

Placental transfer of anti-Plasmodium falciparum circumsporozoite protein antibodies: Mother-Newborn pair

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Abstract

Background

Circumsporozoite protein is a target of malaria vaccines (RTS, S and R21 Matrix-M) for children. Despite its naturally acquired antibody response, limited data exist on the placental transfer of antibodies against circumsporozoite protein. This study aims to investigate the placental transfer of antibodies against full-length *Plasmodium falciparum* circumsporozoite protein (FL-PfCSP), N-terminal, central repeat, and C-terminal regions of PfCSP in naturally malaria-exposed women and their newborns.

Method

We included 351 mother-newborn pairs from two malaria transmission areas in Ghana (Kpone and Maamobi). We expressed FL-PfCSP antigen in *E. coli* and purified it via nickel affinity chromatography and validated it by Coomassie blue SDS-PAGE staining and Western blot. Indirect ELISA was performed to measure total IgG levels of mothers and newborns. FL-PfCSP and twelve peptides covering the full length of PfCSP were evaluated. R software version 4.2.3 was used for analysis.

Results

We found a high seroprevalence of antibodies against FL-PfCSP in both mothers and newborns; 49.6% transferred to their newborns. Of the four peptides spanning the N-terminal region, peptides 2 and 4 efficiently transferred to the newborn; antibodies against peptide 13 (NANP)₄ from the central repeat region efficiently transferred to the newborn. Peptide 20 from the C-terminal region was efficiently transferred.

Conclusion

The study concludes that maternal antibodies against FL-PfCSP and its peptides were placentally transferred to their newborns. Maternal vaccination may boost antibody levels and enhance transfer of antibodies to their newborns.

Background

Malaria is a major public health problem, especially in Sub-Saharan African countries, with an estimated 12 million pregnant women at risk each year [1]. The *Plasmodium falciparum* circumsporozoite protein (PfCSP), which coats sporozoites and mediates hepatocyte invasion [2], is a target of naturally acquired immunity and the antigenic backbone of the RTS, S/AS01 [3] and R21/Matrix-M vaccines [4]. PfCSP consists of an N-terminal domain with conserved motifs, a central NANP repeat region, and a C-terminal thrombospondin-like domain. Current vaccines target the NANP repeats and C-terminal region [5, 6].

Additionally, Antibodies against N-terminal epitopes may also block invasion and have been associated with protection [7].

Maternal IgG to multiple malaria antigens, including PfCSP, is actively transferred across the placenta [8] and provides transient protection to newborns [9]. Anti-PfCSP IgG transfer begins around 12 weeks of gestation, increases toward term and correlates with maternal antibody level [10]. Cord and maternal CSP IgG levels are often comparable at delivery [11], but antibodies wane after 6 months [9]. Prior studies found correlations between full-length CSP, NANP, and C-terminal antibodies [8], though positivity rates for NANP-directed responses were higher in mothers than infants [12]. Factors reduced transfer efficiency are hypergammaglobulinemia [13], placental malaria [11], HIV [14], gravidity [12], geographic and transmission dynamics [15].

Previous studies have focused on NANP-directed responses and have not explored transfer across all PfCSP domains. To address this gap, we used a comprehensive, non-overlapping peptide panel that covers the entire PfCSP sequence (four 20-aa N-terminal peptides covering Region I and junctional motifs; a central repeat peptide containing (NANP)₄ plus an NVDP motif; and seven 20-aa C-terminal peptides spanning the α TSR), together with full-length PfCSP, to evaluate domain-specific placental transfer in a high-transmission setting. These data provide a precise map of which PfCSP regions are most efficiently transferred to newborns and offer a foundation for maternal immunization strategies aimed at maximizing passive protection in early life.

Method

Ethical consideration

The study protocol was reviewed and approved by the Ghana Health Service Ethics Review Committee (GHS-ERC 005/08/20), and the Noguchi Memorial Institute for Medical Research (NMIMR-IRB CPN 005/20–21). Written informed consent was obtained from all participants aged 18 or older. For those under 18 years of age, informed consent was obtained from the parent/guardian with written assent also obtained for children between 12 and 17 years of age. All methods were performed in accordance with the relevant guidelines and regulations.

