Safety and immunogenicity of GBS6 in pregnant women living with and without HIV and their infants in Uganda (PREPARE WP4): a double-blind, randomised, placebo-controlled, phase 2 clinical trial

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Summary

Background Immunisation in pregnancy against group B streptococcus could reduce severe disease in early infancy; however, there are few data on the safety and immunogenicity of vaccines given to women living with HIV and their infants. We aimed to evaluate the safety, tolerability, and immunogenicity of the hexavalent capsular polysaccharide conjugate group B streptococcus vaccine (GBS6) in pregnant women living with and without HIV, assess infant outcomes, and quantify the placental transfer of vaccine-induced antibodies to their infants.

Methods We conducted a double-blind, randomised, placebo-controlled, phase 2 clinical trial evaluating the safety, reactogenicity, and immunogenicity of 20 µg GBS6 compared with placebo in pregnant women living with HIV or without HIV in five antenatal care facilities in Kampala, Uganda. Women aged 18–40 years, between 27 weeks + 0 days and 35 weeks + 6 days, with a low-risk singleton pregnancy were randomly assigned (1:1) to receive placebo (normal saline) or GBS6 vaccine containing serotypes Ia–V, which were given 2 weeks after standard of care tetanus and diphtheria vaccination. We used stratified block randomisation by maternal HIV status, with a block size of eight. The unblinded site pharmacist prepared the investigational product in syringes that were fully masked with opaque labels before being provided to the vaccination nurse, thereby maintaining blinding of both study staff and participants. The primary outcomes were maternal and infant safety following vaccination assessed in all participants 2 weeks post-vaccination, 1 month post-vaccination, at delivery, 6 weeks after delivery, 18 weeks after delivery, 6 months after delivery, and 12 months after delivery. Secondary outcomes included maternal and infant antiserotype-specific group B streptococcus-capsular polysaccharide IgG concentrations and placental transfer of vaccine-induced antibodies at delivery and 18 weeks after delivery, summarised as geometric mean concentrations with 95% CIs, and were assessed in the modified intent-to-treat population. The study was registered at ClinicalTrials.gov (NCT05832502).

Findings Between Oct 25, 2022, and Oct 22, 2024, 300 pregnant women (150 [50%] living with HIV and 150 [50%] without HIV) were randomly assigned to receive either GBS6 or placebo. The mother and infant pair were followed up until 12 months after delivery. Solicited adverse events reported up to 7 days post-vaccination were mostly mild-to-moderate and transient. In total, 86 serious adverse events were recorded: 25 among GBS6-vaccinated women without HIV, 18 among GBS6-vaccinated women living with HIV, 25 among women without HIV receiving placebo, and 18 among women living with HIV receiving placebo. Of 86 serious adverse events, one death (1%) occurred due to suspected poisoning: a woman living with HIV who received a placebo. Of 298 births, there were five (2%) stillbirths: one (1%) among 74 women living with HIV who received the GBS6 vaccine, one (1%) among 74 women without HIV who received placebo, and three (4%) among 76 women living with HIV who received placebo. All serious adverse events, including maternal death, were not related to the study vaccine. There were 55 serious adverse events among the infant participants, all of which were deemed unrelated to the study vaccine. Two (4%) deaths occurred: one early neonatal death (multiple congenital anomalies and birth asphyxia) in the placebo group and one sudden infant death (asphyxia) at age 4 months in the GBS6 group. GBS6 induced maternal antibody concentration to all serotypes, with no statistically significant differences observed between pregnant women living with and without HIV 1 month following vaccination. The geometric mean concentrations for pregnant women living with HIV compared with pregnant women without HIV were Ia 12·02 (6·42–22·50) versus 9·38 (5·06–17·41; p=0·575), Ib 3·71 (2·12–6·48) versus 2·52 (1·35–4·71; p=0·362), II 19·50 (12·93–29·41) versus 17·92 (11·76–27·31; p=0·776), III 4·38 (2·54–7·55) versus 5·64 (3·66–8·70; p=0·469), IV 4·26 (2·78–6·53) versus 4·53 (2·88–7·13; p=0·842), and V 0·49 (0·34–0·70) versus 0·52 (0·31–0·85; p=0·870). There was no evidence of a difference in maternal antibody responses between pregnant women living with HIV and without HIV. GBS6 induced strong early antibody concentrations that declined over time but remained higher than placebo at 1 year after delivery, and HIV-exposed infant showed similar responses to the HIV-unexposed infants.

Interpretation GBS6 elicited anti-capsular polysaccharide conjugate antibodies against group B streptococcus in pregnant women that were transferred to their infants, with no evidence of a difference irrespective of HIV status. No

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statistically significant difference was seen in pregnant women living with HIV compared with pregnant women not living with HIV or their infants in either safety or immunogenicity, suggesting that this vaccine could be used safely in pregnant women living with HIV.

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Introduction

Group B streptococcus is an important global cause of neonatal and infant morbidity and mortality, responsible for an estimated 90 000 infant deaths and 57 000 stillbirths each year.[1–3] This disease burden surpasses the annual mortality from vertical transmission of HIV, underscoring group B streptococcus as a crucial priority for maternal immunisation efforts.

The urgency for an effective group B streptococcus vaccine is most acute in sub-Saharan Africa, which bears a disproportionate share of the global burden, accounting for 54% of cases and 65% of group B streptococcus-associated deaths.[4] Maternal group B streptococcus colonisation, the primary risk factor for early-onset infant invasive disease, ranges from 14·7% to 28·8% in Uganda, where serotypes Ia, III, and V are predominant. Infant invasive group B streptococcus incidence is approximately one per 1000 live births.[5] The applicability of a maternal vaccine in this region is additionally complicated by the high prevalence of HIV. HIV-exposed uninfected infants are at an increased risk of invasive group B streptococcus disease, likely due to immune dysfunction and impaired placental transfer of pathogen-specific antibodies, a phenomenon observed with other vaccine-preventable diseases.[6] Consequently, the success of any maternal group B streptococcus vaccine in Africa is inherently linked to its performance among women living with HIV.

A hexavalent group B streptococcus conjugate vaccine (GBS6) is currently under clinical investigation as a maternal immunisation strategy to induce protective

Research in context

Evidence before this study

We searched MEDLINE, Web of Science, and ClinicalTrials.gov for studies on group B streptococcal vaccines given to pregnant women living with or without HIV published between Jan 1, 1996, and Feb 4, 2026. Published English-language clinical trials, including randomised and non-randomised studies, were eligible if they evaluated an experimental group B streptococcus vaccine in human participants and reported immunogenicity outcomes. Animal studies and studies focused on screening, epidemiology, cost-effectiveness, or attitudes toward group B streptococcus vaccination were excluded. Our search terms were "(Pregnan* [MeSH] OR matern* [MeSH] OR expectan* [MeSH])" AND "(HIV OR AIDS)" AND "(Vaccin* [MeSH] OR immun*[MeSH])" AND "(Group B Streptococcus OR Streptococcus agalactiae OR GBS)". We did not find any published randomised controlled trials of group B streptococcal vaccines administered in the context of HIV. There were two studies (including the current study) registered on ClinicalTrials.gov that compared pregnant women living with HIV with pregnant women living without HIV. However, neither study had posted results at the time of writing. A phase 2, open-label, multicentre trial found a trivalent glycoconjugate group B streptococcal vaccine to be safe and immunogenic, although immunogenicity and maternal antibody transfer were reduced in pregnant women living with HIV. Evidence was of moderate certainty, with an inherent risk of bias due to its non-randomised, open-label design.

