Malaria and immunity during pregnancy and postpartum: a tale of two species

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SUMMARY

It is well established that pregnant women are at an increased risk of Plasmodium falciparum infection when compared to non-pregnant individuals and limited epidemiological data suggest Plasmodium vivax risk also increases with pregnancy. The risk of P. falciparum declines with successive pregnancies due to the acquisition of immunity to pregnancy-specific P. falciparum variants. However, despite similar declines in P. vivax risk with successive pregnancies, there is a paucity of evidence P. vivax-specific immunity. Cross-species immunity, as well as immunological and physiological changes that occur during pregnancy may influence the susceptibility to both P. vivax and P. falciparum. The period following delivery, the postpartum period, is relatively understudied and available epidemiological data suggests that it may also be a period of increased risk of infection to Plasmodium spp. Here we review the literature and directly compare and contrast the epidemiology, clinical pathogenesis and immunological features of P. vivax and P. falciparum in pregnancy, with a particular focus on studies performed in areas co-endemic for both species. Furthermore, we review the intriguing epidemiology literature of both P. falciparum and P. vivax postpartum and relate observations to the growing literature pertaining to malaria immunity in the postpartum period.

Key words: malaria, Plasmodium vivax, falciparum, pregnancy, postpartum, immunity, epidemiology.

INTRODUCTION

Malaria is a mosquito-borne infectious disease caused by the parasite Plasmodium, of which six species can infect humans; Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale curtisi, Plasmodium ovale wallikeri, Plasmodium malariae and Plasmodium knowlesi. Of these, P. falciparum and P. vivax are the predominant species with an estimated 182·2 million clinical cases of P. falciparum malaria, 15·8 million clinical cases of P. vivax malaria and 584 000 deaths attributable to malaria every year (WHO, 2014). The greatest burden of disease is seen in young children and pregnant women. P. falciparum is responsible for the vast majority of global morbidity and mortality (WHO, 2014). It is estimated that over 125 million pregnancies are at risk of malaria, 32 million are at risk of P. falciparum, 40 million are at risk of P. vivax and 53 million are at risk of both species (Dellicour et al. 2010). Women who acquire a Plasmodium spp. infection during pregnancy commonly experience negative maternal and birth outcomes such as anaemia, low birth weight and preterm birth with an estimated 75 000–200 000 infant deaths annually attributable to malaria in pregnancy (Steketee et al. 2001). Malaria in the period following pregnancy, the postpartum period, is also of public health importance. Malaria was the leading indirect cause of death in postpartum women in a study in Zambia (Valley et al. 2005) and the second highest cause of postpartum death in a study in India (Barnett et al. 2008).

In malaria endemic areas, individuals develop naturally acquired immunity to both P. falciparum and P. vivax after repeated infections. This immunity does not generally protect against infection per se, but protects against the development of high parasite densities and clinical symptoms (reviewed in Langhorne et al. 2008). Despite acquiring a degree of protective immunity prior to pregnancy, pregnant women are typically more susceptible to P. falciparum and P. vivax. Broad hormonal and immunological changes that occur during pregnancy are likely to play a role, with a general shift from cell-mediated immunity toward humoral immunity (Jamieson et al. 2006; Robinson and Klein, 2012). In the case of P. falciparum the increased susceptibility has been largely attributed to the lack of
Table 1. *Plasmodium vivax* risk in pregnancy compared to non-pregnant women and comparisons with *P. falciparum* risk in co-endemic areas