Study setting

At delivery, maternal and newborn blood samples were obtained from participants enrolled at Maamobi and Kpone General Hospital, located in Accra, Ghana. Transmission of malaria was high in Kpone compared to Maamobi (62.1 Vs 44.7 infectious bites per person per year), respectively. April-July and September to November are seasons that malaria transmission became high.

Study population

The study population consisted of pregnant women admitted for delivery at the maternity wards of Maamobi General Hospital and Kpone General Hospital. All participants were HIV-negative.

Sample size

No prior sample size calculation was performed because the study used archived paired maternal–newborn serum samples. The sample size was determined by availability; all eligible samples were included to maximize statistical power. Consequently, 351 paired samples were analyzed for full-length PfCSP, peptide 20, 21, and 6, and 276 paired samples were analyzed for the remaining PfCSP peptide epitopes.

Data collection, and plasmodium falciparum detection

The methods of data collection and detection of plasmodium falciparum have been previously described [16]. Briefly, demographic and clinical data were obtained at delivery using standardized questionnaires and checklists. Three ml of cord blood from neonates and venous blood from mothers were collected into separate EDTA-coated tubes. In addition, a placental biopsy was obtained from the maternal side of the delivered placenta, targeting the intervillous space, and blot samples were subsequently prepared.

All blood samples were processed within a few hours of collection. Tubes were centrifuged to separate plasma from cellular components. Plasma aliquots were stored at – 80°C, while red blood cell pellets were preserved at – 20°C until further laboratory analysis.

Genomic DNA was extracted from red blood cell pellets using the QIAamp DNA Blood Mini Kit (Qiagen, France)[17]. Plasmodium falciparum detection and quantification were conducted in duplicate through real-time quantitative polymerase chain reaction targeting 18s rDNA. The amplification process consisted of 40 cycles. Parasite density was determined by extrapolating cycle threshold (Ct) values against a standard curve generated from serial dilutions of *P. falciparum* 3D7 culture-infected erythrocytes, which was included on each assay plate.

Recombinant PfCSP expression

A fragment of the PfCSP; amino acids 26–383, containing 19 NANP repeats (NCBI Reference Sequence: XP_001351122), corresponding to the 3D7 strain, was synthesized by GeneScripts Technologies Inc. and cloned into the pET30a plasmid vector containing an N-terminal His₆-tag. The recombinant plasmid was transformed into *Escherichia coli* BL21 (DE3) competent cells by heat shock.

Protein expression was induced with 0.5 mM isopropyl β-D-1-thiogalactopyranoside (IPTG) when bacterial cultures reached an optical density (OD 600) of ~ 0.6. Induction was carried out at 37°C for 4 hours with constant shaking. Recombinant PfCSP was purified from the culture supernatant by nickel-

affinity chromatography, and eluted using a buffer containing 300 mM NaCl, 50 mM Tris-HCl, and 250 mM imidazole at pH 7.5.

SDS-PAGE

Supernatant from the purified recombinant PfCSP was denatured by boiling at 94°C for 5 minutes in SDS-PAGE sample buffer and subsequently resolved on a 10% SDS-PAGE gel alongside a prestained molecular weight marker. Gels stained with Coomassie blue confirmed the purity of the preparation, showing a predominant band corresponding to the recombinant protein at ~ 33 kDa.

Western blot analysis

For immunodetection, proteins were transferred from the SDS-PAGE gel onto a PVDF membrane, which was blocked with 3% bovine serum albumin (BSA) in phosphate-buffered saline containing 0.1% Tween-20 (PBST). The membrane was incubated with an anti-His tag primary antibody (Sigma, 1:1000 dilution) for 1 hour, followed by a horseradish peroxidase (HRP)-conjugated anti-rabbit secondary antibody (1:10,000 dilution) for 1 hour at room temperature. After four washes with 1× PBST, bound antibodies were detected by chemiluminescence using the Amersham Imager 600 system. A clear band was observed at the expected molecular weight of ~ 33 kDa.