Added value of this study

To the best of our knowledge, this is the first randomised controlled trial to assess the safety and immunogenicity of a hexavalent capsular polysaccharide conjugate group B streptococcus vaccine (GBS6) administered to pregnant women living with HIV and their infants. Our study also describes infant immune responses following primary immunisations in infants whose mothers received the GBS6 vaccine in the context of HIV and includes follow-up to 12 months post-delivery for the mother–infant pair. We found similar patterns of reactogenicity to group B streptococcal by HIV status, with no differences in serious adverse events. However, there was no evidence of a difference in GBS6-elicited antiserotype-specific group B streptococcal IgG concentrations between pregnant women living with HIV and pregnant women without HIV, measured at 2 weeks and 4 weeks post-vaccination and at delivery. Infants born to GBS6-vaccinated women showed substantially higher antiserotype-specific group B streptococcal IgG concentrations at birth compared with those born to placebo recipients. This study provides the first randomised evidence that GBS6 vaccination during pregnancy is safe and elicits similar maternal and infant antibody responses in women living with and without HIV, addressing a critical evidence gap for maternal group B streptococcal immunisation in the context of HIV.

Implications of all of the available evidence

Taking into consideration the burden of group B streptococcal disease globally and the growing need for effective low-cost vaccines for vulnerable populations in low-income and middle-income countries and special populations like pregnant women living with HIV, this vaccine could represent a promising option for policy makers in countries with both a high prevalence of HIV and group B streptococcal burden of disease in infancy.

antibodies that can be transferred to the fetus. Early phase studies have shown that GBS6 elicits robust serotype-specific IgG responses in healthy pregnant women, with evidence suggesting efficient placental antibody transfer. Comparative immunogenicity data in women living with HIV are scarce, but earlier studies of group B streptococcus conjugate vaccines indicate that HIV infection might reduce antibody concentrations and functional activity, highlighting the importance of evaluating vaccine responses specifically in this population.[7]

Currently, a substantial knowledge gap exists regarding the immunogenicity and safety of group B streptococcus vaccines in pregnant women living with HIV.[8] Crucial questions remain as to whether vaccination elicits a robust and functional antibody response in this population and whether these antibodies are effectively transferred to the fetus. Without such evidence, a group B streptococcus vaccine might provide suboptimal protection in the infants at greatest risk,[9] thereby perpetuating health inequities. Licensure strategies for group B streptococcus vaccines will likely rely on serological thresholds of risk reduction; defining immunogenicity thresholds in women with and without HIV and their infants is an important data gap.

We aimed to evaluate the safety, tolerability, and immunogenicity of the investigational GBS6 vaccine in pregnant women living with HIV and pregnant women without HIV and to quantify the placental transfer of vaccine-induced antibodies to their infants and antibody concentrations following the infants' primary immunisation series.

Methods

Study design

PREPARE WP4 is a phase 2, randomised, placebo-controlled, double-blind trial investigating the safety and immunogenicity of the GBS6 vaccine in pregnant women living with HIV or without HIV and their infants. The study was conducted at five antenatal care facilities in Kampala, Uganda (the Kawempe National Referral Hospital, the Kawaala Health Centre III, the Komamboga Health Centre III, the Wakiso Health Centre IV, and the Kisenyi Health Centre IV). Ethical approval was granted by St George's, University of London (2020.0317); the School of Medicine Research and Ethics Committee at Makerere University (Mak-SOMREC-2021-194); the Uganda National Council for Science and Technology (HS1991ES); and the Ugandan National Drug Authority (CTA 0212/2022). The approval was renewed annually. The community advisory board and pregnant women attending antenatal care were consulted during the design and development of the trial and regarding all public-facing materials, and their feedback informed recruitment procedures.

Participants

Pregnant women aged 18–40 years, with a singleton pregnancy between 27 weeks + 0 days and 35 weeks + 6 days gestation, verified by ultrasound, were eligible. Participants were required to be at low obstetric risk based on clinical judgement, have documented negative tests for hepatitis B, hepatitis C, and syphilis, and have normal haematological, renal, and hepatic function. HIV status was documented per national guidelines; women living with HIV were required to be stable on antiretroviral therapy (ART) for at least 3 months before enrolment. Participants were required to plan to give birth at one of the study sites, remain in the area for follow-up until 12 months after delivery, and provide informed consent for themselves and their infant. Women were excluded if they had a prior group B streptococcus vaccination, a high-risk pregnancy, significant maternal comorbidities, an immunodeficiency other than HIV, immunosuppressive therapy, recent participation in another investigational study, or any investigator-assessed condition that could compromise participant safety or study integrity. Full eligibility criteria are detailed in the study protocol.[10]

The study was registered with ClinicalTrial.gov (NCT05832502) and is now closed to new participants.

Randomisation and masking

Participants were individually randomly assigned (1:1) to receive a single intramuscular injection of either the GBS6 vaccine or a saline placebo (0·5 mL into the deltoid muscle). The randomisation sequence was computer-generated with stratification by maternal HIV status and a block size of eight, creating four study groups: pregnant women without HIV receiving placebo, pregnant women without HIV receiving GBS6, pregnant women living with HIV receiving placebo, and pregnant women living with HIV receiving GBS6 (n=75 per group; N=300). Participants were enrolled by the study clinician and randomised by the data manager, who were not involved in participant safety assessments or follow-up.

The study was double-blind. An unmasked site pharmacist prepared the investigational product, and syringes were completely covered with an opaque label before being handed to the vaccination nurse. The GBS6 vaccine or placebo was administered by a nurse masked to group allocation, who had no other involvement in the study. Participants, investigators, site staff, and laboratory personnel performing serological assays remained masked to treatment allocation throughout the study.

Procedures

Informed consent was obtained from all participants before any study procedures. For participants unable to read, the consent form was read to them, in the presence of an impartial witness, and consent was documented with a thumbprint.

After a screening visit, eligible participants received a single dose of GBS6 or placebo, administered 2 weeks after standard-of-care tetanus–diphtheria vaccination. Participants completed a paper diary card for 7 days post-vaccination to record solicited local reactions (injection site pain, redness, swelling, etc) and systemic reactions

(fever, headache, fatigue, etc). Maternal blood samples for immunogenicity (anti-capsular polysaccharide IgG and opsonophagocytic activity) were collected at baseline (vaccination), 2 weeks post-vaccination, 1 month post-vaccination, delivery, 6 weeks after delivery, and 12 months after delivery.

Rectal and vaginal swabs were collected for group B streptococcus colonisation in the pregnant woman at vaccination, delivery, and 6 weeks after delivery.

Infants were followed up from birth until age 12 months. Infant blood samples for immunogenicity were collected at birth (via cord blood or neonatal blood obtained up to 72 h after delivery) and 6 weeks, 18 weeks, and 12 months after delivery. All infants received routine vaccinations per the Ugandan Expanded Programme on Immunisation.[11]

The investigational product was the GBS6 vaccine, a hexavalent capsular polysaccharide conjugate vaccine (serotypes Ia, Ib, II, III, IV, and V) without aluminium phosphate adjuvant, supplied by Pfizer (New York, NY, USA). The dose was 20 µg without AlPO4, equivalent to 240 µg/mL or 20 µg of each capsular polysaccharide per serotype in a 0·5 mL dose. The capsular polysaccharides are individually conjugated to the cross-reactive material 197 (CRM197) carrier protein, a non-toxic variant of diphtheria toxin.[12] The placebo was a 0·9% saline solution.

