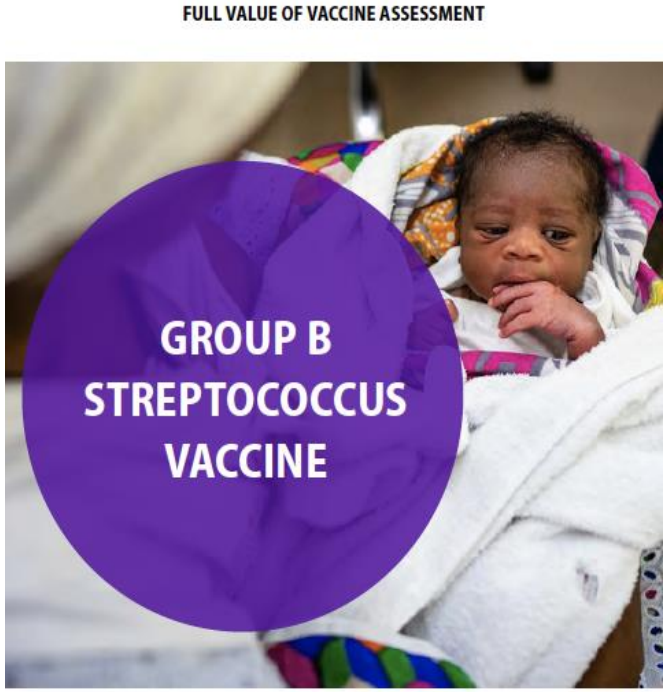
***Minervax EMA PRIME : 15/09/2022

Key : M=maternal, E=elderly, Protein carriers: TT = tetanus toxoid, CRM = CRM 197, GBS-SP = GBS surface proteins

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 LMIC as a priority





LONDON SCHOOL of HYGIENE & TROPICAL MEDICINE | World Health Organization

Major gaps highlighted in the FVVA - GBS

1	2	3	4
GEOGRAPHIC with more data required particularly from Asia	**OUTCOMES** with particular gaps identified for stillbirth, impairment after infant GBS sepsis and maternal disease	**ECONOMIC** including translation of outcomes to disability adjusted life years and assessment of vaccine cost-effectiveness	**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 ICP

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**

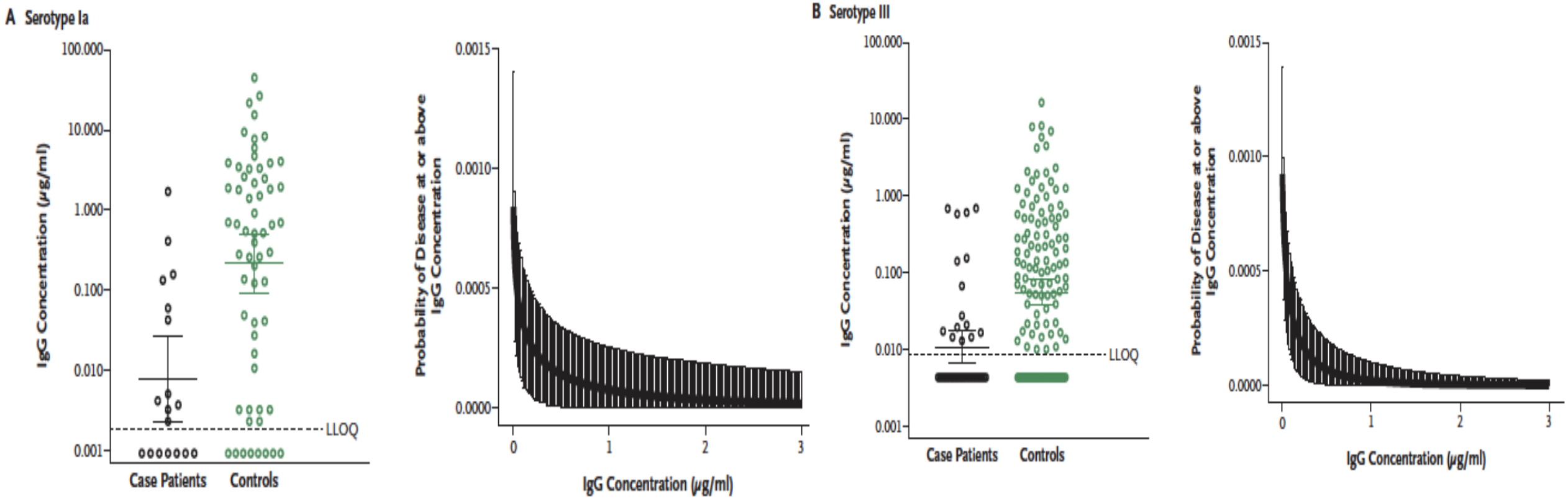
1. extremely rapid progression of GBS sepsis before and soon after birth
2. the need to investigate stillbirth and fatal cases
3. the needs for adequate safety oversight and efficacy monitoring requiring invasive sampling (blood and CSF) and bacteriologic analyses