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th><em>Plasmodium vivax</em></th>
<th>Magnitude (95% CI)</th>
<th><em>Plasmodium falciparum</em></th>
<th>Magnitude (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk/odds of infection</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Campbell et al. (1980)</td>
<td>El</td>
<td>Similar</td>
<td>RR = 1:13</td>
<td>Increased</td>
<td>RR = 1:23</td>
</tr>
<tr>
<td>Singh et al. (1995)b</td>
<td>Salvador</td>
<td>Increased</td>
<td>OR = 1:30</td>
<td>Increased</td>
<td>OR = 2:34</td>
</tr>
<tr>
<td>Singh et al. (1999)b</td>
<td>India</td>
<td>Increased</td>
<td>OR = 3:36</td>
<td>Increased</td>
<td>OR = 2:11</td>
</tr>
<tr>
<td>Parekh et al. (2007)</td>
<td>Peru</td>
<td>Similar</td>
<td>RR = 0:92</td>
<td>Increased</td>
<td>RR = 2:28</td>
</tr>
<tr>
<td>Multiplicity of infection</td>
<td></td>
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</tr>
<tr>
<td>Marin-Menendez et al. (2013)</td>
<td>Brazil</td>
<td>Similar MOI</td>
<td>1:17 MOI vs 1:17</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Thanapongpichat et al. (2013)</td>
<td>Thailand</td>
<td>Increased MOI</td>
<td>2:03 MOI vs 1:65</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Species-specific parasite mean density</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campbell et al. (1980)</td>
<td>El</td>
<td>Increased</td>
<td>MD = +1615/</td>
<td>Increased</td>
<td>MD = +3093/</td>
</tr>
<tr>
<td>(Singh et al. 1999)b</td>
<td>Salvador</td>
<td>Increased</td>
<td>mm$^3$a</td>
<td></td>
<td>mm$^3$a</td>
</tr>
<tr>
<td>Species ratio</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Barcus et al. (2007)$^c$</td>
<td>Indonesia</td>
<td>Increased</td>
<td>1:2:6 vs 1:3:7</td>
<td>Decreased</td>
<td>2:6:1 vs 3:7:1</td>
</tr>
<tr>
<td>Almeida et al. (2010)$^b$</td>
<td>Brazil</td>
<td>Similar</td>
<td>5:8:1 vs 5:5:1</td>
<td>Similar</td>
<td>1:5:8 vs 1:5:5</td>
</tr>
</tbody>
</table>

NB – ratios within 0:2 of 1 were considered similar to 1. Abbreviations: MD, mean difference; OR, odds ratio; RR, risk ratio; N/A, not available; MOI, multiplicity of infections. All measures of association are unadjusted unless otherwise specified.

$^a$ Calculated from data in paper.

$^b$ Women in study restricted to those with history of fever.

$^c$ Women with slide-confirmed diagnoses of malaria.

immunity to pregnancy-specific isolates that seques-ter in the placenta (well documented and extensively reviewed elsewhere, e.g. (Desai et al. 2007; Duffy, 2007; Hviid and Salanti, 2007; Rogerson, 2010; Umbers et al. 2011)). The ability of *P. vivax* to bind and sequester in the placenta, its role in pathogenesis and the role of immunity against this process are debated (Mayor et al. 2012a). Importantly, *P. vivax* possesses the ability to form hypnozoites in the liver, a dormant stage which can lead to relapses of blood-stage infections (Krotoski et al. 1982; Krotoski, 1985). The immunological mechanisms that mitigate *P. vivax* in pregnancy are unclear, as is the effect of an altered immunological state during pregnancy on the risk of relapse.

The rate at which a woman returns to a normal immunological state after pregnancy, and how this affects malaria risk postpartum has not been well characterized. There is increasing evidence for the altered susceptibility to *P. falciparum* and *P. vivax* postpartum (Boel et al. 2012) and a growing literature investigating the immune response to malaria in the postpartum period which may account for observed epidemiological patterns. In this review we highlight the similarities and differences of *P. vivax* and *P. falciparum* infection during pregnancy and the postpartum period with respect to epidemiology, clinical pathogenesis and immunology.

*Plasmodium falciparum and P. vivax risk in pregnancy*

Numerous studies have demonstrated that pregnant women are at increased risk of *P. falciparum* infection and experience higher parasite densities and rates of clinical malaria when compared to non-pregnant women (reviewed in Desai et al. 2007). We therefore reviewed the *P. vivax* literature in addition to studies investigating *P. vivax* and *P. falciparum* in co-endemic areas. Few studies have investigated the risk of *P. vivax* infection during pregnancy and available data is conflicting (Table 1). An increased risk of *P. vivax* infection (Singh et al. 1995, 1999) and increased density of *P. vivax* infections (Campbell et al. 1980; Singh et al. 1999) have been observed in pregnant compared to non-pregnant women from El Salvador and India (Table 1). An increased multiplicity of *P. vivax* infections during pregnancy in Thailand has also been observed (Thanapongpichat et al. 2013) though no difference was observed in Brazil (Marin-Menendez et al. 2013). Other studies have failed to detect substantial
Table 2. Adverse maternal outcomes due to *P. vivax* infection in pregnancy compared to non-infected pregnant women and comparisons with *P. falciparum* risk in co-endemic areas