Serum samples were processed and stored in Uganda and analysed at City St George's, University of London. Group B streptococcus serotype-specific IgG antibody concentrations (µg/mL) for all six serotypes were determined using a multiplex immunoassay first described by Gaylord and colleagues[13] and endorsed by the group B streptococcal standardisation (GASTON) consortium, an initiative funded by the Gates Foundation to standardise immunological approaches for the measurement of immune responses to potential group B streptococcus vaccine candidates in human populations.[14] The GASTON multiplex immunoassay measures serotype-specific anti-capsular polysaccharide IgG concentrations for six group B streptococcus serotypes (Ia, Ib, II, III, IV, and V).[13]

Outcomes

The primary outcomes were safety and tolerability. For mothers, these include solicited local and systemic adverse events within 7 days, unsolicited or spontaneously reported non-serious adverse events within 1 month, and serious adverse events, medically attended adverse events, and obstetric complications throughout the study. For infants, primary safety outcomes include unsolicited or spontaneously reported non-serious adverse events from birth to age 6 weeks and serious adverse events, medically attended adverse events, and adverse events of special interest (eg, major congenital anomalies, developmental delay, and group B streptococcus infection) from birth to age 12 months. All reports of unsolicited or spontaneously reported non-serious adverse events, serious adverse events, and medically attended adverse events were collected, assessed, and monitored by medically qualified study staff. Solicited adverse events were documented on paper diary cards by the study participants.

Secondary outcomes were group B streptococcus serotype-specific IgG antibody concentrations in mothers (at baseline, 2 weeks post-vaccination, 1 month post-vaccination, at delivery, 6 weeks after delivery, and 12 months after delivery) and infants (at delivery and age 6 weeks, 18 weeks, and 12 months), functional antibody concentrations (opsonophagocytic activity) in mothers at baseline and at delivery and in infants at age 18 weeks, and the placental transfer ratio of group B streptococcus-specific antibodies in mother–infant pairs. The 12-month post-delivery maternal antibody concentration endpoint was considered exploratory. A post-hoc analysis of placental transfer was also undetaken.

The results from the opsonophagocytic killing assay titres measured at baseline and at delivery in pregnant women with HIV and in HIV-exposed infant participants measured at age 18 weeks and exploratory objectives will be available in a subsequent publication.

Statistical analysis

The safety analysis included all participants who received the investigational product (ie, the safety population). Proportions of participants with adverse events were calculated, with comparisons between GBS6 and placebo within each HIV stratum performed using Fisher's exact test. No formal adjustment for multiple comparisons was applied, and safety outcomes were primarily interpreted descriptively.

The immunogenicity analysis was performed on the modified intention to treat and evaluable immunogenicity populations. Geometric mean concentrations (GMCs) of IgG antibody concentrations with 95% CIs were calculated for each serotype. Antibody concentrations were log-transformed for analysis, and groups were compared using unpaired *t* tests or non-parametric alternatives if log-concentrations were not normally distributed. Geometric mean ratios (GMRs) were estimated from log-transformed data using models adjusted for baseline HIV status. The placental transfer ratio was calculated as the ratio of infant GMC at birth to maternal GMC at delivery. Ratios were compared between GBS6 and placebo within each HIV stratum, and between pregnant women with and without HIV within the GBS6 group, using unpaired *t* tests on log-transformed values, with 95% CIs calculated on the log scale and back-transformed. In a post-hoc exploratory analysis, serotype-specific linear regression models adjusted for gestational age at vaccination, time from vaccination to delivery, birthweight, and maternal HIV status were used to estimate adjusted GMRs for placental transfer. The proportion of missing data was less than 5%. Missing data were not imputed; a complete case analysis was conducted.

The sample size of 300 (75 per group) was primarily based on feasibility for this phase 2 study and to provide

preliminary safety and immunogenicity data. For safety, this provides 80% power (α=0·05) to detect an increase in prematurity from an assumed baseline rate of 10% in the placebo group to 22% in the vaccine group. For secondary immunogenicity outcomes, assuming a standard deviation of 2·55 $\log_e$ units for antibody concentrations (based on previous data), 75 participants per group provides 80% power (α=0·05) to detect a 3·24-fold difference in

	GBS6 group		Placebo group		Overall (N=300)
	HIV-negative (n=76)	HIV-positive (n=74)	HIV-negative (n=74)	HIV-positive (n=76)	
Age, years					
Mean	24·9 (5·0)	28·6 (5·5)	24·3 (4·3)	29·1 (5·2)	26·7 (5·5)
Range	18·0–38·0	19·0–40·0	18·0–36·0	18·0–40·0	18·0–40·0
Nationality					
Ugandan	74 (97%)	73 (99%)	73 (99%)	73 (96%)	293 (98%)
Rwandan	1 (1%)	0	0	2 (3%)	3 (1%)
Tanzanian	1 (1%)	1 (1%)	0	1 (1%)	3 (1%)
Congolese (DR Congo)	0	0	1 (1%)	0	1 (<1%)
Race					
Black	76 (100%)	74 (100%)	74 (100%)	76 (100%)	300 (100%)
Marital status					
Married	51 (67%)	51 (69%)	57 (77%)	46 (61%)	205 (68%)
Cohabiting	18 (24%)	14 (19%)	11 (15%)	18 (24%)	61 (20%)
Single	7 (9%)	9 (12%)	6 (8%)	12 (16%)	34 (11%)
Highest level of education					
Some secondary	41 (54%)	36 (49%)	38 (51%)	36 (47%)	151 (50%)
Some primary	15 (20%)	12 (16%)	10 (14%)	13 (17%)	50 (17%)
Completed primary	11 (14%)	10 (14%)	10 (14%)	10 (13%)	41 (14%)
University, college, or tertiary	6 (8%)	13 (18%)	10 (14%)	7 (9%)	36 (12%)
Completed secondary	3 (4%)	1 (1%)	6 (8%)	6 (8%)	16 (5%)
None	0	2 (3%)	0	4 (5%)	6 (2%)
Delivered at the study site					
Yes	65 (88%)	63 (85%)	62 (84%)	69 (91%)	259 (87%)
No	9 (12%)	11 (15%)	12 (16%)	7 (9%)	39 (13%)
Gestational age at receipt of GBS6 or placebo, weeks					
Mean	31 (3)	30 (3)	31 (3)	30 (3)	30 (3)
Range	27–35	27–35	27–35	27–35	27–35
Gestational age at delivery, weeks					
Mean	39·42 (1·23)	39·45 (1·17)	39·67 (1·12)	39·47 (1·06)	39·50 (1·14)
Range	37–42	36–42	37–42	36–42	36–42
Mode of delivery					
Spontaneous vaginal	46 (62%)	47 (64%)	50 (68%)	61 (80%)	204 (68%)
Emergency caesarean section	20 (27%)	15 (20%)	18 (24%)	12 (16%)	65 (22%)
Planned caesarean section	5 (7%)	12 (16%)	4 (5%)	3 (4%)	24 (8%)
Vaginal breech	2 (3%)	0	2 (3%)	0	4 (1%)
Assisted vaginal (forceps)	1 (1%)	0	0	0	1 (<1%)
Complications of labour					
No	52 (70%)	53 (72%)	52 (70%)	53 (70%)	210 (70%)
Yes	22 (30%)	21 (28%)	22 (30%)	23 (30%)	88 (30%)
CD4⁺ count at enrolment					
Mean	NA	716 (249)	NA	695 (305)	706 (278)
Range	NA	258–1553	NA	159–1754	159–1754
Dolutegravir-based antiretroviral therapy regimen					
No	NA	5 (7%)	NA	1 (1%)	6 (4%)
Yes	NA	69 (93%)	NA	75 (99%)	144 (96%)

Data are mean (SD), range, or n (%). NA=not applicable.

