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Association of serum anti-gbs2106 protein immunoglobulin G (IgG) in newborns and risk reduction of invasive group B streptococcus disease during early infancy.

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ABSTRACT

Background: Human immunoglobulin G (IgG) directed against Group B *streptococcus* (GBS) epitopes is transferred transplacentally from the mother to the fetus. A GBS putative protein, gbs2106, has been previously identified as a potential GBS protein antigen vaccine candidate. However, its genetic prevalence and surface expression in GBS-isolates has not been evaluated. In this study, we evaluated the prevalence, surface expression and association of maternal-acquired serum anti-gbs2106 IgG in newborns and risk reduction of infant invasive GBS disease through to 90 days of age in a South African-based cohort.

Methods: We conducted a nested case-control study within a previously established birth cohort that was designed to investigate serological markers associated with risk reduction of invasive GBS disease. In the parent study, additional cases were identified through a hospital surveillance system which included infants diagnosed with culture-confirmed invasive GBS disease outside the original cohort study. In this current study, surface expression of gbs2106 was analyzed on recto-vaginal colonizing isolates from mothers whose infants remained healthy, and on isolates from infants who developed invasive GBS disease. Flow cytometry was used to determine surface expression levels. The anti-gbs2106 IgG in maternal and infant or cord blood was measured using a bead-based assay on the Luminex platform.

Results: The gbs2106 gene was present on all colonizing GBS-isolates from women in the control group and infant invasive GBS-isolates. The gbs2106 protein was expressed on 81.6 % (71/87) and 82.2 % (48/58) of maternal colonizing isolates and invasive GBS-isolates, respectively. There was a strong positive correlation ($r = 0.855$, $p < 0.0001$) of maternal and cord serum anti-gbs2106 IgG levels, with the combined cord to maternal anti-gbs2106 IgG geometric mean concentration ratio being 0.9 (IQR 0.7–1.1). Serum anti-gbs2106 IgG geometric mean concentrations in the infants were lower among the invasive disease cases (158.7 arbitrary units [AU]/ml; 95 % CI: 102.3–246.2) compared with controls (304.8 AU/ml; 95 %CI: 226.8–409.8; $p = 0.012$).

Conclusion: Our study demonstrates an inverse association between infant serum anti-gbs2106 IgG and risk of invasive GBS disease, indicating gbs2106 protein as a potential vaccine candidate.

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1. Introduction

Group B *Streptococcus* (GBS) is a major cause of early- and late-onset sepsis and meningitis in newborns and young infants. Furthermore, GBS is attributed to the pathogenesis of stillbirths, and maternal GBS colonization is associated with increased risk of premature delivery [1]. The global prevalence of maternal recto-vaginal GBS colonization is estimated to be 18 % (95 % Confidence Interval CI, 16.9 %–19.1 %) post-adjustment, while the pre-adjustment estimate is 15 % (95 % CI, 14 %–16 %) [2]. However, in African women, maternal recto-vaginal GBS colonization remains elevated compared to other geographies as shown by the estimated value of 21.3 % (95 % CI, 18.5 %–24.2 %) [2]. Approximately 1 to 3 % of offspring born to women colonized with GBS at the time of labor develop invasive GBS disease [3]. In the US, the use of intrapartum antibiotic prophylaxis (IAP) in women colonized with GBS from 36 to 37 weeks of gestational age and onward has reduced the incidence of invasive GBS disease in infants in the first seven days of age (i.e., early-onset disease; EOD) by 80 %, but is not effective in preventing disease between 7 and 90 days age (i.e., late onset disease; LOD) [4]. Importantly, universal screening for GBS is not widely deployed in low- and middle-income countries (LMIC) due to logistical and cost constraints [5].