Synthetic peptides

Twenty-seven overlapping PfCSP peptides, each consisting of 20 amino acids and spanning the entire protein, were synthesized. Of these, 12 peptides were purposefully selected to ensure complete coverage of the PfCSP protein (see Supplementary material S1). Dot plot analysis was performed to confirm peptide reactivity. Peptides 2, 4, 6, and 8 from the N-terminal region, peptide 13 from the central repeat region and peptides 16, 18, 20, 21, 22, 24, and 26 from the C-terminal region were selected for indirect ELISA.

Indirect ELISA

We measured antibody levels against FL-PfCSP and synthetic peptides from the N-terminal, central repeat, and C-terminal regions of PfCSP using indirect ELISA (Thermo Fisher Scientific). Briefly, MaxiSorp 96-well plates (Nunc-Immuno Plate, Thermo Fisher Scientific, Denmark) were coated overnight at 4°C with 100 µL/well of each recombinant protein or peptide at a concentration of 1.0 µg/mL. Plates were washed three times with 200 µL/well of PBST, then blocked with 200 µL/well of 5% skim milk in PBST for 1.5 hours at room temperature.

Following three additional washes, 100 µL/well of diluted primary antibody (human serum, 1:750 in dilution buffer) was added, and plates were incubated for 1 hour at 37°C. Plates were washed three times with PBST and subsequently incubated with 100 µL/well of goat anti-human IgG conjugated to

horseradish peroxidase (HRP) (1:10,000 dilution) for 1 hour at 37°C. After three washes, 50 µL/well of TMB substrate was added for color development. The reaction was stopped after 5 minutes by adding 50 µL/well of sulfuric acid. OD was measured at 450 nm using an automated microplate reader (Thermo Fisher Scientific).

For assay quality control, pooled hyperimmune serum obtained from individuals with prior malaria exposure was used as a positive control, while negative control sera were collected from malaria-naïve adults residing in non-endemic regions of the UK. Each plate also included two blank wells. All samples, standards, negative controls, and blanks were tested in duplicate. The positivity threshold was defined as the mean OD of the negative controls plus three standard deviations (mean + 3 SD).

Statistical Analysis

The data were cleaned and exported to R software for analysis. Descriptive statistics including frequency and percentage were reported. Median and interquartile range was determined. Mann-Whitney U test was used to determine the median significant difference between mother and newborn antibody levels. From those seropositive mothers, we determined the transfer ratio. Transfer ratio (newborn to maternal) was determined by dividing the optical density (OD) value of newborns by mothers. Logistic regression was used to determine associated factors of reduced transplacental transfer of anti-FL-PfCSP antibodies. R software version 4.3.2 was used to analyze the data, and the dplyr and ggplot2 packages were used [18]. All statistical significances were determined at $P < 0.05$.

Result

Demographic characteristics of study participants

We assessed the placental transfer of anti-PfCSP IgG in naturally malaria exposed women in Ghana. Three hundred fifty-one mother-newborn paired serum samples were used. The median (IQ) age of mothers was 28(8). Majority 277(78.9%) of the participants are from Maamobi General Hospital, 287(81.8%) of the participants were multigravida and 6(1.7%) had placental malaria (Table 1).

Table 1
Mother characteristics at enrolment

Variables	Frequency (n)	Percentage (%)
Age in years		
<20	23	6.6
20–34	280	79.7
34–49	48	13.7
Marital status		
Co-habiting	20	5.8
Single	67	19.3
Married	260	74.9
Education		
None	34	9.79
Primary	56	16.13
Junior high school	149	42.9
Senior high school	71	20.46
Tertiary	27	7.78
Vocational	10	2.88
Study site		
Maamobi	277	78.9
Kpone	74	21.1
Gravida status		
Primigravida	64	18.2
Multigravida	287	81.8
Hemoglobin level		
Normal (≥ 11 g/dl)	188	55.8
Anemia (< 11 g/dl)	149	44.2
Placenta malaria		
Yes	6	1.7
No	345	98.3

Variables	Frequency (n)	Percentage (%)
Peripheral malaria		
Yes	17	4.8
No	334	95.2