Table 1: **Baseline characteristics of maternal participants**

antibody responses between vaccine and placebo groups within each HIV stratum. Statistical analyses were performed using R, version 4.5.1.

An independent data and safety monitoring board reviewed safety data. The study was first submitted to ClinicalTrials.gov on Feb 20, 2023, and posted on April 27, 2023, after enrolment had begun because of operational disruptions during the COVID-19 pandemic affecting non-COVID-19 research activities. The protocol had been finalised before study initiation, and no changes were made to the prespecified objectives, endpoints, eligibility criteria, or statistical analysis plan between trial initiation and registration (appendix pp 35–183).

See Online for appendix

	GBS6 group		Placebo group		Overall (N=298)
	HIV-negative (n=74)	HIV-positive (n=74)	HIV-negative (n=74)	HIV-positive (n=76)	
Livebirth	74 (100%)	73 (99%)	73 (99%)	73 (96%)	293 (98%)
Stillbirth	0	1 (1%)	1 (1%)	3 (4%)	5 (2%)
Sex					
Male	38 (51%)	41 (55%)	38 (51%)	34 (45%)	151 (51%)
Female	36 (49%)	33 (45%)	36 (49%)	42 (55%)	147 (49%)
Gestational age at birth, weeks*					
Median	40 (39–41)	40 (39–41)	40 (39–41)	40 (39–41)	40 (39–41)
Range	37–42	36–42	37–42	36–42	36–42
24–<28	0	0	0	0	0
28–<34	0	0	0	0	0
34–<37	0	2 (3%)	0	2 (3%)	4 (1%)
37–<42	69 (93%)	66 (90%)	69 (95%)	69 (95%)	273 (93%)
≥42	5 (7%)	5 (7%)	4 (5%)	2 (3%)	16 (5%)
Apgar score, 5 min*†					
<4	0	0	0	1 (1%)	1 (<1%)
4–<7	0	0	1 (1%)	0	1 (<1%)
7–10	70 (95%)	68 (93%)	65 (89%)	69 (95%)	272 (93%)
Median	10 (7–10)	10 (7–10)	10 (6–10)	10 (3–10)	10 (3–10)
Birthweight					
Extremely low birth weight (≤1000 g)	0	0	0	0	0
Very low birth weight (>1000–1500 g)	0	0	0	2 (3%)	2 (1%)
Low birth weight (>1500–<2500 g)	2 (3%)	3 (4%)‡	3 (4%)	5 (7%)	13 (4%)
Normal birth weight (≥2500 g)	72 (97%)	69 (93%)‡	71 (96%)	69 (91%)	281 (94%)
Head circumference (cm)	35·00 (33·60–35·60)	34·70 (33·65–35·55)	34·75 (34·00–35·50)	34·50 (33·55–35·45)	34·70 (33·70–35·50)
Length (cm)	49·00 (47·50–50·00)	48·50 (47·35–50·00)	49·00 (48·00–50·00)	48·35 (47·00–50·00)	48·85 (47·50–50·00)
Weight (g)	3103 (2940–3500)	3228 (2815–3460)	3185 (2930–3400)	3140 (2800–3500)	3185 (2900–3460)
Mid-upper arm circumference (cm)	10·65 (10·00–11·50)	10·55 (10·00–11·50)	10·95 (10·20–11·50)	10·65 (10·00–11·50)	10·80 (10·00–11·50)
Resuscitation required at birth§	2 (3%)	2 (3%)	2 (3%)	2 (3%)	8 (3%)
Admitted to NICU from the labour ward	3 (4%)	4 (5%)	3 (4%)	6 (8%)	16 (5%)
Any congenital abnormalities at birth	2 (3%)	1 (1%)	1 (1%)	6 (8%)	10 (3%)
Breastfeeding*	74 (100%)	71 (97%)	72 (99%)	72 (99%)	289 (99%)

Data are in n (%), median (IQR) unless stated otherwise. NICU=neonatal infant care unit. *In livebirth infants. †Data were missing or unavailble for 19 infants. ‡Data were missing for two infants in this group. §All infants who require resuscitation survived.