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Plasmodium vivax</th>
<th>Magnitude (95% CI)</th>
<th>Plasmodium falciparum</th>
<th>Magnitude (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk/odds of anaemia</td>
<td>Nair and Nair (1993)*</td>
<td>India</td>
<td>Increased(^b)</td>
<td>OR = 1.24 (0.53, 2.81)*</td>
<td>Increased(^b)</td>
</tr>
<tr>
<td></td>
<td>Nosten et al. (1999)</td>
<td>Thailand</td>
<td>Increased(^d)</td>
<td>OR = 1.91 (1.42, 2.56)*</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Dreyfuss et al. (2000)</td>
<td>Nepal</td>
<td>Increased(^d)</td>
<td>OR = 2.24 (0.91, 5.52)*</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Mean difference in haemoglobin

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Magnitude (95% CI)</th>
<th>Magnitude (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh et al. (1999)*</td>
<td>India</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Poespiprodjo et al. (2008)</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Yasnot et al. (2013)</td>
<td>Similar</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Machado Filho et al. (2014)</td>
<td>Decreased</td>
<td>N/A</td>
</tr>
</tbody>
</table>

NB – ratios within 0.2 of 1 and mean differences of less than 0.2 g dl\(^{-1}\) were considered similar. All measures of association are unadjusted unless otherwise specified. Abbreviations: MD, mean difference; OR, odds ratio; N/A, not available.

\(^a\) Women in study restricted to those with history of fever.

\(^b\) Anaemia defined as <8 hb g dl\(^{-1}\).

\(^c\) Calculated from data in paper.

\(^d\) Anaemia defined clinically or by haematocrit <30%.

\(^e\) Adjusted for age, location, gestational age at first visit, compliance to attendance at the antenatal clinic.

\(^f\) Anaemia defined as <11 hb g dl\(^{-1}\).

\(^g\) Adjusted for hookworm infection, vitamin A deficiency and trimester of pregnancy.

Differences in *P. vivax* risk between pregnant women and non-pregnant women (Campbell et al. 1980; Parekh et al. 2007) (Table 1). Furthermore, a study in Brazil found an increased frequency of *P. falciparum* relative to *P. vivax* infections in pregnant compared to non-pregnant women (Martínez-Espinosa et al. 2004). However, another study from the same Brazilian population failed to replicate these findings (Almeida et al. 2010) and to further complicate matters, a study in Indonesia found an increased frequency of *P. vivax* relative to *P. falciparum* in pregnancy (Barcus et al. 2007) (Table 1). The available evidence is somewhat conflicting but together suggests that there is an increased risk of *P. vivax* infection during pregnancy compared to non-pregnancy, albeit a smaller increased risk than that observed in regards to pregnancy and *P. falciparum* infection.

The clinical consequences of *Plasmodium* infection occur during the blood-stage of infection and are exacerbated by high densities of the blood-stage parasite. *P. falciparum* invades all erythrocytes, whereas *P. vivax* selectively invades young erythrocytes (reticulocytes), and thus *P. vivax* parasitaemia is typically lower than *P. falciparum* parasitaemia (Collins and Jeffery, 1999a, b; Simpson et al. 1999; Collins et al. 2004). *P. vivax* has a lower pyrogenic threshold compared to *P. falciparum*, provoking a stronger inflammatory response for a given level of parasitaemia (Ross and Thomson, 1910; Luxemburger et al. 1996; Hemmer et al. 2006; Yeo et al. 2010). However, *P. vivax* infections less frequently progress to severe disease compared to *P. falciparum* infections, which can result in cerebral malaria, metabolic acidosis, respiratory distress and severe anaemia. *P. vivax* can lead to severe clinical symptoms such as severe anaemia, respiratory distress and thrombocytopenia (reviewed in Anstey et al. 2012).