Due to the pathogenesis and development of invasive GBS disease as early as the first day of life in the newborn, vaccination of pregnant women with a GBS alpha-like family proteins (GBS Alp) or multivalent polysaccharide-protein conjugate vaccines are being investigated to reduce the risk of invasive GBS disease in young infants [6,7]. Furthermore, other genetically conserved surface proteins that are prevalent in the majority of invasive GBS disease strains could be explored as potential vaccine antigens. Investigating the association of transplacentally-acquired serum immunoglobulin G (IgG) to potential protein vaccine epitopes in newborns and the risk of invasive GBS disease could inform vaccine development initiatives. Multiple studies have reported an inverse association between naturally acquired maternal and/or infant serum capsular polysaccharide (CPS) serotype-specific IgG and risk reduction of invasive GBS disease in the infant due to the homotypic serotype [8–13]. Also, an inverse association of serum IgG to some common GBS proteins and risk reduction of invasive GBS disease has been reported for Alp proteins (αC, Alp 1 (epsilon), Alp 2, Alp 3, Alp 4, and Rib [14], and Pilus Islands (BP-1, -AP1-2a and -BP-2b) [15], albeit with conflicting findings [14,16].

A surface protein antigen that is widely expressed across all GBS strains, and is genetically conserved, could be used as a carrier protein for a polysaccharide-conjugate vaccine (such as the hexavalent polysaccharide-protein conjugate vaccine), or it could be added (as a vaccine antigen) to a polysaccharide conjugate vaccine, or it could be added to a protein-based vaccine: the Alp family protein vaccine being developed for vaccination of pregnant women [6,17]. Whilst there is a long history of protection from invasive bacterial disease with polysaccharide conjugate vaccines, the theoretical advantages of a GBS protein-based vaccine over a polysaccharide-conjugate vaccine include its potential to stimulate a broader protection against multiple serotypes of GBS and their induction of dominantly IgG1 subclass antibody [18,19]. IgG1 antibodies are more efficiently transferred across the placenta compared with IgG2, which is mainly induced by polysaccharide-based vaccines antigens [18,20].

We previously identified a putative GBS surface protein, gbs2106, as a potential vaccine antigen [14,20–22]. Gbs2106 is a conserved portion of the Soluble Lytic Transglycosylase (SLT) domain containing protein [23]. Soluble Lytic Transglycosylase is an enzyme which is involved in bacterial cell wall metabolism, degradation and construction of peptidoglycan layer, and antibiotic response [24]. Additionally, SLT has been associated with cytotoxin production in bacteria, indicating involvement in pathogenicity [24]. Targeting SLT through vaccination could be pivotal in potentially preventing GBS infections by disrupting essential bacterial processes involved in cell wall integrity and virulence.

The aim of this study was to determine the association of transplacentally acquired serum anti-gbs2106 IgG in newborns and risk of developing invasive GBS disease in strains expressing gbs2106.

2. Materials and methods

2.1. Study design and participants

This study utilized stored serum samples and GBS-isolates collected from participants evaluated in an earlier parent study which evaluated the association of serum serotype-specific capsular antibody and risk reduction of serotype Ia and III invasive disease [28]. Briefly, the parent study was a longitudinal observational study, registered at ClinicalTrials.gov (NCT02215226), conducted between July 2014 and December 2016 at Chris Hani Baragwanath Academic Hospital (CHBAH) in Johannesburg, South Africa. This parent study included a cohort of 38,233 pregnant women ≥18 years age who had live births at CHBAH and their live offspring. Blood from the women and cord blood were collected upon delivery. Hospital-based surveillance was undertaken for invasive GBS disease in infants through to 90 days of age, which contributed to the cases in the study. Infants born to women colonized with GBS, but who did not develop invasive GBS disease nor were hospitalized with suspected sepsis through 90 days of age, served as controls. Furthermore, to increase the number of invasive GBS disease cases, infants diagnosed with culture-confirmed GBS invasive disease that were not part of the cohort study were enrolled (along with their mothers) within 48 h of a positive culture of GBS from a normally sterile body site, and blood samples were obtained at that time point. The latter group are referred to as non-cohort cases and were also matched to controls enrolled in the cohort-study. The blood samples were processed and stored at the Wits Vaccines and Infectious Diseases Analytics Research Unit (Wits-VIDA) in Johannesburg, South Africa.

In the current study, GBS-isolates from colonized mothers ($n = 109$) and infants with invasive GBS disease ($n = 58$) were tested for the surface expression of gbs2106-protein using flow-cytometry [19]. Participants were included if their culture samples exhibited bacterial growth on Strep B Colorex agar plates, their GBS isolates expressed gbs2106 protein, and sufficient paired maternal and infant serum samples were available for IgG analysis.