Table 2: **Baseline characteristics of infant participants**

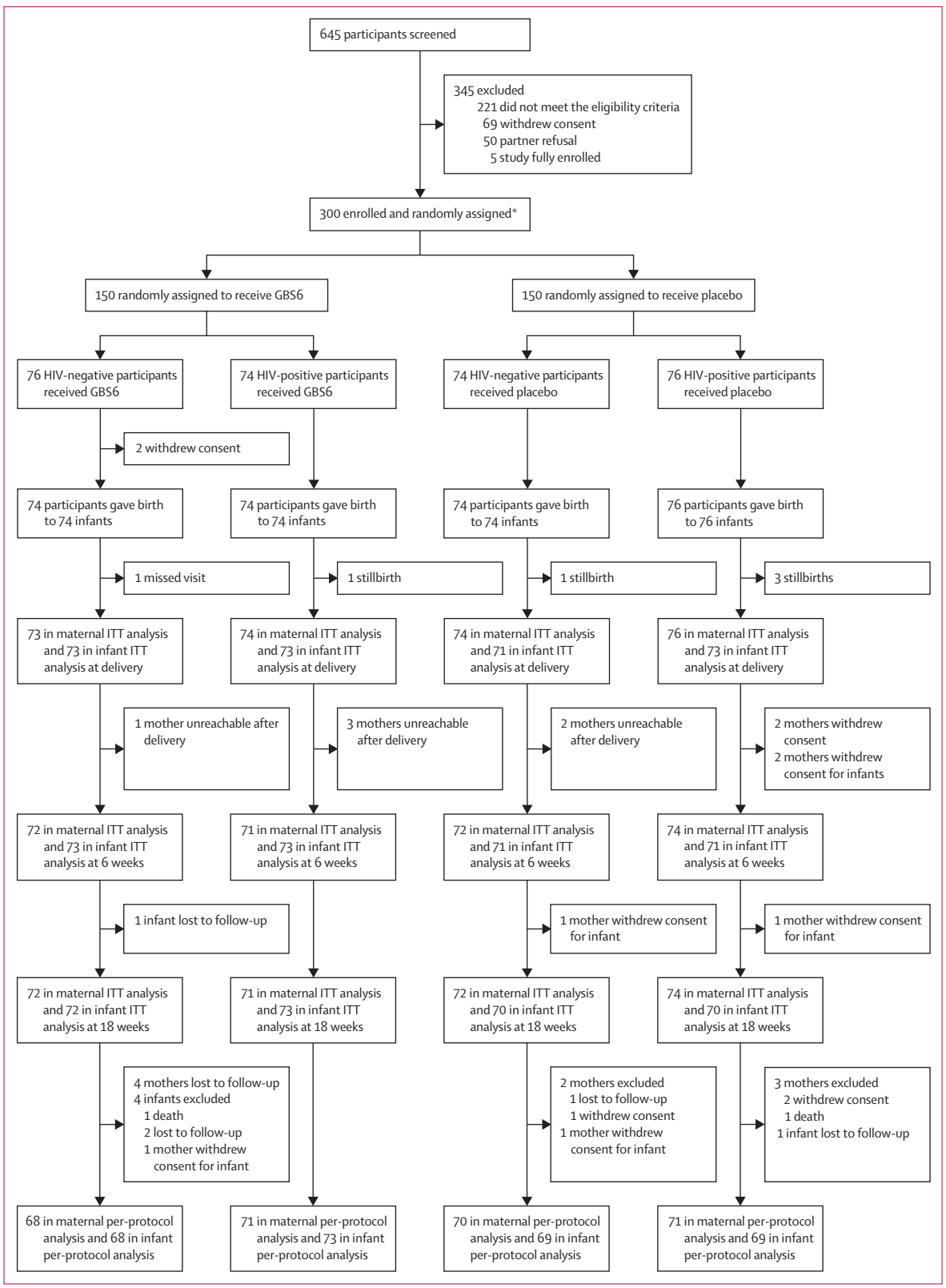

Figure 1: **Trial profile**
Due to changes in family circumstances some mothers might have withdrawn or been lost to follow-up while their infant continued in the study and vice versa. ITT=intent-to-treat. *150 participants were HIV-positive and 150 participants were HIV-negative.

Role of the funding source
The funder had no role in study design, data collection, analysis, data interpretation, or writing of the report. The GBS6 vaccine was provided by Pfizer, who contributed to study design and writing of the report, but had no role in data collection and analysis.

Results

From Oct 25, 2022, to Oct 22, 2024, 645 pregnant women across five study sites in Kampala, Uganda, were screened (figure 1). Of these, 300 were deemed eligible and were enrolled and randomly assigned to one of the four study groups: pregnant women without HIV receiving placebo, pregnant women without HIV receiving GBS6, pregnant women living with HIV receiving placebo, and pregnant women living with HIV receiving GBS6. All 300 pregnant women received a routine tetanus–diphtheria vaccination and either a placebo or GBS6 vaccine. All 300 randomised participants were included in the primary endpoint analysis. The maternal and infant modified intent-to-treat populations comprised participants with at least one valid and determinate assay result for the relevant immunogenicity analysis; therefore, denominators varied by endpoint and study visit and are reported with each analysis. Two maternal participants withdrew before delivery. Consequently, delivery outcomes were available for 298 women, resulting in 293 liveborn infants and five stillbirths. The 293 liveborn infants were enrolled into the infant safety follow-up, with the numbers contributing to individual immunogenicity analyses varying by study visit because of participant retention and sample availability (figure 1).

The participant demographics were similar across study groups. The mean age of enrolled pregnant women was 26·7 years (SD 5·5, range 18·0–40·0). Of the 300 women, 293 (98%) were Ugandan, three (1%) were Rwandan, three (1%) were Tanzanian, and one was Congolese (<1%) and all participants were Black (table 1). All enrolled pregnant women living with HIV were on combined ART for at least 3 months before study entry, with a mean $CD4^+$ T lymphocyte count of 706 cells per µL (SD 278, range 159–1754). 144 (96%) of 150 pregnant women living with HIV were receiving a dolutegravir-based regimen. The mean gestational age at vaccination with the GBS6 or placebo was 30 weeks (SD 3, range 27–35), and the mean gestational age at delivery was 39·5 weeks (SD 114, range 36–42), with four preterm livebirths (born at <37 weeks' gestation; table 2).

Most women delivered at a study site (259 [87%] of 298); 204 (68%) of 298 had a spontaneous vaginal delivery, 65 (22%) had an emergency caesarean section, 24 (8%) had a planned caesarean section, four (1%) had a vaginal breech, and one (<1%) had an assisted vaginal delivery (table 1). 94 women experienced obstetric complications at delivery, with perineal tears accounting for 72 (77%) of these (appendix pp 12–13). Overall, 34 (11%) of 300 women were colonised with any group B streptococcus serotype at baseline.

Women self-reported mostly mild to moderate, transient solicited adverse events in days 1–7 after vaccination (figure 2). The reactogenicity profiles were similar between the GBS6 and placebo groups for solicited systemic adverse events (p=0·87 pregnant women without HIV and p=0·14 for pregnant women living with HIV). For solicited local adverse events, the proportion of pregnant women without HIV reporting at least one adverse events was 41 (54%) of 76 in the GBS6 group and 22 (30%) of 74 in the placebo group (p=0·0030 Fisher's exact test). No differences were found between the pregnant women living with HIV placebo group and the pregnant women living with HIV GBS6 group (p=0·080).

There were 82 unsolicited or spontaneously reported non-serious adverse events in 300 women 28 days post-vaccination; all of them were mild to moderate (appendix p 5). Assessments were performed while the study team was still blinded to treatment allocation and all unsolicited or spontaneously reported non-serious adverse events deemed possibly related to the investigational product (n=12) occurred only in the placebo group. Overall, 30 (20%) of 150 women receiving GBS6 and 40 (27%) of 150 women receiving placebo reported at least one unsolicited or spontaneously reported non-serious adverse event (table 3); there were 33 unsolicited or spontaneously reported non-serious adverse events in the GBS6 group and 49 in the placebo group (appendix p 5). Within the GBS6 group, 19 (58%) of 33 unsolicited or spontaneously reported non-serious adverse events occurred in pregnant women without HIV and 14 (42%) in pregnant women living with HIV; within the placebo group, 23 (47%) of 49 occurred in pregnant women without HIV and 26 (53%) in pregnant women living with HIV. Comparing groups within each HIV stratum, no significant differences were observed: 17 (22%) of 76 pregnant women without HIV receiving GBS6 had at least one unsolicited or spontaneously reported non-serious adverse event versus 21 (28%) of 74 receiving placebo (p=0·46 Fisher's exact test), and 13 (18%) of 74 pregnant women with HIV receiving GBS6 experienced at least one unsolicited or spontaneously reported non-serious adverse event versus 19 (25%) of 76 receiving placebo (p=0·32).