Commercially unviable

Madhi 2017; Vekemans 2017

Proposed serocorrelates of protection against invasive neonatal and young GBS disease – South Africa

Serotype Ia & III account for 81% of infant disease (95% of late onset disease)



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

Madhi 2023

Proposed serocorrelates of protection against invasive neonatal and young GBS disease - Finland

Serotypes Ia & III account for 74% of infant disease; 77% of late onset disease

Protective antibody concentrations

	Type III only (32 cases; 133 controls)	All types combined (55 cases; 228 controls)
Protective IgG concentrations, µg/mL		
Target risk reductions*		
70%	0·097	0·132
75%	0·120	0·168
80%	0·151	0·217
90%	0·266	0·404

Predictive vaccine efficacy

	GBS6 20 µg	
	With aluminium phosphate	Without aluminium phosphate
Serotype Ia	74·8% (54·5–90·2)	96·0% (86·8–100·0)
Serotype Ib	55·1% (37·6–70·7)	63·5% (47·0–78·5)
Serotype II	88·3% (75·3–97·0)	96·0% (89·5–99·9)
Serotype III	65·3% (48·7–80·4)	82·3% (70·1–92·1)
Serotype IV	79·5% (69·3–88·3)	90·7% (85·3–95·2)
Serotype V	55·0% (40·6–68·6)	59·2% (45·3–72·6)
All serotypes*	66·7% (55·6–76·9)	82·8% (74·9–89·4)

Similar to Madhi study, despite differences in standard of care and IAP policy

Similar for serotype III and all serotypes combined – suggests an aggregate approach might be used

Considerations for policy following market authorization using an immunological correlate of protection

1. **Strength of the ICP** – unlikely that there will be an ICP against all serotypes,
    - strength of the correlation between antibody and protection for most prevalent serotypes needs to be demonstrated for a policy decision