Cases consisted of infants who developed culture-confirmed invasive GBS disease within 90 days of life and whose GBS isolates expressed gbs2106 protein. The GBS invasive disease cases were categorized into cohort cases, which included infants from the original birth cohort who developed invasive GBS disease; and non-cohort cases which refer to infants identified through hospital surveillance for invasive GBS disease but who were not part of the cohort study. The controls were defined as mother-infant dyads where the mother was colonized with a gbs2106-expressing GBS strain but their infants did not develop invasive GBS disease or any suspected sepsis within 90 days of age. Cases were included irrespective of gestational age at time of birth, and we aimed to match at least two controls for each case based on serotype, gestational age at delivery and maternal age.

2.2. Anti-gbs2106 specific IgG analysis

Paired maternal and infant/cord serum was analyzed for anti-gbs2106 IgG using bead-based assay on the Luminex assay. Briefly, the assay included in-house reference serum comprising pooled human IgG (Polygam®, National Bioproducts, South Africa) and in-house pooled human serum high and low anti-gbs2106 IgG antibody concentration (AU/mL) controls. Assays were performed in true duplicates with paired maternal and infant or cord serum samples on the same plate. The optimal serum and secondary antibody dilution (Jackson ImmunoResearch), USA) was 1:100 and 1:200, respectively. The results were reported as arbitrary units per mL (AU/mL). Bead Fluorescence was read with the Bio-Plex 200 instrument using Bio-Plex Manager version 6.1

software (Bio-Rad Laboratories, Inc., Hercules, CA, USA).

2.3. Statistical analysis

The linear relation between maternal and cord IgG of the Cohort group was analyzed using Pearson correlation coefficient after $\log_{10}$ transforming the IgG concentrations. Additionally, to determine the efficiency of transplacental IgG transfer, cord to maternal IgG ratios were calculated by dividing the IgG Geometric mean concentration (GMC) in cord serum by the IgG GMC in the paired maternal serum. Statical significance and group comparisons of the cord to maternal ratios were calculated using One way ANOVA test followed by Holm-Šídák's multiple comparison test.

The IgG GMC between the cases and controls of both cohort and non-cohort groups were compared using *t*-test. Data was considered as statistically significant at p-value <0.05. Bayesian modelling was used to calculate the probability of an infant developing invasive GBS disease given a certain threshold of anti-gbs2106 IgG present in a pregnant woman colonized by gbs2106-protein expressing GBS, as previously described [10,16].

Data was analyzed using GraphPad Prism (version 10.3.1, GraphPad Software, San Diego, CA, USA), STATA (version 13, Stata Corp, College Station, TX, USA), R version 2.15 (Vienna, Austria) and JAGS.

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (HREC140203, M220251) and informed consent was obtained from mothers for themselves and their infants.