There were 78 unsolicited or spontaneously reported non-serious adverse events among the infants from birth to age 6 weeks; all of them were of mild to moderate in severity and all events were deemed unrelated to the investigational product (appendix p 6; table 4). Overall, 28 (19%) of 147 infants in the GBS6 group and 45 (31%) of 146 in the placebo group had at least one unsolicited or spontaneously reported non-serious adverse event; there were 30 unsolicited or spontaneously reported non-serious adverse events that

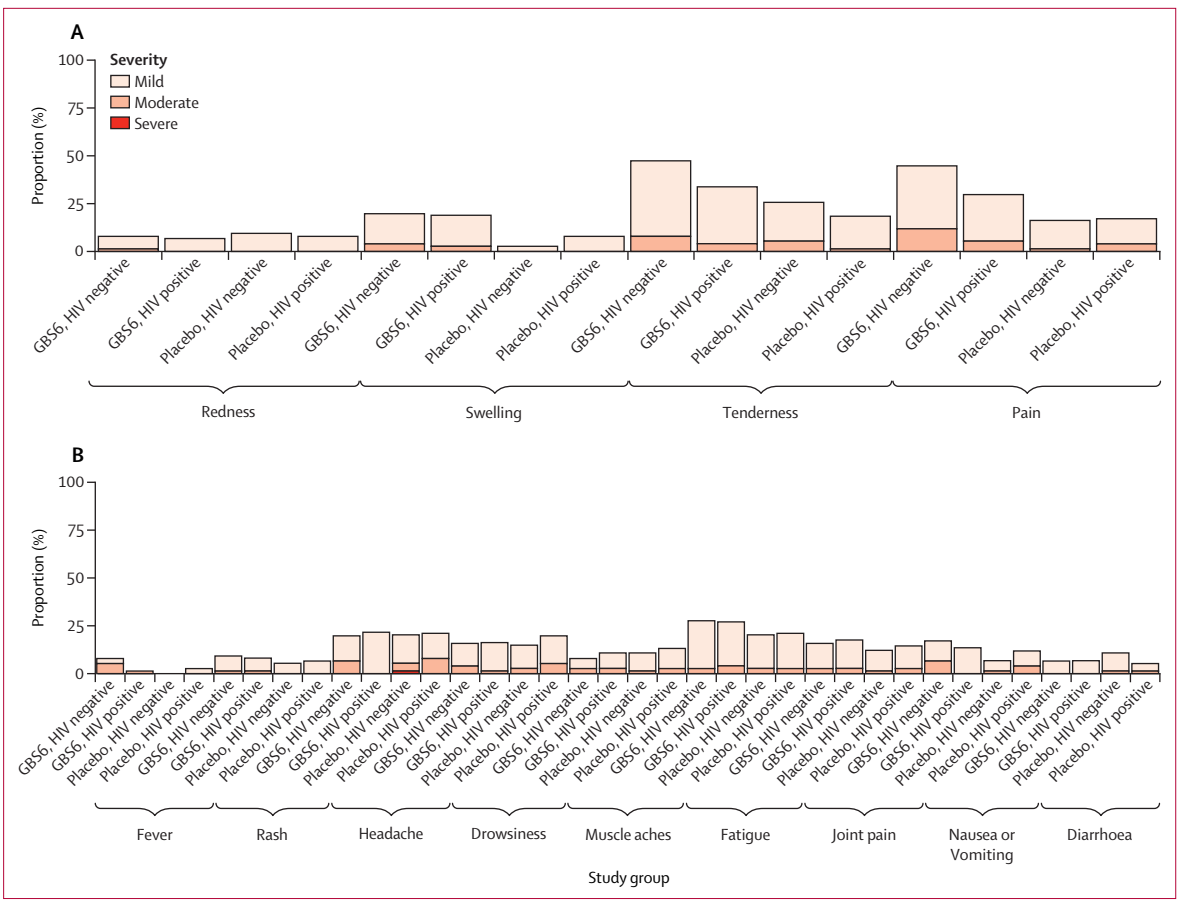

Figure 2: **Solicited local and systemic adverse events in 7 days after vaccination by study group as self-reported in participant diaries (safety analysis population)**

Reactogenicity severity of solicited adverse events in the 7 days after vaccination, shown by study group and HIV status as self-reported in participant diaries. (A) Local reaction at the vaccine injection site. (B) Systemic reactions (affecting the whole body or the rest of the body). Percentages represent the proportion of participants reporting each specific solicited adverse event. The severity presented is the participant's highest severity for 7 days following the vaccination for each solicited adverse event. The participants self-reported local and systemic adverse events following vaccination as none, mild, moderate, or severe.

occurred in 147 infants in the GBS6 group and 48 unsolicited or spontaneously reported non-serious adverse events in 146 infants in the placebo group. Among the GBS6 group, 14 (47%) of 30 unsolicited or spontaneously reported non-serious adverse events occurred in HIV-unexposed infants and 16 (53%) in HIV-exposed infants, whereas in the placebo group, 21 (44%) of 48 unsolicited or spontaneously reported non-serious adverse events occurred in HIV-unexposed infants and 27 (56%) occurred in HIV-exposed infants. Comparing groups within each HIV stratum, no significant differences were observed: 13 (18%) of 74 HIV-unexposed infants experienced at least one unsolicited or spontaneously reported non-serious adverse event in the GBS6 group versus 20 (27%) of 73 in the placebo group (p=0·24) and 15 (21%) of 73 HIV-exposed infants experienced at least one unsolicited or spontaneously reported non-serious adverse event in the GBS6 group versus 25 (34%) of 73 in the placebo group (p=0·068; table 3).

	GBS6 group		Placebo group		p value	
	HIV-negative (n=76)	HIV-positive (n=74)	HIV-negative (n=74)	HIV-positive (n=76)	GBS6 *vs* placebo (HIV-negative)	GBS6 *vs* placebo (HIV-positive)
Unsolicited adverse events	17 (22%)	13 (18%)	21 (28%)	19 (25%)	0·46	0·32
Medically attended adverse events	50 (66%)	56 (76%)	52 (70%)	54 (71%)	0·602	0·58
Serious adverse events	25 (33%)	18 (24%)	25 (34%)	18 (24%)	1·000	1·000
Obstetric complications	41 (54%)	33 (45%)	38 (51%)	40 (53%)	0·87	0·33

Data are n (%). p values from Fisher's exact test comparing GBS6 versus placebo within each HIV stratum. All unsolicited adverse events, medically attended adverse events, and serious adverse events were unrelated to study vaccination.

Table 3: **Maternal participants with adverse events**

There were 495 medically attended adverse events among 300 mothers and 824 among 293 infants. All events were mild to moderate except four (<1%) in the

	GBS6 group		Placebo group		p value	
	HIV-negative (n=74)	HIV-positive (n=73)	HIV-negative (n=73)	HIV-positive (n=73)	GBS6 *vs* placebo (HIV-negative)	GBS6 *vs* placebo (HIV-positive)
Unsolicited adverse events	13 (18%)	15 (21%)	20 (27%)	25 (34%)	0·24	0·068
Medically attended adverse events	61 (82%)	57 (78%)	60 (82%)	59 (81%)	1·000	1·000
Serious adverse events	12 (16%)	7 (10%)	16 (22%)	9 (12%)	0·53	0·79

Data are n (%). p values from Fisher's exact test comparing GBS6 versus placebo within each HIV stratum. All unsolicited adverse events, medically attended adverse events, and serious adverse events were unrelated to study vaccination.