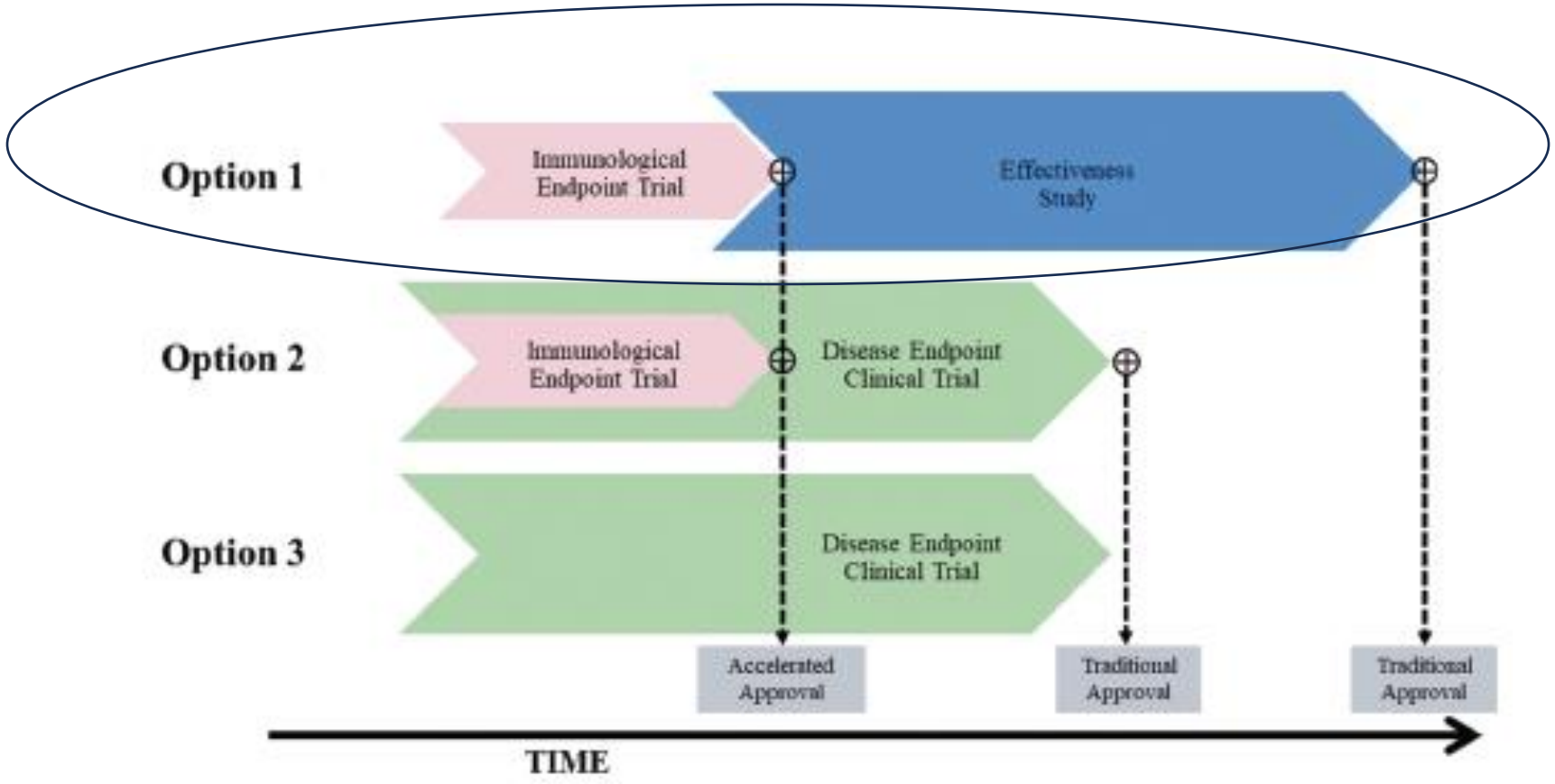
2. Requirement for high confidence in vaccine safety, especially in special populations such as pregnant women and their communities

- safety data needs to be paramount

3. Maternal immunisation relies on passive immunity (Vaccinating the woman to protect woman AND her offspring). Challenges:

- Measuring maternal antibody levels in infants is crucial to assess the effectiveness of maternal vaccination.
- timing and dosage of vaccines for maximum antibody transfer needs to be optimised.
- Duration of protection needs to be demonstrated for both early and late onset disease (Ab waning over first 3 months of life).

Regulatory strategies for a GBS vaccine for use in pregnancy in LMIC



Absolon, Human Vaccinology 2022

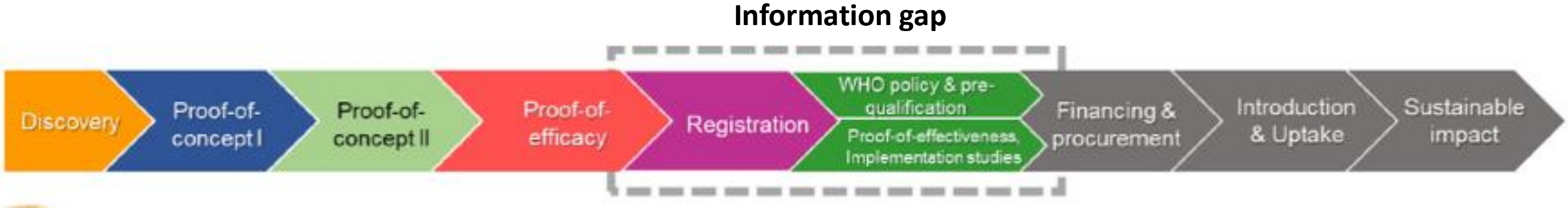
Criteria to be met for conditional market authorization regulatory pathway