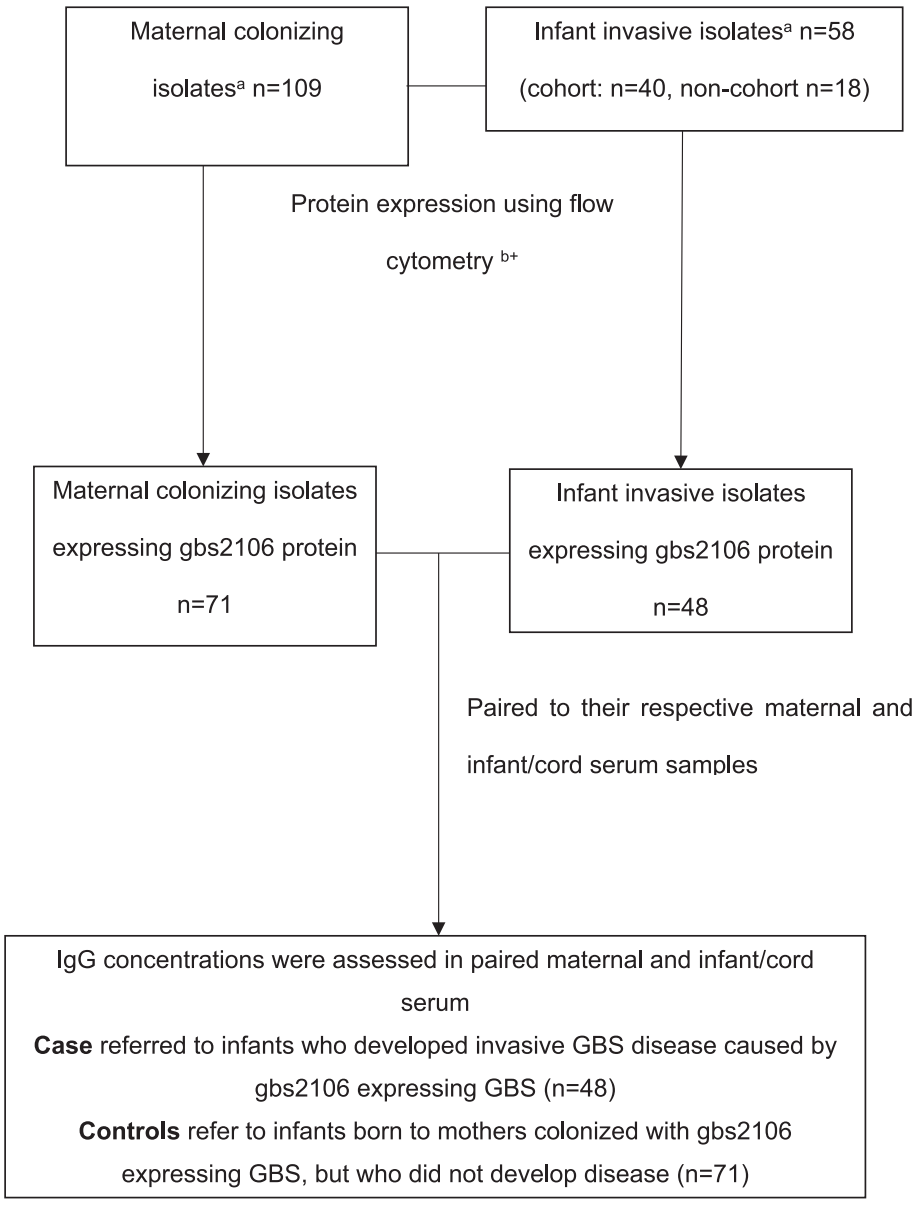

Fig. 1. Study CONSORT diagram indicating selection of analyzed cases and controls to investigate the association of anti-gbs2106 IgG and risk reduction of invasive GBS disease in infants. [a]Infant invasive isolates were matched (1:1 or 1:2) to the maternal colonizing isolates by homotypic serotype, gestational age, and maternal age. [+]Samples that resulted in GBS growth on Colorex™ Strep B agar plates and had available matched and paired serum (Colonizing $n = 87$, Invasive isolates $n = 58$). [b]gbs2106 protein was defined as expressed when there was a 2-fold increase in the median fluorescence intensity (MFI) between the pre-immunization and post-immunization serum. Additionally, expression was further confirmed by observing a clear shift in signal intensity between the pre-immunization and post-immunization histograms.

3. Results

The parent study included 1099 women colonized by GBS whose infants did not develop invasive GBS disease and/or were not admitted for suspected neonatal sepsis. There were 84 infants with invasive GBS disease (termed "cases"), including 47 in the cohort group and 37 from the non-cohort group. Here, we selected samples from the parent study that were matched for same serotype, gestational age at delivery, maternal age and expressed gbs2106 protein on their surface. Due to sample availability, a 1:1 matching ratio was used for some cases, while a 1:2 ratio was used for others to maximize statistical power. We analyzed a total of 119 matched samples that fulfilled this criteria. There were 48 infant cases and 71 controls (Fig. 1). Demographic information of participants included in the study presented in the supplementary materials. **(**Suppl. Table 1**).**

All the maternal colonizing and infant invasive isolates analyzed contained the *gbs2106* gene. Nevertheless, surface protein expression based on flow cytometry analysis showed that only 81.6 % (71/87) of maternal colonizing and 82.8 % (48/58) of infant invasive GBS-isolates expressed gbs2106-protein on their surface **(Suppl. Table 2 & 3)**.