Table 4: **Infant participants with adverse events**

infant participants, which were severe. Two HIV-exposed infants had severe anaemia and two infants had severe malnutrition: one in the HIV-unexposed and one in the HIV-exposed groups (appendix pp 7–8). Three (1%) maternal medically attended adverse events were deemed related to vaccination, all in the pregnant women living with HIV placebo group. All infant medically attended adverse events were deemed unrelated to study vaccination. Consistent with a maternal and newborn population, serious adverse events were common, with 101 events occurring in 86 (29%) of 300 maternal participants and 55 events occurring in 44 (15%) of 293 infant participants. All were unrelated to the vaccination and most were resolved by the conclusion of the study period (appendix pp 7, 9–10). There were five stillbirths across all groups: one in pregnant women living with HIV receiving GBS6, one in pregnant women without HIV receiving placebo, and three in pregnant women living with HIV receiving placebo (appendix p 11). Two pregnant women living with HIV receiving placebo had antepartum stillbirths, one resulting from comorbidities of malaria in pregnancy and pre-eclampsia, whereas the other did not have any known comorbidities. There were three intrapartum stillbirths: one in pregnant women without HIV receiving placebo, which resulted from placental artery thrombus; one in pregnant women living with HIV receiving placebo, where the mother used herbal remedies to expedite delivery and delivered by caesarean section; and one in pregnant women without HIV receiving GBS6, which was an obstructed labour, with associated delays in conducting caesarean section due to theatre congestion. Three deaths occurred in one woman and two infants (appendix pp 9–10).

One pregnant women living with HIV in the placebo group died of suspected poisoning, one HIV-exposed infant in the placebo group died within 24 h of birth as a result of severe birth asphyxia and multiple congenital anomalies, and one HIV-unexposed infant in the GBS6 group died at age 4·5 months as a result of suspected accidental asphyxia. There were no non-fatal adverse events that led to study withdrawal among the women and their infants.

Interim analyses were not performed. The protocol included predefined stopping rules for participant safety; however, no safety threshold requiring suspension or termination of the trial was reached (appendix pp 33–44).

Maternal participants' GMCs of IgG antibodies over time are shown in figure 3A and the appendix (pp 20–26). Before vaccination, GMCs against most group B streptococcus serotypes (Ia–V) were low, with GMCs ranging from 0·03 µg/mL for serotypes 1b and V to 0·048 µg/mL for serotype II. Following GBS6 vaccination, marked increases in serotype-specific GMCs were observed, peaking at 2 weeks after vaccination. GMCs rose approximately 30–100-fold from baseline (ie, enrolment or vaccination) to 2 weeks after vaccination for all serotypes, with significant differences between GBS6 and placebo groups across all serotypes and all post-vaccination visits ($p<0·0001$ for all comparisons). Serotype II, which had the highest baseline titres, showed the largest absolute and fold increase, reaching the highest GMC overall, while serotype V showed the lowest absolute and fold increase in addition to low baseline titres. Across all serotypes, pregnant women living with HIV and without HIV consistently exhibited similar antibody concentrations across all study visits (appendix pp 20–26).

GMCs in infants are shown in figure 3B and the appendix (pp 26–28). Across all serotypes (Ia–V), infants born to GBS6-vaccinated women showed substantially higher GMCs at birth compared with those born to participants who received placebo. GMRs at birth comparing vaccinated to placebo groups ranged from 8·45 (5·90–12·10) for serotype V to 84·06 (48·16–146·74) for serotype 1a (appendix p 30). At 18 weeks, GMCs remained significantly higher in the GBS6 group compared with placebo for all serotypes ($p<0·0001$ for all comparisons), before declining progressively by 12 months after delivery (appendix pp 26–28). The highest GMCs were observed for serotypes Ia and II and the lowest for serotype V. There were no significant differences in antibody concentrations for infants born to pregnant women living with HIV compared with those who were HIV-negative, at birth or at age 18 weeks, for any serotype.

Placental transfer of group B streptococcus-specific antibodies from pregnant women vaccinated with GBS6 to their infants did not differ significantly between pregnant women living with HIV and pregnant women without HIV for any serotype (appendix p 31). Placental transfer ratios were significantly higher in GBS6 recipients compared with placebo for serotype II in pregnant women living with HIV ($p=0·026$), and for serotype III in both pregnant women living with HIV ($p=0·0020$) and pregnant women without HIV ($p=0·0004$). In pregnant women without HIV, placental transfer was also significantly higher in GBS6 recipients for serotype V ($p=0·0007$). No significant differences were observed for serotypes Ia, Ib, or IV (appendix p 29). In a post-hoc exploratory analysis,

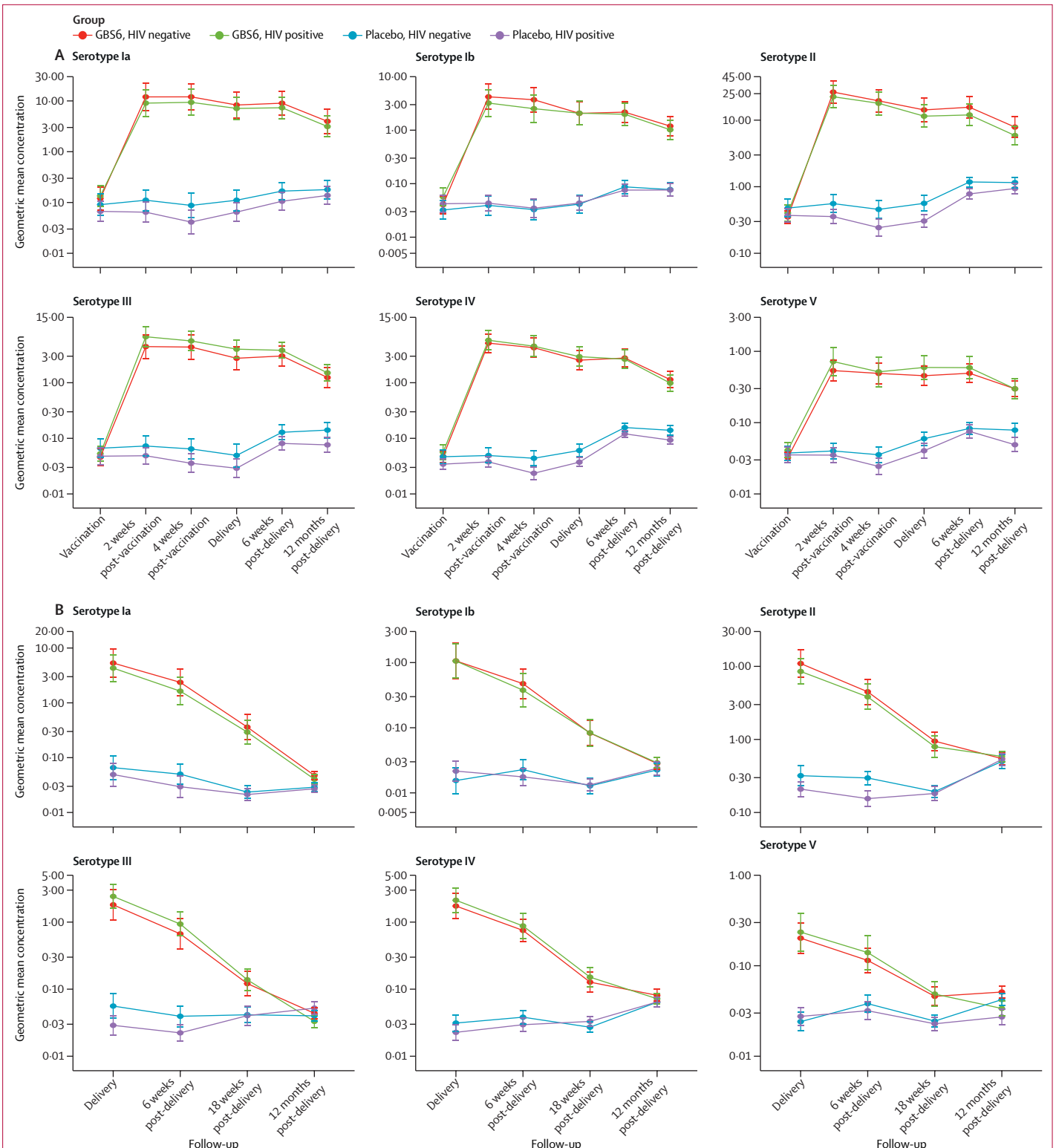

Figure 3: **Geometric mean concentrations of GBS6 serotype-specific IgG at different study visits in maternal and infant participants**
(A) Geometric mean concentrations (μg/mL) derived from log-transformed antibody concentrations with 95% CIs for group B streptococcus serotypes Ia–V measured over six study visits (maternal participants). (B) Geometric mean concentrations (μg/mL) derived from log-transformed antibody concentrations and 95% CIs for each group B streptococcus serotypes Ia–V measured over four study visits (infant participants). Note that scales on y axes differ between plots.