Few studies have investigated the relative severity of *P. falciparum* compared to *P. vivax* during pregnancy on maternal outcomes in co-endemic populations. Most studies show that *P. falciparum* is associated with more severe maternal and birth outcomes (Tables 2 and 3). Studies in Thailand, India and Indonesia have demonstrated that pregnant women infected with *P. falciparum* have increased severity and odds of anaemia compared to those infected with *P. vivax* (Nair and Nair, 1993; Nosten et al. 1999; Singh et al. 1999; Poespiprodjo et al. 2008). Interestingly, a study in Thailand has indicated a potential interaction in disease severity between the two species demonstrating a protective effect of *P. vivax* infection against severity and number of *P. falciparum* episodes during pregnancy (Luxemburger et al. 1997; Nosten et al. 1999). Both *P. falciparum* and *P. vivax* infections during pregnancy are associated with detrimental birth outcomes such as low birth weight, preterm delivery and miscarriage (Table 3). Studies conducted in
Table 3. Adverse birth outcomes due to *P. vivax* infection in pregnancy compared to non-infected pregnant women and comparisons with *P. falciparum* risk in co-endemic areas

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Plasmodium vivax</th>
<th>Magnitude (95% CI)</th>
<th>Plasmodium falciparum</th>
<th>Magnitude (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk/odds of low birth weight</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>McGready et al. (2004)</td>
<td>Thailand</td>
<td>Decreased</td>
<td>OR = 0.31 (0.01, 4.21)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Increased</td>
<td>OR = 1.76 (0.44, 10.18)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Poespoprodjo et al. (2008)</td>
<td>Indonesia</td>
<td>Increased</td>
<td>OR = 1.9 (1.2, 3.1)</td>
<td>Increased</td>
<td>OR = 1.9 (1.4, 2.7)</td>
</tr>
<tr>
<td>Tobon-Castano et al. (2011)</td>
<td>Colombia</td>
<td>Increased</td>
<td>RR = 1.26 (0.80, 1.98)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Increased</td>
<td>RR = 2.12 (1.24, 3.60)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean difference in birth weight</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nosten et al. (1991)</td>
<td>Thailand</td>
<td>Similar</td>
<td>MD = −49 g&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Decreased</td>
<td>MD = −128 g&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nair and Nair (1993)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>India</td>
<td>Decreased</td>
<td>MD = −390 g&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Decreased</td>
<td>MD = −780 g&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nosten et al. (1999)</td>
<td>Thailand</td>
<td>Decreased&lt;sup&gt;d&lt;/sup&gt;</td>
<td>MD = −107 g (−154, 61)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Singh et al. (1999)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>India</td>
<td>Decreased</td>
<td>MD = −310 g (−356, −264)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Decreased</td>
<td>MD = −380 g (−425, −335)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>McGready et al. (2004)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Thailand</td>
<td>Similar</td>
<td>MD = −10 g (−182, 162)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Decreased</td>
<td>MD = −80 g (−288, 128)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Poespoprodjo et al. (2008)</td>
<td>Indonesia</td>
<td>Decreased</td>
<td>MD = −108 g (−199, −18)</td>
<td>Decreased</td>
<td>MD = −192 g (−265, −119)</td>
</tr>
<tr>
<td>Arango et al. (2011)</td>
<td>Colombia</td>
<td>Decreased</td>
<td>MD = −525 g (−780, −270)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Decreased</td>
<td>MD = −278 g (−771, 215)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yasnot et al. (2013)</td>
<td>Colombia</td>
<td>Decreased</td>
<td>MD = −215 g (−539, 109)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Machado Filho et al. (2014)</td>
<td>Brazil</td>
<td>Decreased</td>
<td>MD = −434 g (−742, −127)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Risk/odds of preterm delivery</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nair and Nair (1993)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>India</td>
<td>Increased</td>
<td>OR = 7.07 (3.02, 16.7)</td>
<td>Increased</td>
<td>OR = 9.17 (4.02, 21.1)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>McGready et al. (2004)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Thailand</td>
<td>Similar</td>
<td>OR = 1.00 (0.01, 81.3)</td>
<td>Increased</td>
<td>OR = 3.5 (0.46, 157.2)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tobon-Castano et al. (2011)</td>
<td>Colombia</td>
<td>Increased</td>
<td>RR = 1.47 (0.95, 2.28)</td>
<td>Increased</td>
<td>RR = 3.17 (2.02, 4.97)</td>
</tr>
<tr>
<td>Mean difference in gestational age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nosten et al. (1999)</td>
<td>Thailand</td>
<td>Similar</td>
<td>MD = 0 weeks (−0.3, 0.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Similar</td>
<td>MD = −0.2 weeks (−0.4, 0.0)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>McGready et al. (2004)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Thailand</td>
<td>Similar</td>
<td>MD = 0.5 weeks (−0.79, 1.79)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Similar</td>
<td>MD = −0.4 weeks (−1.35, 0.55)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yasnot et al. (2013)</td>
<td>Colombia</td>
<td>Decreased</td>
<td>MD = −1.9 weeks (−3.11, −0.69)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Machado Filho et al. (2014)</td>
<td>Brazil</td>
<td>Decreased</td>
<td>MD = −2 weeks</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Odds of miscarriage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nair and Nair (1993)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>India</td>
<td>Increased</td>
<td>OR = 4.64 (0.63, 52.4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Increased</td>
<td>OR = 20.4 (4.40, 187)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nosten et al. (1999)</td>
<td>Thailand</td>
<td>Decreased</td>
<td>OR = 0.65 (0.41, 0.97)&lt;sup&gt;b,f&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>McGready et al. (2012)</td>
<td>Thailand</td>
<td>Increased&lt;sup&gt;e&lt;/sup&gt;</td>
<td>OR = 3.99 (3.10, 5.13)&lt;sup&gt;b,j&lt;/sup&gt;</td>
<td>Increased&lt;sup&gt;e&lt;/sup&gt;</td>
<td>OR = 3.99 (3.10, 5.13)&lt;sup&gt;b,j&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR = 2.70 (2.04, 3.59)&lt;sup&gt;b,j&lt;/sup&gt;</td>
<td></td>
<td>OR = 2.70 (2.04, 3.59)&lt;sup&gt;b,j&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NB – ratios within 0.2 of 1 were considered similar to 1. Birth weight MDs <50 g were considered similar. Gestational age MDs <1 week were considered similar. Low birth weight defined as <2500 g. All measures of association were unadjusted unless otherwise specified. Abbreviations: MD, mean difference; OR, odds ratio; RR, Risk Ratio.