Lastly, a strong linear positive correlation between maternal and cord serum was detected in a total of 77 paired maternal and infant/cord serum (Fig. 2).

3.1. Transplacental transfer of anti-gbs2106 IgG from mother to fetus

Analysis of the maternal sera identified detectable gbs2106 antibody in all the women. A significantly strong positive linear correlation between the maternal and cord serum concentration of anti-gbs2106 IgG in total population mother-newborn dyads ($r = 0.8551$; $p < 0.0001$) was detected (Fig. 2A). Similarly, stratification by cases ($r = 0.8688$; $p < 0.0001$) (Fig. 2B), and control groups ($r = 0.8594$, $p < 0.0001$) (Fig. 2C), also yielded significantly strong positive correlation. Whereas, for the total population, the anti-gbs2106 IgG cord to maternal ratio were 0.9 (IQR 0.7–1.1), including 0.9 (IQR 0.7–1.1) for cases, and 0.9 (IQR 0.8–1.2) for controls.

3.2. Association of serum anti-gbs2106 IgG and invasive GBS disease

Overall, anti-gbs2106 IgG GMC was lower in composite cases (158.7 AU/ml; 95 %CI: 102.3–246.2) compared to composite controls (304.8 AU/ml; 95 %CI: 226.8–409.8; $p = 0.012$). Similarly, the infant anti-gbs2106 IgG GMC was lower in non-cohort cases compared to controls (49.8 AU/ml; 95 %CI: 21.2–117.4 vs. 275.9, 95 %CI: 162.7–468.0; $p = 0.001$). A similar trend was observed for cohort-cases compared with controls, albeit not being statistically significant (255.7 AU/ml, vs 325.3 AU/ml; $p = 0.391$); (Table 1, Fig. 3).Table 1**:** Anti-gbs2106-protein immunoglobulin G (IgG) geometric mean concentration (AU/ml) of Infant/cord cases and controls.

Stratified analysis by time of disease onset (EOD and LOD), lower infant serum anti-gbs2106 IgG GMC were observed in LOD cases (94.3 AU/ml, 95 %CI:38.9–228.8) compared with controls (255.2 AU/ml, 95 %CI: 158.1–412.0; $p = 0.031$); and similarly so for EOD (223.2 AU/ml, 95 %CI: 143.6–347.0 in cases vs. 344.7 AU/ml, 95 %CI: 234.0–507.7; $p = 0.142$ in control), albeit not statistically significant (Table 1). The predicted absolute risk of invasive GBS disease in infants born to mothers colonized with gbs2106 expressing GBS declined gradually, up until anti-gbs2106 IgG concentrations of 1000 AU/ml (Fig. 4C-D). Predicted absolute disease risk of non-cohort cases gradually decreased as anti-gbs2106 IgG concentration increased (Fig. 4E) although the absolute disease risk stayed above 0.3 per 1000 cases for all concentrations.

Table 1
Anti-gbs2106-protein immunoglobulin G (IgG) geometric mean concentration (AU/ml) of Infant/cord cases and controls.

Category	Cord/Infant		
	GMC (AU/ml) (95 %CI) no. of cases	GMC (AU/ml) (95 %CI) no. of controls	P value
All invasive GBS disease			
Composite cohort and non-cohort	158.7 (102.3–246.2) n = 48	304.8 (226.8–409.8) n = 71	0.012
Cohort only	255.7 (165.0–396.2) *n* = 34	325.3 (226.1–468.0) *n* = 43	0.391
Non-cohort only	49.8 (21.2–117.4) *n* = 14	275.9 (162.7–468.0) *n* = 28	0.001
EOD composite cohort and non-cohort	223.2 (143.6–347.0) *n* = 29	344.7 (234.0–507.7) *n* = 42	0.142
LOD composite cohort and non-cohort	94.3 (38.9–228.8) *n* = 19	255.2 (158.1–412.0) n = 29	0.031