Seroprevalence of antibodies to PfCSP and its peptide

To investigate placental transfer of anti-PfCSP antibodies, we expressed the full-length PfCSP protein in *E. coli* BL21 (DE3) cells as a soluble His-tagged fusion protein and assessed antibody responses by indirect ELISA. The seroprevalence of antibodies against FL-PfCSP were 75.2% in mother and 79.2% of newborn. Of the four peptides spanning the N-terminal region, peptide 6 showed the highest seroprevalence 68.1% among women and 72.7% among newborn. Peptide 13 (NANP)₃ from the central repeat region, 51.4% women were seropositive. Of seven peptides spanning the C-terminal region, peptide 20 showed highest seropositive 61.4% (Fig. 1).

that's

Figure 1: Seroprevalence of PfCSP and its peptides. Seropositive was determined using the cut-of value above the mean value of negative control + 3 *(standard deviation).

To assess the overall differences in mother and newborn antibodies response against the FL-PfCSP, N-terminal, central repeat, and C-terminal regions, median OD compared using Wilcoxon rank-sum test. Newborn showed significantly higher median OD to peptide 2 and peptide 6 from the N-terminal, and peptide 20 and 21 from the C-terminal region compared to mothers (Table 2).

Table 2
Median OD difference between mother and newborn

Peptides/antigens	Mother, median [IQR]	Newborn, median [IQR]	P-value
FL PfCSP	0.13[0.18]	0.12[0.19]	0.9
Peptide 2	0.27[0.16–0.48]	0.37[0.25–0.54]	< 0.0001
Peptide 4	0.52[0.34–0.71]	0.42[0.3–0.57]	< 0.0001
Peptide 6	0.57[0.26–0.82]	0.85[0.54–1.06]	< 0.001
Peptide 8	0.58[0.39–0.86]	0.41[0.28–0.61]	< 0.0001
Peptide 13	0.31[0.18–0.45]	0.35[0.2–0.52]	0.04
Peptide 16	0.32[0.21–0.47]	0.29[0.19–0.43]	0.01
Peptide 18	0.44[0.29–0.65]	0.42[0.3–0.61]	0.6
Peptide 20	0.423[0.26–0.65]	0.58[0.36–0.74]	< 0.001
Peptide 21	0.35[0.16–0.66]	0.48[0.28–0.71]	0.003
Peptide 22	0.647[0.45–1.14]	0.32[0.19–0.56]	< 0.001
Peptide 24	0.62[0.37–0.91]	0.37[0.23–0.58]	< 0.001
Peptide 26	0.50[0.34–0.69]	0.42[0.24–0.59]	< 0.001
FL PfCSP: Full Length <i>Plasmodium falciparum</i> circumsporozoite protein, bold: those transfer their antibodies to the newborn			

Antibodies against FL-PfCSP, peptide 6, peptide 20, and peptide 22 were efficiently transferred among participants residing in Maamobi. Antibodies against peptide 2 and peptide 13 were efficiently transferred to newborns among participants residing in Kpone (Fig. 2; Supplementary material S2).

Anti-PfCSP and its peptide IgG efficiently trasfered

To determine anti-PfCSP IgG is placental transferred to the newborns or not, the transfer ratio was calculated, defined as the newborn-to-mother OD ratio in each paired sample from the seropositive samples. Ratios ≥ 1 were considered as efficient placental transfer. Of 272 seropositive to FL-PfCSP, 140 (49.8%) had transferred their anti-PfCSP antibodies to the newborns. From the N-terminal region, peptide 4 and 2 showed efficient transferred (71.4% and 70.0%, respectively), though based on few seropositive samples.

Peptide 13 [(NANP)3] from the central repeat region had a transfer rate of 58.2%. In the C-terminal region, peptide 20 showed the highest transfer rate (Fig. 3A). The median OD transferred ratio was 1.1 which is efficiently transferred. Peptide 2, peptide 6, peptide 13, peptide 20 were efficiently transferred (Fig. 3B).

The percentage of antibody transfer ratios by site showed that peptides 2 and 13 had higher transfer rates in Kpone, while peptides 6 and 20 exhibited higher transfer rates in Maamobi (see Supplementary material S3).

To assess the effect of gravidity on mother and newborn anti-PfCSP IgG levels across the two study sites, antibody responses were compared between primigravidae and multigravida. No significant differences were observed between the groups at either Kpone or Maamobi (see Supplementary material S4).