EMA (conditional market authorization)	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 confirmatory trial shows that the medicinal product	✓
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

CMA 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, there will be **NO** clinical efficacy data at time of first registration.

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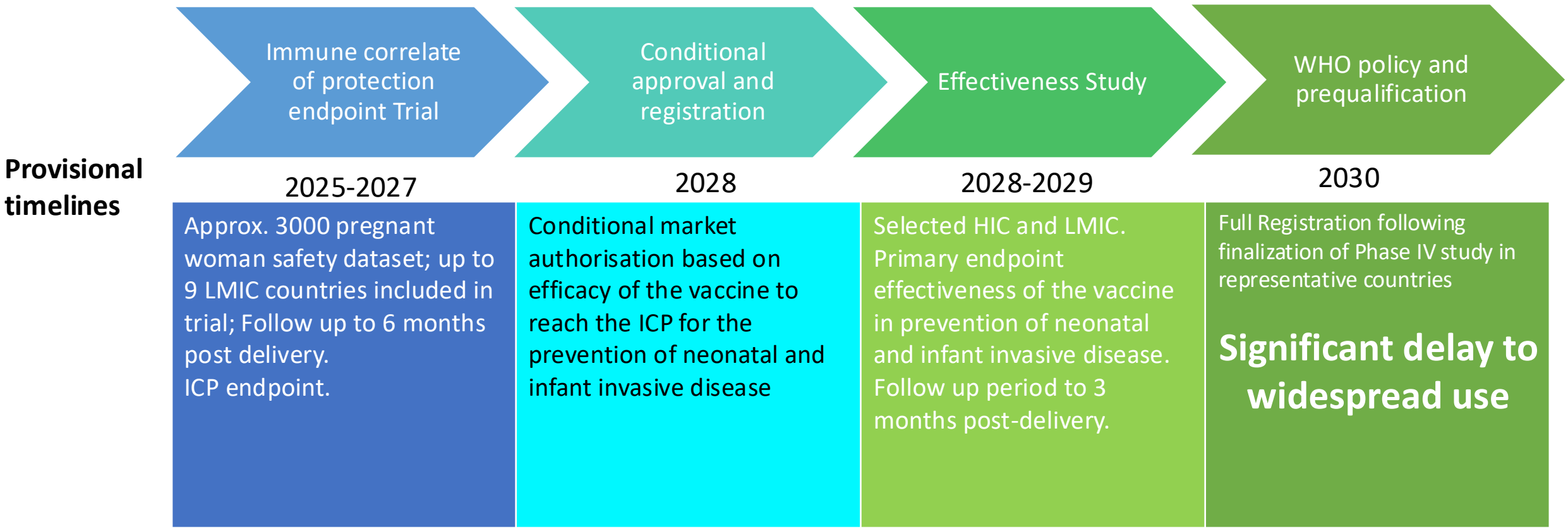
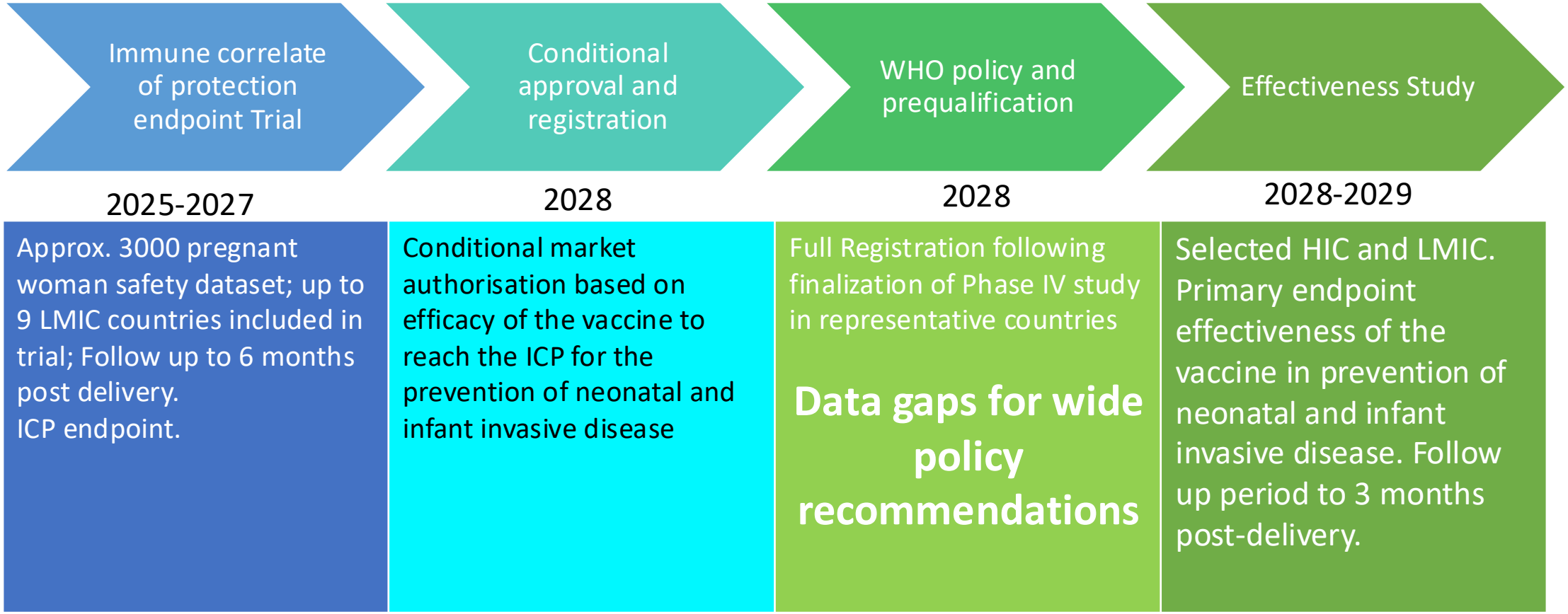
Wide policy recommendation **MAY NOT** be possible until **AFTER** the effectiveness studies