<sup>a</sup> Cases included *P. malariae* and *P. vivax* cases.
<sup>b</sup> Calculated from data in paper.
<sup>c</sup> Women in study restricted to those with history of fever.
<sup>d</sup> Adjusted for age, location, gestational age at first visit, compliance to attendance at the antenatal clinic.
<sup>e</sup> Adjusted for hookworm infection, vitamin A deficiency and trimester of pregnancy.
<sup>f</sup> Error in the published paper, the reported events in the *P. vivax* group should read 447, not 44. Confirmed by authors of the paper.
<sup>g</sup> Single episode of *P. vivax* or *P. falciparum* in first trimester.
<sup>h</sup> Adjusted for age, smoking and estimated gestational age.
<sup>i</sup> Symptomatic malaria.
<sup>j</sup> Asymptomatic malaria.
Thailand, India, Colombia and Indonesia have tended to find a greater reduction in birth weight and greater increase in the risk of preterm delivery amongst pregnant women with *P. falciparum* infections compared to *P. vivax* infections in pregnancy (Nair and Nair, 1993; Nosten et al. 1999; Singh et al. 1998, 1999; McGready et al. 2004; Poespoprodjo et al. 2008; Tobon-Castano et al. 2011) (Table 3). A study in India showed reduced odds of foetal loss in *P. vivax* compared to *P. falciparum* infections (Nair and Nair, 1993), whereas studies in Thailand which have specifically examined miscarriage found similar odds in *P. falciparum* and *P. vivax* infections (McGready et al. 2012). Taken together the above findings suggest that some of the underlying mechanisms by which the two species mediate negative birth outcomes are independent.