Peripheral and placental malaria on placental transfer of anti-PfCSP IgG

To determine the effect of maternal *Plasmodium falciparum* infection, which is detected peripherally on transfer of anti-PfCSP antibodies to newborns. Mothers with peripheral *Plasmodium falciparum* infection had higher antibody titer to PfCSP, however their transfer was reduced (Fig. 4A). Similarly, the presence of placental *Plasmodium falciparum* infection was high antibody titer in the mother, but their transfer to their newborn was reduced (Fig. 4B).

Factors associated with placental transfer of anti-PfCSP antibodies

To examine factors associated with reduced placental transfer of anti-PfCSP-specific antibodies, logistic regression analysis was performed. No significant associations were observed with maternal demographic, obstetric, or clinical characteristics (Table 3).

Table 3 Factors associated with reduced transplacental transfer of anti-PfCSP antibodies				
Variables		Transfer of PfCSP		COR (95%CI)
		Yes	No	
Gravida status	Primigravida	5	1	0.929 [0.481–1.79]
	Multigravida	127	130	1
Age in years	< 20	7	9	1
	20–34	104	99	1.34[0.480–3.87]
	> 34	21	23	1.17[0.372–3.82]
Study site	Kpone	13	15	1
	Maamobi	127	117	1.34[0.617–2.94]
IPTp-received	No	29 (46.8)	33 (53.2)	1.23[0.699–2.18]
	Yes	103 (51.5)	97 (48.5)	1

Discussion

Malaria affects both pregnant women and children under 5 years of age. Although currently no malaria vaccine is available for pregnant women, the only strategy to prevent them were vaccination during pregnancy or preconception. In the current study, we aimed to profiled total IgG immune response against FL-PfCSP, N-terminal, central repeat region, and C-terminal region of PfCSP.

Highest proportion of participants against FL-PfCSP in both mothers and newborns. These finding is consistent with a study conducted in Cameroon [8], and Benin 82% among newborn [19]. Majority of the participants efficiently transferred anti-PfCSP antibodies. Beyond the full-length protein, we evaluated peptide-specific responses across the N-terminal, central repeat, and C-terminal regions of PfCSP. Interestingly, we observed placental transfer of antibodies against peptides spanning both the N-terminal, central repeat and C-terminal regions.

From the N-terminal region when comparing maternal and neonatal antibody levels, we observed distinct patterns. Antibodies against peptides 2 and 6 were significantly higher in newborns than in mothers. The highest proportion of participants transferred antibodies against peptide 2 and 4, though the number of seropositive participants were relatively small. Antibodies targeting this region have previously been shown to block sporozoite entry into hepatocytes[20].

Highest proportion of participants transferred their antibodies against peptide 13 (NANP)₄, the central repeat region. The antibody levels in newborn were significantly higher than mothers. This finding contrasts with previous study that reported reduced antibodies against (NANP)₅ in both mother and newborn[14]. The reason may be due to differences in study population, as the previous study included HIV positive mothers, whereas all participants in our study were HIV naïve. Maternal HIV infection has been associated with reduced transfer of antibodies to newborn[21]. The NANP repeat motif is the immunodominant B-cell epitope of PfCSP and constitutes the major target of RTS, S and R21 vaccines.

From the C-terminal region, the highest antibody response against peptide 20 and 21 was observed in both mother and newborn. The highest transfer efficiency was observed antibodies against 20. This C-terminal region consists of T- cell epitopes.

Based on the study site, antibody titers in both mother and newborn were higher in Maamobi than Kpone. This difference may be due to sample size difference, more participants enrolled from Maamobi than from Kpone (Kpone to Maamobi ratio, 1:10). In addition, the relatively low antibody titers in Kpone may be associated with the high malaria transmission intensity in the area, which may induce chronic immune activation and B-cell exhaustion, by impairing the maintenance of functional antibody response.