4. Discussion

A prophylactic maternal GBS vaccine that will protect the fetus and neonates after birth against diverse GBS-isolates will likely need to elicit robust antibodies that recognize a highly conserved protein antigen on the surface of GBS, while efficiently crossing the placenta barrier [4,5,25]. Our study showed that the putative GBS protein, gbs2106, is highly conserved and surface expressed on maternal colonizing and infant invasive GBS-isolates, and is immunogenic, with induced anti-gbs2106 antibodies efficiently crossing the placenta. Furthermore, anti-gbs2106 IgG was inversely associated with a lower risk of invasive GBS disease in an African setting where there is a high burden of invasive GBS disease [26,27]. Although the function of gbs2106 remains unknown [28], the high genome conservation and ubiquitous presence of *gbs2106* gene, indicates it plays a role in GBS survival or pathogenicity, making it an ideal vaccine antigen target. The genetic stability reduces the likelihood of antigenic variation, which is a common challenge in vaccine development [4,19,29], thereby providing comprehensive protection against various GBS strains and reducing the potential for vaccine escape through genetic variation.

The high frequency of gbs2106 protein expression in 81 % of the colonizing isolates, and 83 % of invasive isolates indicates that it is an accessible target for the immune system, thus, capable of eliciting immune responses [19]. This ubiquitous expression could also enhance its recognition to the host immune system [19], further justifying it as a promising vaccine antigen target.

The efficient transplacental transfer of anti-gbs2106 IgG has implications for neonatal immunity and the strategic development of maternal vaccination programs [30]. The ability of anti-gbs2106 IgG to cross the placenta and confer passive immunity to the fetus, further underscores its potential as a vaccine candidate for pregnant women, aimed at protecting their young infants against invasive GBS disease [5,31,32]. The anti-gbs2106 IgG transplacental ratios observed in our study were higher than observed for GBS capsular polysaccharide specific IgG [7,33,34], possibly due to gbs2106-protein inducing predominantly IgG1 subclass antibodies [18]. Similar findings of higher IgG transfer ratios have been observed in studies focusing on other surface GBS proteins such as PI-1, PI-2a, PI-2b, Rib, and FbsA [12,15]. These studies also observed that, when protein-based vaccine approaches were compared to GBS capsular vaccines, the protein-based approaches elicited antibodies with more efficient transplacental transfer capabilities [7,33,34].

The observed lower anti-gbs2106 antibody levels in infants who developed invasive GBS disease compared to infants who did not develop disease highlight the protective role of these antibodies. The low IgG titres observed in the non-cohort group could be attributed to IgG adsorption by the actively replicating GBS and natural decay of the

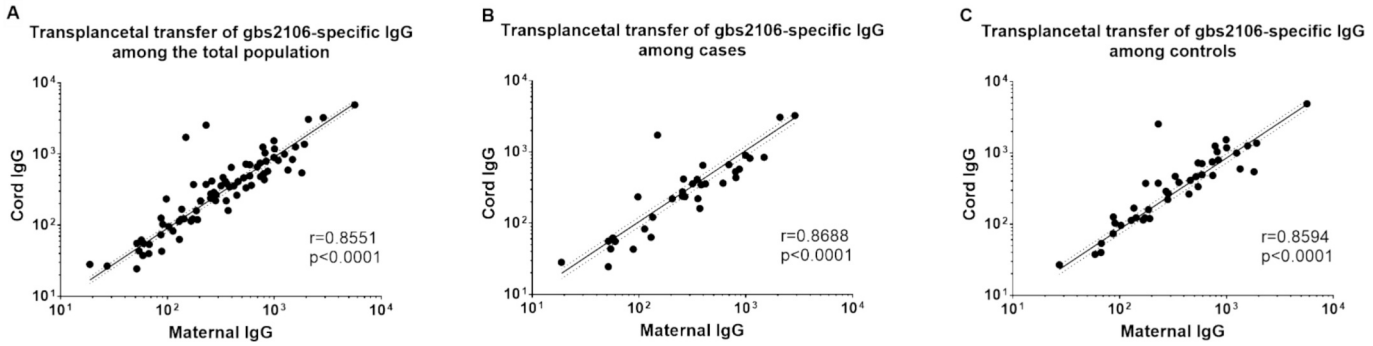

Fig. 2. Association between concentrations of gbs2106-specific IgG in cord and maternal sera in total population (A), Controls (B), and Cases (C). A total number of 77 maternal and cord pairs (cohort-only) were analyzed.