It is well documented that the risk of *P. falciparum* infection during pregnancy is highest amongst primigravid women (reviewed in Desai et al. 2007). Studies in Thailand, India and Indonesia have also found that primigravidae are more at risk of *P. vivax* infection than multigravidae (Brabin et al. 1990; Singh et al. 1998, 1999; Nosten et al. 1999; Poespoprodjo et al. 2008; Fowkes et al. 2012), although this finding is not consistent across all study sites (Singh et al. 1995; Luxemburger et al. 2001; Appleyard et al. 2008) (Table 4). Broad immunological and hormonal changes that take place with successive pregnancies could play a role in the decreasing risk of both *P. falciparum* and *P. vivax* with gravidity (Vluegels et al. 1987, 1989; Riley et al. 1989; Bouyou-Akotet et al. 2004, 2005). Additionally, a degree of protective immunity is acquired to both species during pregnancy, which may play a stronger role in *P. falciparum* infections than *P. vivax* infections (reviewed below).

A review of the epidemiological data indicates that consolidation of data is challenging due to differences in transmission and clinical criteria. In summary, the data suggest that pregnant women may be at an increased risk of *P. vivax* during pregnancy, but are relatively more susceptible to *P. falciparum* than *P. vivax* compared to their non-pregnant counterparts. Infection with *P. falciparum* during pregnancy tends to lead to more severe negative maternal and birth outcomes than infection with *P. vivax*. Evidence suggests that primigravidae are at increased risk of *P. falciparum* and *P. vivax* compared to multigravidae. The differential risk, severity and gravidity effects could be attributed to the distinct pathologies of *P. falciparum* and *P. vivax* during pregnancy and/or differential immunity to the two species.

Key differences in *P. falciparum* and *P. vivax* clinical pathogenesis

During pregnancy, specific *P. falciparum* variants emerge that can escape pre-existing immunity and
Table 5. Key differences in *P. falciparum* and *P. vivax* placental and binding pathogenesis

<table>
<thead>
<tr>
<th>Feature</th>
<th><em>Plasmodium vivax</em></th>
<th><em>Plasmodium falciparum</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Finding</td>
<td>References</td>
</tr>
<tr>
<td>Infections detected in placenta</td>
<td>Rare</td>
<td>Singh et al. (2003)</td>
</tr>
<tr>
<td>Altered placental histology</td>
<td>Yes (less severe than <em>Pf</em>)</td>
<td>McGready et al. (2004)</td>
</tr>
<tr>
<td>Binding to placcental cryossection <em>in vitro</em></td>
<td>Yes (decreased binding compared to <em>Pf</em>)</td>
<td>Carvalho et al. (2010)</td>
</tr>
<tr>
<td>Binding to hyaluronic acid <em>in vitro</em></td>
<td>Yes</td>
<td>Chotivanich et al. (2012)</td>
</tr>
<tr>
<td>Binding to IgG <em>in vitro</em></td>
<td>Unknown</td>
<td>N/A</td>
</tr>
<tr>
<td>Binding to IgM <em>in vitro</em></td>
<td>Unknown</td>
<td>N/A</td>
</tr>
<tr>
<td>Differential binding in pregnancy compared to non-pregnancy isolates</td>
<td>No</td>
<td>Marin-Menendez et al. (2013)</td>
</tr>
<tr>
<td>Leading placental ligand candidate</td>
<td>Members of the VIR family</td>
<td>(Carvalho et al. 2010; Chotivanich et al. 2012)</td>
</tr>
</tbody>
</table>

Abbreviations: *Pf*, *Plasmodium falciparum*; *Pv*, *Plasmodium vivax*; IgG, immunoglobulin G; IgM, immunoglobulin M; N/A, not available.