High titers of anti-PfCSP antibodies have previously been associated with protection against severe malaria in infants. However, an important caution is that naturally acquired antibodies may also interfere with CSP-based vaccines such as RTS, S/AS01, R21-MM by masking epitopes or competing with vaccine-induced antibodies[22]. This phenomenon may be especially relevant in areas with high malaria

transmission intensity, where preexisting antibodies are more prevalent and might dampen vaccine responsiveness. At the same time, the potential for maternal antibodies to interfere with infant responses to CSP-based vaccines must be carefully evaluated. Antibody-mediated epitope masking or immune complex formation may reduce the effectiveness of vaccination programs targeting infants.

While this study did not conduct a longitudinal design to determine subsequent malaria outcomes in infants, the observed efficient transplacental transfer of PfCSP-specific peptide antibodies indicates that maternal immunity provides neonates with a degree of passive protection in early life. However, the duration of this protection is limited, as maternal antibodies typically wane within the first 3–6 months after birth. This highlights the importance of considering maternal vaccination as a strategy to boost both maternal and neonatal immunity against malaria.

The interpretation of these findings should take into consideration the following limitations. First, only total IgG was measured; second: subclass-specific transfer and Fc glycosylation, which strongly influence transfer, were not assessed.

Overall, these findings suggest that the efficiency of transplacental transfer may vary depending on the specific regions of PfCSP. This study revealed that maternal and neonatal seropositivity to PfCSP, with efficient transplacental transfer of antibodies across multiple regions of the protein. Placental transfer of anti-PfCSP IgG was observed in nearly half of the participants. Transfer efficiency also varied by peptide regions, with some peptides preferentially transferred to newborn. Anti-peptide 2 and 6 IgG from N-terminal, anti-peptide 13 from central repeat, and anti-peptide 20 antibodies from C-terminal were efficiently placental transferred to newborns.

Abbreviations

CSP
Circumsporozoite protein
ELISA
Enzyme Linked Immunosorbent Assay
FL-PfCSP
full-length *Plasmodium falciparum* circumsporozoite protein
IgG
Immunoglobulin G
OD
Optical Density
PBS
Phosphate Buffer Saline

Declarations

Conflict of interest

The authors declare no conflicts of interest.

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Author Contribution

A.M.B.: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. HG: Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – review & editing. D.D.: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. L.A.L.: Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing. H.A.D.: Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing – review & editing. B.T.: Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. N.T.N.: Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. M.F.O.: Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. G.A.A.: Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. L.N.A-E.: Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. A.C.: Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. Y.A.: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Data Availability

All data supporting the findings of this study are available within the paper and its Supplementary Information.

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Figures

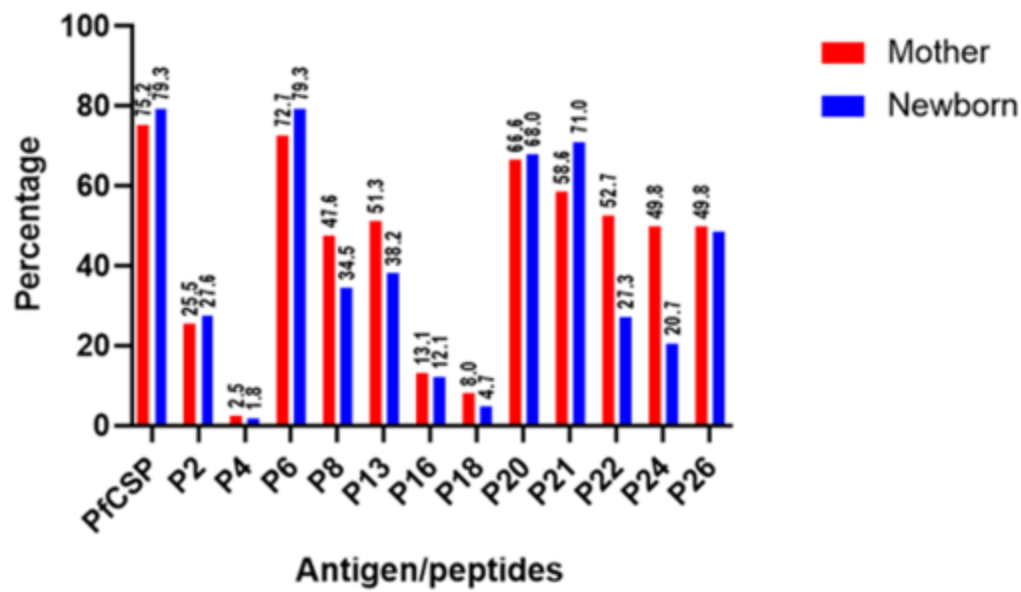


Figure 1

Seroprevalence of PfCSP and its peptides. Seropositive was determined using the cut-of value above the mean value of negative control + 3 *(standard deviation).