serotype III showed significantly lower adjusted placental transfer ratios in GBS6 recipients compared with placebo (adjusted GMR 0·29, 95% CI 0·18–0·47; p<0·0001; appendix pp 30–31).

Discussion

In this double-blind, randomised, placebo-controlled, phase 2 trial in Uganda, the hexavalent GBS6 vaccine was safe, well tolerated, and immunogenic in pregnant women regardless of HIV status, and vaccine-induced antibodies were transferred to their infants. To our knowledge, this study is the first randomised controlled trial to evaluate a maternal group B streptococcus vaccine in women living with HIV and their infants—an evidence gap of direct relevance to countries bearing the highest burden of HIV and invasive group B streptococcus disease.

The reactogenicity profile of GBS6 was consistent with expectations for maternal immunisation trials in similar low-income and middle-income country settings. Serious maternal and infant adverse events were similar between the GBS6 and placebo groups and occurred at background rates consistent with a maternal population in Uganda.[15–17] No safety concerns related to vaccination were identified, including among women living with HIV. Stillbirths and deaths were unrelated to vaccination, clinically explained, and reflective of obstetric and neonatal risks in the study population. These findings are concordant with the safety experience of other maternal vaccines, including tetanus, pertussis, influenza, and COVID-19 vaccines, supporting the acceptability of GBS6 in antenatal care programmes.[18–22]

GBS6 elicited robust serotype-specific IgG responses in pregnant women, with substantial increases from baseline across all serotypes. There was no difference in responses in any of the GBS6 groups, similar to other studies of pregnant women living with HIV.[21–24] These data indicate that vaccine responses are similar in pregnant women living with HIV on stable ART and pregnant women without HIV. Our findings are consistent with antibody concentrations elicited following GBS6 vaccination in pregnancy in pregnant women without HIV in a multicountry study.[12]

Infants born to vaccinated mothers had high cord serum antibody concentrations across all serotypes, confirming effective placental transfer. Antibody concentrations declined through early infancy as expected, but remained above placebo levels at age 18 weeks, an age at which infants remain vulnerable to invasive group B streptococcus disease. These observations are particularly important in sub-Saharan Africa, where HIV exposure is common, and where infants face the greatest early-life risk of invasive group B streptococcus disease, group B streptococcus-related stillbirth, and neurodevelopmental impairment following invasive group B streptococcus.[25,26]

Our finding that pregnant women living with HIV generated and transferred similar antibody concentrations to their infants compared with pregnant women without HIV differs from earlier studies. Previous studies were undertaken before the widespread roll-out of highly active ART in pregnancy.[8] Our study shows how successful highly active ART enables pregnant women living with HIV to reach similar antibody responses compared with pregnant women without HIV. As vaccine licensure strategies for group B streptococcus are likely to rely on serological thresholds of risk reduction, rather than large-scale clinical efficacy trials, empirical evidence of vaccine responsiveness and antibody transfer in populations with high HIV prevalence is essential to ensure that pregnant women living with HIV and their infants can mount protective antibody responses following GBS6 vaccination, similar to HIV-unexposed women and their infants. The demonstration of favourable safety and immunogenicity in a high-burden setting provides crucial reassurance for countries planning group B streptococcus maternal immunisation strategies. This trial has several strengths, including the randomised, placebo-controlled design, its conduction within routine antenatal services in a high-prevalence HIV setting, longitudinal follow-up to 12 months, and high retention of mother–infant pairs. The use of validated serological assays and the inclusion of both HIV-exposed and HIV-unexposed infants strengthen the relevance of these findings to real-world implementation.

However, some limitations must be acknowledged. The study was not powered to detect uncommon adverse events with a prevalence of less than 10% or for small differences in immunogenicity responses, which could introduce the possibility of type II error comparisons. The absence of a statistical difference might be due to a lack of power for some endpoints. In addition, some deliveries occurred outside study facilities, reducing the completeness of perinatal outcome data. Many immunogenicity comparisons are made across six serotypes, multiple timepoints, vaccine groups, and HIV strata. No formal adjustment for multiple testing was undertaken, which increases the chance of false-positive findings. Visit windows were occasionally broad due to operational constraints, although sensitivity analyses showed consistency across timepoints. The population consisted mainly of young, low-risk Ugandan women, and those with HIV had high $CD4^+$ counts and were stable on ART, and therefore findings might not generalise to high-risk pregnancies or women with poorly controlled or uncontrolled HIV. Functional antibody measurements in infants were not included, limiting assessment of the correspondence between IgG concentrations and functional protection. Due to the narrow gestational age window at recruitment, we were unable to assess the impact of gestational age at vaccination on serological responses. Future research directions could be evaluating the durability and functional activity of vaccine-induced antibodies in women living with HIV and their infants to inform licensure and implementation strategies.

In summary, GBS6 was safe and immunogenic when administered during pregnancy, including in women living with HIV, and vaccine-induced antibodies were

transferred to infants at levels likely to be associated with reduced risk of invasive group B streptococcus disease. These findings fill a crucial gap for an important target population and support continued development of GBS6 as a maternal vaccine. As global policymakers consider pathways toward licensure and introduction, evidence from diverse settings—particularly those with high HIV prevalence—will be essential to ensure equitable and effective protection of mothers and infants worldwide.

Contributors

KLD and PTH conceived the trial. KLD and PTH were joint chief investigators. KLD, PTH, MV, RM, MS, TH, and OD contributed to the protocol and design of the study. RM led the implementation of the study. TH, EB, OD, and CCK performed the laboratory analyses. MV and IK did the statistical analysis and accessed and verified the underlying data. RM, KLD, and MV drafted the manuscript. PM, GBB, AA, GR, and ZM contributed to the implementation and data collection. MG and IM were involved in protocol development and manuscript writing. All authors reviewed and approved the final report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

PTH are investigators on projects funded by Pfizer to their institutions. MG and IM report being employees of Pfizer and holders of Pfizer stock and stock options. All other authors declare no competing interest.

Data sharing

De-identified individual participant data and a data dictionary defining each field in the dataset will be made available. The shared dataset will correspond to the data used for publication; raw data will not be provided. Additional related documents (including the study protocol, statistical analysis plan, and informed consent form) will not be publicly available but can be obtained from the corresponding author upon reasonable request. Data were made available on July 29, 2026, via the City St George's, University of London research data repository (https://sgul.figshare.com/). Data will be accessible for general research purposes without restriction.

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