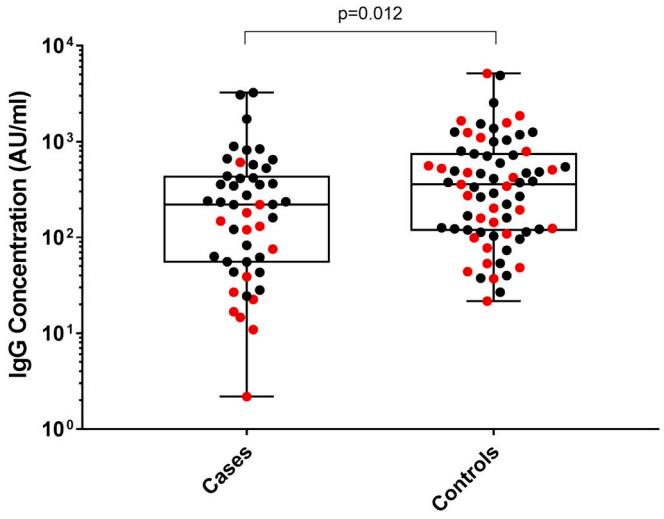

Fig. 3. Anti-gbs2106 IgG antibody concentrations (AU/ml) among infant cases (n = 48) and controls (n = 71). The black dots represent the cohort samples while the red dots represent the non-cohort samples. Analysis was performed on $\log_{10}$ transformed antibody geometric mean concentrations (GMC), using student t-test. Data was considered significant when p value <0.05. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

maternal antibodies that were transferred to the infant [32]. This disparity in antibody levels suggests that elevated infant antibody concentrations contribute to the prevention of GBS disease.

To assess the potential impact of the recruitment strategy on our findings, we conducted a sensitivity analysis comparing the IgG titres between Cohort and non-cohort cases. A statistical comparison using an independent t-test yielded a p-value of 0.9678 for maternal serum (271.9 AU/ml vs 265.0 AU/ml) and 0.5049 for infant/cord serum (272.45 AU/ml vs 268.1 AU/ml), indicating no significant difference in IgG titres between the two groups, therefore, this suggests that the recruitment strategy did not introduce a major bias affecting the study's conclusions. While difference in sample collection timings could be a potential limitation, the sensitivity analysis supports the validity of this approach and mitigates concerns regarding systematic bias.

In this study, the cases and controls were matched according to serotype, gestational age at delivery and maternal age which are potential confounders in assessing the association between levels of specific antibodies and invasive GBS disease risk. By ensuring comparability across these variables, the risk of confounding is minimized. Nevertheless, other residual confounding may still exist which were not addressed in our analyses.

A key limitation of our study is the low study sample size, which may lack sufficient power to determine statistical association between anti-gbs2106 IgG levels and EOD, and the cohort-only analysis for the LOD samples. Another limitation is that, although the IgG concentration in maternal cases and their matched controls was not significantly different, the functional activity of these antibodies may vary, potentially impacting disease susceptibility in their infants [35]. Further research into the assessment of antibody functional activity, especially in infant serum, is important for understanding the protective role of anti-gbs2106 antibodies and potentially establishing correlates of protection.

In conclusion, the study shows a high correlation between anti-gbs2106-specific IgG concentrations in infants and their mothers, suggesting effective transfer of these antibodies across the placenta. Additionally, data from this study demonstrates an inverse association between anti-gbs2106 IgG concentrations and risk of developing invasive GBS disease in infants. While our findings contribute valuable insights, further preclinical research is needed to strengthen understanding and support the extrapolation of our observations.

Authors contributions

S.A.M., A.I., Z.D., S.J., C.B., and GK. designed the original clinical trial and study protocol, oversaw the clinical trial, performed clinical data collection and management. V.G., N.D., G.K., and S.A.M. designed the current study. V.G. generated the anti-gbs2106 Immunoglobulin G data and protein expression data. V.G., A.I., G.K., N.D., and S.A.M. conducted the statistical analysis. V.G. wrote the first draft of the manuscript. All authors contributed to subsequent drafts and read and approved the final version of the manuscript.

