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Title	**Reduced risk of placental parasitemia associated with complement fixation on *Plasmodium falciparum* by antibodies among pregnant women**
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Reduced risk of placental parasitemia associated with complement fixation on *Plasmodium falciparum* by antibodies among pregnant women

Burnet Institute
Medical Research. Practical Action.

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Introduction

Malaria in pregnancy (MiP) contributes to poor pregnancy outcomes

P. falciparum MiP is characterised by accumulation of parasites in the placenta mediated by the PfEMP1 variant VAR2CSA

Antibodies to placental binding parasites and VAR2CSA are associated with improved outcomes but mechanisms of action are poorly understood

Protective antibody responses are predominantly IgG1 and IgG3 suggesting a role for complement

Aims

1. Test for complement fixation on placental-binding *P. falciparum* infected red blood cells (pRBCs) by antibodies from malaria-exposed pregnant women

2. Identify the antigenic targets on pRBCs for complement fixing antibodies

3. Examine evidence for an association between complement fixing antibodies and protection from placental malaria

Methods

In a longitudinal cohort of PNG pregnant women (302) and malaria naive Australian donors (15):

1. Tested for complement fixation on placental binding pRBCs and recombinant VAR2CSA

2. Tested for associations between complement fixation and reduced risk of placental parasitaemia

Antibodies from pregnant women fix complement on the surface of pRBCs

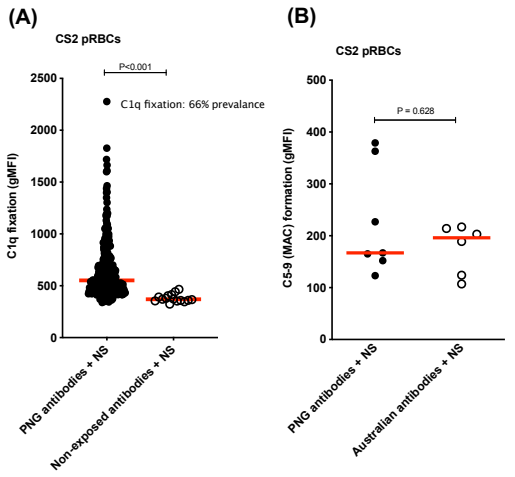

Figure 1: Antibodies from malaria-exposed PNG pregnant women mediated complement fixation on CS2 pRBCs but there was limited membrane attack complex (C5-9) formation
(A) Antibodies from PNG pregnant women (N=302) fixed complement C1q on the surface of CS2 pRBCs (that bind to CSA and express VAR2CSA) at significantly higher levels than antibodies from Australian malaria non-exposed donors (N=15).

(B) No evidence for elevated C5-9 fixation on CS2 pRBCs in the presence of PNG malaria-exposed antibodies (N=7) and active complement (NS) compared to malaria non-exposed donors (N=6).

PfEMP1 is a major target on pRBCs for complement fixing antibodies

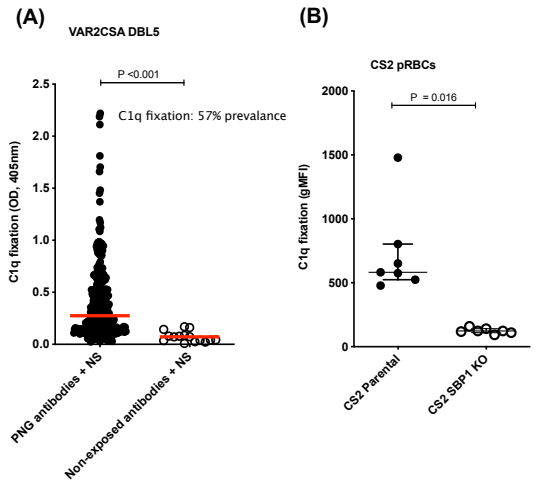

Figure 2: VAR2CSA is a major target of complement fixing antibodies
(A) Antibodies from malaria-exposed PNG pregnant women fixed complement C1q on recombinant VAR2CSA DBL5 domain at significantly higher levels than Australian malaria non-exposed donors.

(B) C1q fixation was significantly reduced in a CS2 *P. falciparum* isolate genetically-modified to reduce PfEMP1 pRBC surface expression (CS2 SBP1 knockout (CS2 SBP1 KO)), compared to the parental line with normal PfEMP1 expression, tested in the presence of NS and 7 PNG antibody samples with high IgG reactivity to CS2 pRBCs.

Complement fixation is associated with protection against placental malaria and enhanced inhibition of pRBC binding to CSA

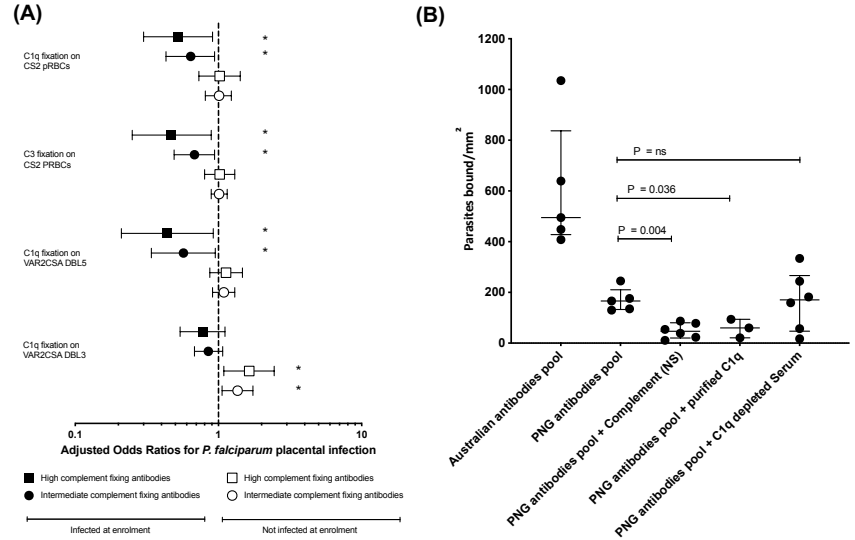

Figure 3: Complement fixing antibodies are associated with reduced risk of *P. falciparum* placental infection and enhanced pRBC-CSA binding inhibition
(A) Among women with evidence of *P. falciparum* infection at enrolment those having high or intermediate levels of complement fixing antibodies were associated with significantly reduced risk of placental *P. falciparum* infection when compared to those with low complement-fixing antibodies.

(B) Antibodies from malaria-exposed pregnant women were associated with enhanced CS2 pRBC-CSA binding inhibition in the presence of complement

Conclusion: We provide new insights into mechanisms mediating immunity to malaria in pregnancy and reveal new strategies for developing malaria vaccines that harness antibody-complement interactions.