Sequester in the placenta. *Plasmodium falciparum* isolates in pregnant women upregulate the expression of *Pf*VAR2CSA, an antigen located on the *P. falciparum*-infected erythrocyte (*Pf*-IE) surface. *Pf*VAR2CSA is a specific form of the variant protein PFEmp1 (*P. falciparum* erythrocyte membrane protein 1) that binds to placental chondroitin-sulphate A (CSA) and helps mediate parasite sequestration in the placenta (reviewed in Khunrae et al. 2010). The increased burden and detrimental effects of *P. falciparum* infection observed in pregnant women has been largely attributed to elevated parasite densities and the placental sequestration of *Pf*-IEs (reviewed in Desai et al. 2007; Hviid and Salanti, 2007; Rogerson, 2010; Umbers et al. 2011). *Plasmodium falciparum* infection during pregnancy is typically associated with a very pronounced sequestration, or selective accumulation, of mature forms of blood-stage parasites in the placenta with a parasitaemia many fold higher than that observed in the peripheral blood (Walter et al. 1982; Beeson et al. 2002). The accumulation of large numbers of *Pf*-IEs at the placenta results in changes to placental histology including inflammation, deposition of pigment in fibrin or inflammatory cells, syncytiotrophic knotting and thickening of the trophoblastic basement membrane (Walter et al. 1982; Bulmer et al. 1993; Ismail et al. 2000; Rogerson et al. 2003). *P. vivax* lacks the *Pf*VAR2CSA protein, or any known *Pf*VAR2CSA orthologues, and *P. vivax*-IEs (*Pv*-IEs) are rarely found in the placenta (Singh et al. 2003; Mayor et al. 2012a; Carmona-Fonseca et al. 2013). Despite this, infections with *P. vivax* during pregnancy have been associated with some of the same histological changes observed in *P. falciparum* infections, though these changes are typically less severe (McGready et al. 2004; Souza et al. 2013) (Table 5). The binding of *Pv*-IEs to CSA (as well as other endothelial cells) has been described in vitro and may be partly mediated by *Pv*VIR (Variant Interspersed Repeats) proteins expressed on the surface of *Pv*-IEs. However, the level of cytoadherence of *Pv*-IEs to CSA is around ten-fold lower than that displayed by *Pf*-IEs (Carvalho et al. 2010; Chotivanich et al. 2012) and cytoadherence to CSA does not differ between *P. vivax* isolates from pregnant and non-pregnant individuals (Marin-Menendez et al. 2013). The low level of CSA-adherence exhibited by *Pv*-IEs likely plays a minor role in pathogenesis compared to *P. falciparum*. The existence of *Pf*VAR2CSA in *P. falciparum* represents a crucial difference between the two species and explains much of the different infection outcomes experienced by pregnant women. The reduced level of *P. vivax* cytoadherence in *vitro relative to *P. falciparum* explains the rarity of clinical observations of *P. vivax* placental sequestration (Mayor et al. 2012a; Carmona-Fonseca et al. 2013; Souza et al. 2013; Chaikitgosiyakul et al. 2014). Although other ligand/receptor combinations...
have been proposed as contributing to the sequestration of parasites in the placenta (Table 5) the evidence currently favours P/VAR2CSA/CSA as the principal interaction responsible for placental sequestration of *P. falciparum*.

Another pathophysiological feature mediated by IE surface ligands is rosetting, whereby IEs bind to uninfected erythrocytes. Rosetting is a feature of both *P. falciparum* and *P. vivax* isolates from infections in non-pregnant individuals (Udeinya et al. 1981; Udomsanpetch et al. 1995). Recent evidence suggests that rosetting occurs more frequently in *P. vivax* isolates than *P. falciparum* isolates (Lee et al. 2014) likely due to differential erythrocyte or receptor preferences. Glycophorin C is a ligand for both *P. falciparum* and *P. vivax* rosetting (Lee et al. 2014) whilst numerous other receptors have been identified for *P. falciparum* rosetting (reviewed in Sherman et al. 2003). Interestingly, rosetting is uncommon in placental *P. falciparum* isolates (Maubert et al. 1998; Rogerson et al. 2000) and is lacking in isolates that adhere to CSA and upregulate VAR2CSA (Beeson and Brown, 2004). In the absence of placental sequestration, the rosetting phenotype may contribute more strongly to clinical outcomes in *P. vivax* infection; rosetting is strongly associated with anaemia and increased parasitaemia in both *P. falciparum* and *P. vivax* infection (Rowe et al. 2002; Dounou et al. 2009; Marin-Menendez et al. 2013).