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



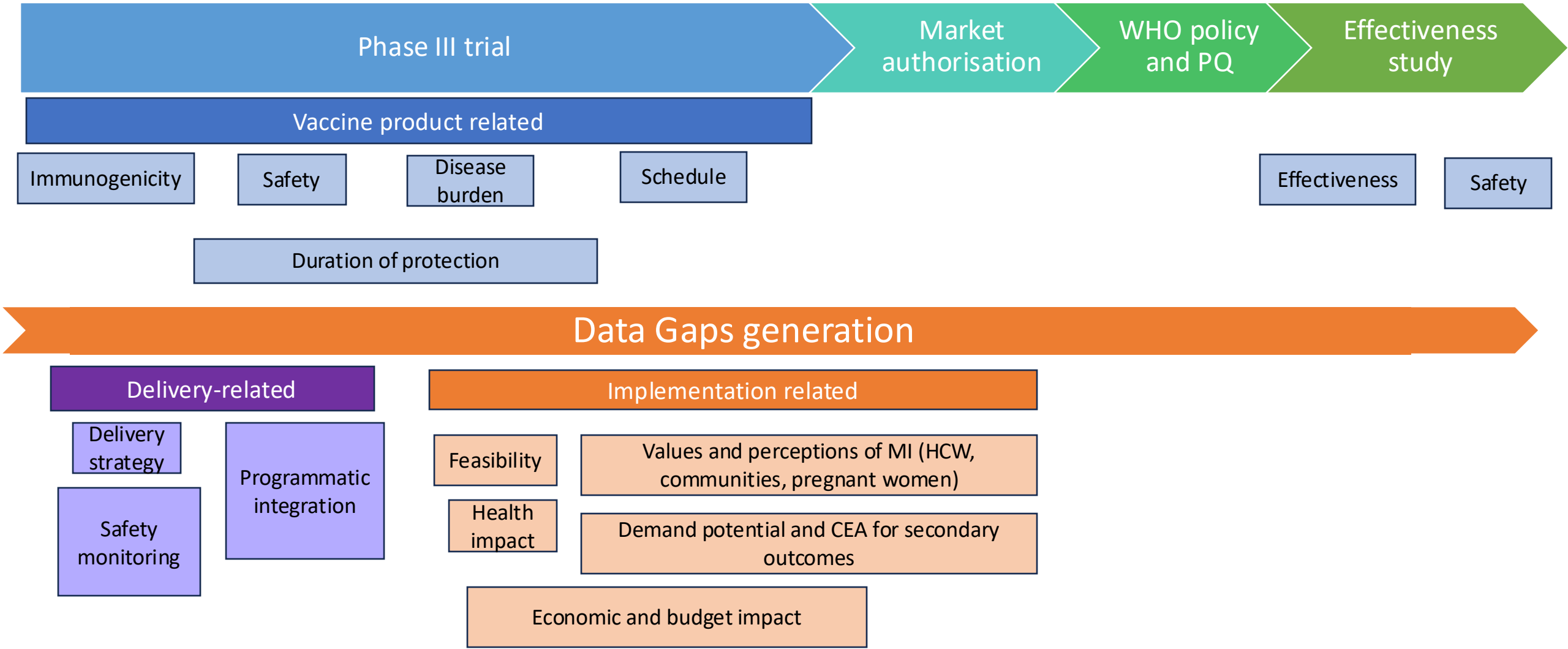
ACCELERATING the Pathway to policy for a GBS vaccine for use in pregnancy in LMIC