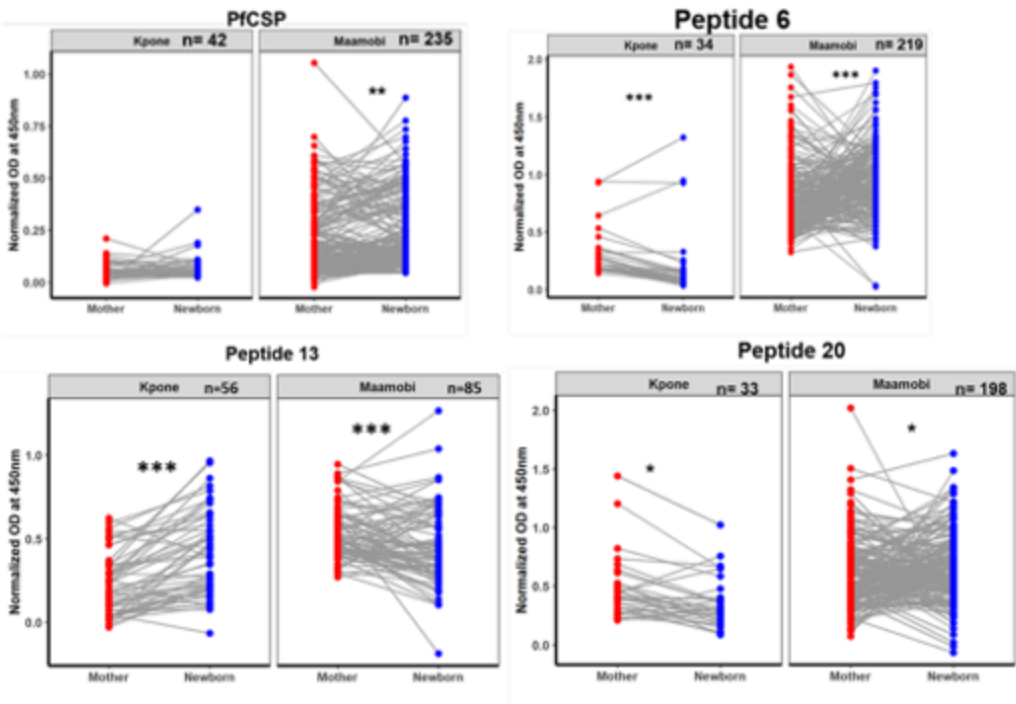


Figure 2

Transfer of antibodies against FL-PfCSP and peptides by site. The line connects mother (red) and newborn(blue). n= number of seropositive, **= p<0.01, *= p<0.05, *** = p<0.0001.