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Potential conflicts of interest

S.A.M. has received grant funding on GBS, separate from this study, from Pfizer, GlaxoSmithKline and Minervax. Other author declares no conflict of interest.

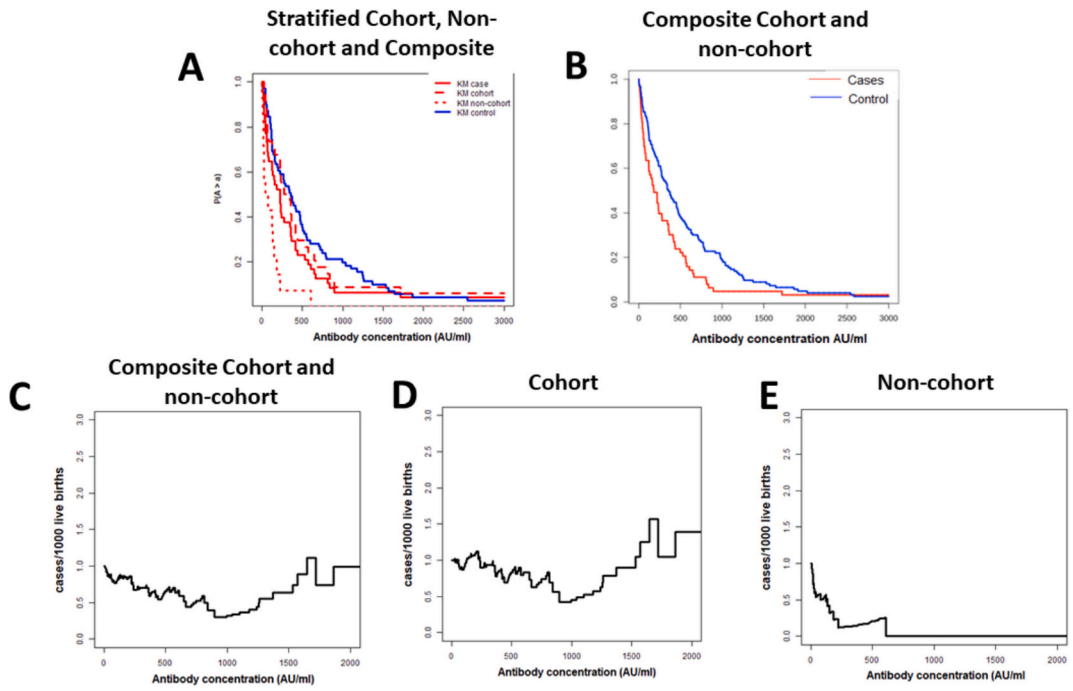

Fig. 4. Reverse cumulative plot illustrating gbs2106 protein specific IgG concentrations in infant cases and controls. **(A)**Proportion of infant cases (red line) and controls (blue line), stratified by timing of collection. The dashed red line represents the cohort group, the dotted red line represents the non-cohort group, and the solid red line represents the composite of both groups. **(B)** Composite of the cohort and non-cohort groups combined. **(C)** Absolute disease of infant GBS disease in infants born to mothers colonized with gbs2106-expressing GBS, determined using Bayesian modelling. **(D)** Absolute Disease risk of the cohort group. **(E)** Absolute Disease risk of the non-cohort group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

CRediT authorship contribution statement

Vicky Gent: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nisha Dhar:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Alane Izu:** Writing – review & editing, Formal analysis. **Stephanie Jones:** Writing – review & editing, Methodology, Investigation. **Ziyaad Dangor:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Carmen Briner:** Writing – review & editing, Methodology, Investigation. **Nancy Hosken:** Writing – review & editing, Formal analysis, Conceptualization. **Gaurav Kwatra:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Shabir A. Madhi:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Gaurav Kwatra reports financial support was provided by Bill & Melinda Gates Foundation. Shabir Madhi reports financial support was provided by The Oppenheimer Memorial Trust. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127016.

Data availability

Data will be made available on request.

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