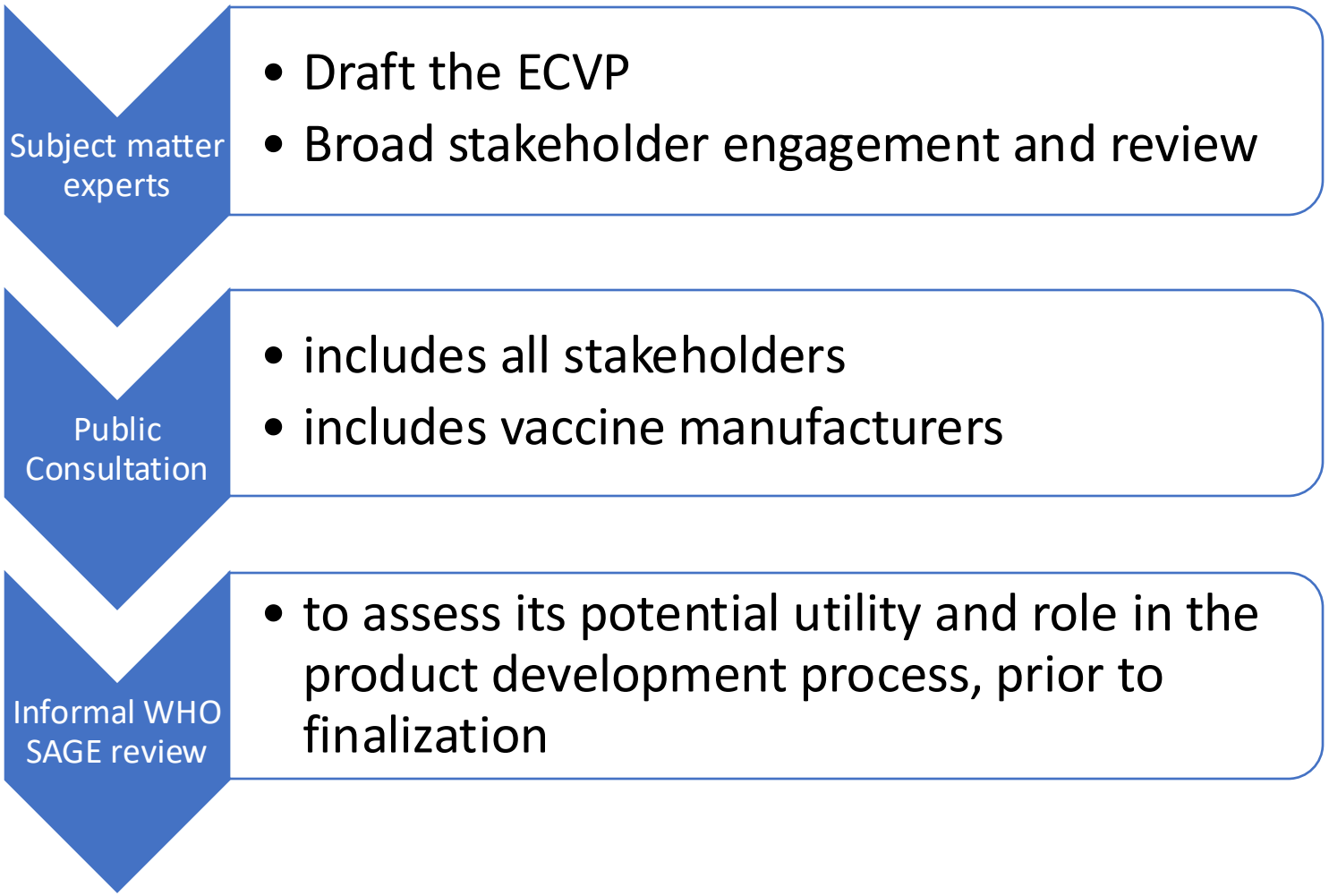
Data requirements for WHO policy review

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 ICP 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



The ECVP in detail



Thank you

Supplementary slides

An Immune marker suitable to infer protection exists for 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.