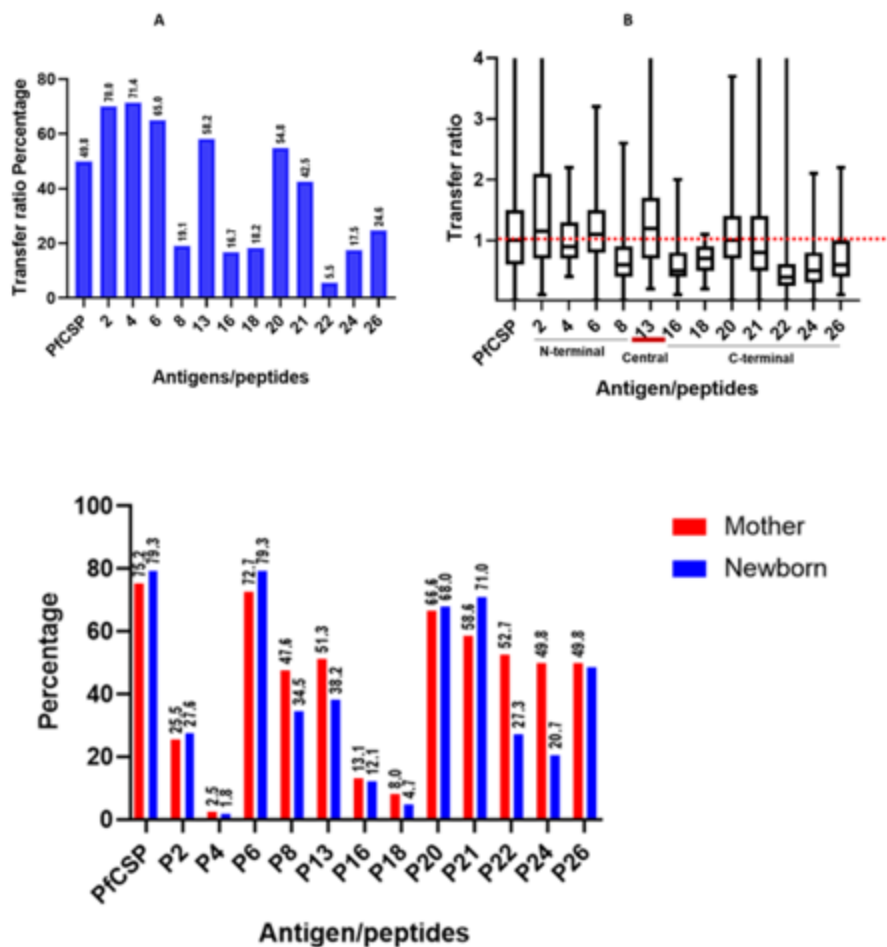


Figure 3

Median transfer ratio. A) percentage transfer ratio, B) median transfer ratio. The horizontal red dotted line indicates that 100% efficient transferred.

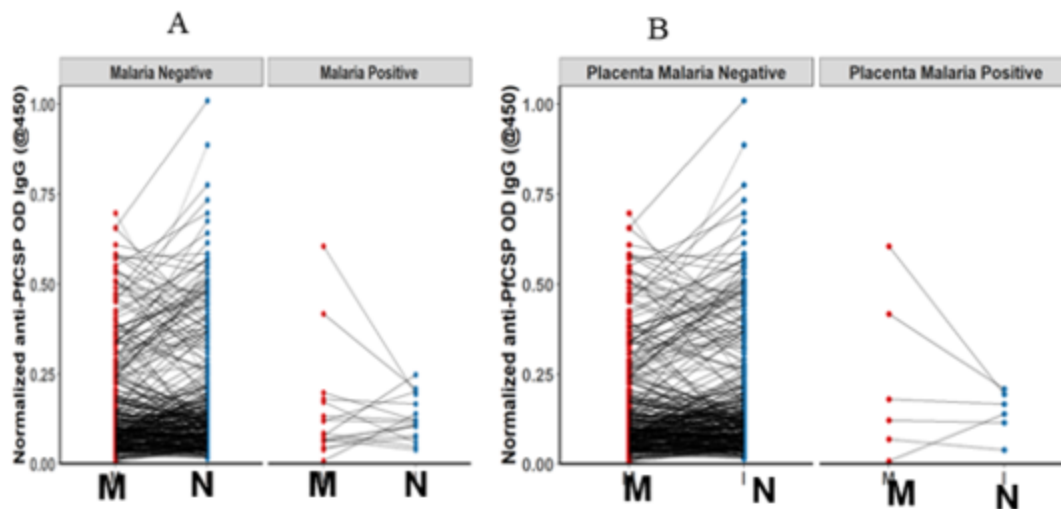


Figure 4

Mother and newborn anti-PfCSP IgG levels stratified by peripheral and placental malaria status. A) Dot line showing antibody levels between malaria-negative and malaria-positive mothers and their corresponding newborns. B) Dot line showing antibody levels between placenta malaria-negative and placenta malaria-positive mothers and their newborn. Each line connects paired mother and newborn samples. Red dots indicate mother samples, and blue dots indicate newborn samples. M: Mother, N: Newborn.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementaryfile.pdf](#)