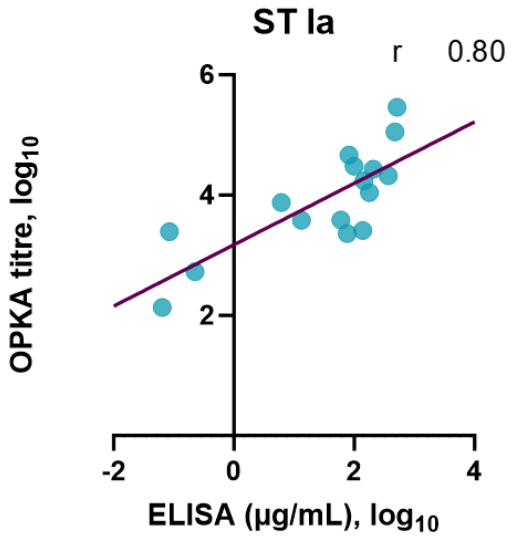
2. Comparison of immune response between candidate vaccine and a licensed vaccine for which efficacy and /or effectiveness has been shown

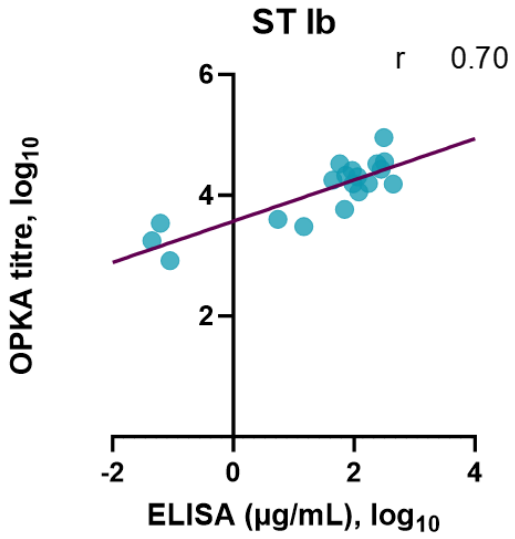
Table 2. Maternal and Infant Anti-CPS IgG Concentrations for Different GBS6 Formulations (Evaluable Immunogenicity Population).*

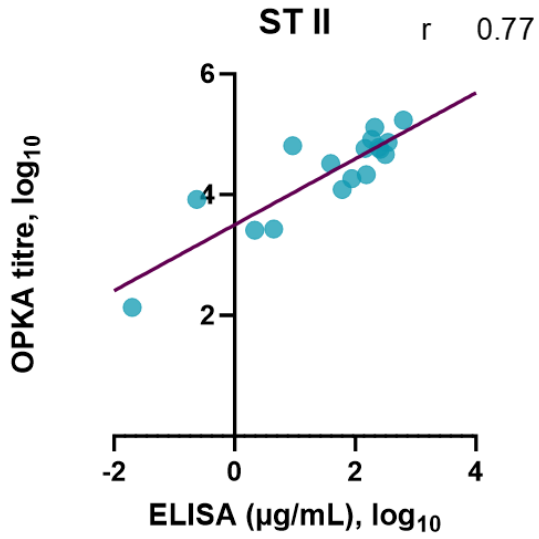
Variable	5-μg GBS6 with $AlPO_4$ (N=34–37)	5-μg GBS6 (N=29–36)	10-μg GBS6 with $AlPO_4$ (N=29–37)	10-μg GBS6 (N=29–34)	20-μg GBS6 with $AlPO_4$ (N=35–38)	20-μg GBS6 (N=34–40)	Placebo (N=91–108)
Maternal GMC at delivery — μg/ml (95% CI)							
Serotype Ia	11.94 (5.57–25.61)	14.71 (6.16–35.11)	14.26 (6.57–30.96)	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)

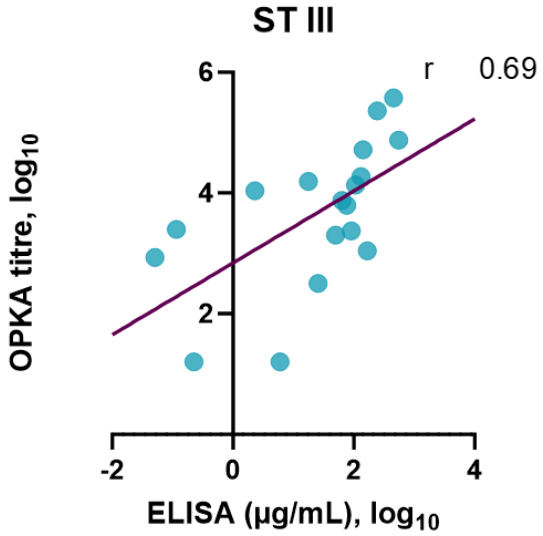
* The numbers of participants in each group are presented as ranges because of occasional missing values in assays for a particular serotype. The total GBS6 dose in the 5-μg GBS6 groups was 30 μg (5-μg CPS per serotype); in the 10-μg GBS6 groups, 60 μg (10-μg CPS per serotype); and in the 20-μg GBS6 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.

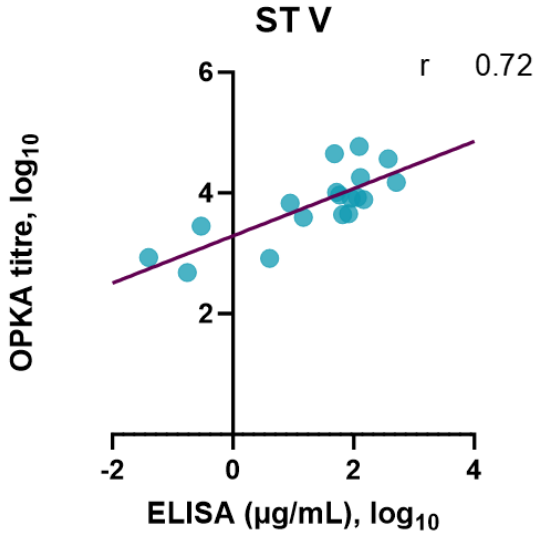
Good correlation between Quantity and function











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