In the absence of considerable interactions between the placenta and Pr-IEs, the altered placental histology associated with *P. vivax* infection is likely due to broad effects of peripheral infection, such as maternal anaemia, fever or the effect of the cytokine response to infection (Mayor et al. 2012a; Souza et al. 2013). These mechanisms likely also act in *P. falciparum* peripheral infections in conjunction with the direct effects of placental sequestration. Reticulocytosis occurs in some populations during pregnancy and may contribute to an increased risk of *P. vivax* (Traill, 1975). Taken together, current data show that interactions between *P. vivax* and placental receptors are rare in contrast to the common interaction of *P. falciparum* ligands with placental receptors which largely explains the reduced magnitude of negative outcomes in *P. vivax* infections in pregnancy compared to *P. falciparum* infections.

*Plasmodium falciparum* and *P. vivax* risk in the postpartum period

How the increased burden and risk of *P. falciparum* and *P. vivax* malaria during pregnancy relates to the risk of malaria in the postpartum period is the focus of increasing research. The World Health Organization defines the postpartum period as beginning 1 h after the delivery of the placenta and continuing until 6 weeks after the birth of the infant (WHO, 2011). This definition is rarely adhered to in the malaria literature, so for the purpose of this review the postpartum period is defined as the period from delivery to 6 months post-delivery. The majority of postpartum studies have been conducted in Africa and have compared the risk of *P. falciparum* infection postpartum to the risk during pregnancy; with these studies observing a reduced risk of *P. falciparum* infection in the postpartum period (Table 6) (Bray and Anderson, 1979; Watkinson and Rushton, 1983; Steketee et al. 1996; Fievet et al. 1997; Green et al. 2007; Menendez et al. 2008; Serra-Casas et al. 2011). Conversely, the single study that investigated *P. falciparum* clinical malaria found an increased risk during the 60 days postpartum compared to each trimester of pregnancy (Diagne et al. 2000). The sole study assessing the risk of *P. vivax* and *P. falciparum* infection in postpartum compared to pregnant controls (in Papua New Guinea) found the incidence of *P. vivax* and *P. falciparum* parasitaemia increased from delivery until 4 months postpartum (Brabin et al. 1990) with a greater relative increase in postpartum *P. vivax* incidence than *P. falciparum* incidence. Importantly, chemoprophylaxis was ceased at delivery so this finding may be more reflective of a ‘rebound effect’ than an indication of the natural course of susceptibility during the postpartum period (Brabin et al. 1990). Overall, the heightened risk of *P. falciparum* seen during pregnancy is typically reduced in the postpartum period, whilst the limited evidence of *P. vivax* risk postpartum compared to pregnancy suggests that the risk is elevated.

To truly evaluate whether malaria risk returns to non-pregnant levels immediately after pregnancy, the postpartum risk needs to be compared to non-pregnant controls. Two studies in Africa (Senegal and Gabon) found an increased risk of *P. falciparum* infection relative to non-pregnant women (Diagne et al. 2000; Ramharter et al. 2005) (Table 6). Both studies also found a greater increase in the risk of clinical malaria relative to the risk of *Plasmodium* spp. infection indicating that the postpartum state is more susceptible to clinical malaria than the non-pregnant state independent of an increased risk of infection. Depressed immunity may explain this finding with the Senegal study finding that after 90 days postpartum the risk of clinical *P. falciparum* malaria returned to the level seen prior to pregnancy, suggesting that the responsible factor for altered postpartum risk returns to normal after 3 months (Diagne et al. 2000). In contrast to African findings, a recent study on the Thai–Myanmar border found that postpartum women had decreased risk of *P. falciparum* episodes than age and location matched non-pregnant controls, whilst there was an increased risk of *P. vivax* episodes in postpartum women compared to
non-pregnant controls (Boel et al. 2013). Further research into postpartum risk of malaria will help address the current conflicting evidence of the risk of malaria in the postpartum period.

It has been suggested that the differential risk of malaria in the postpartum period may be due to immunological changes that occur during pregnancy and gradually return to ‘normal’ in the postpartum period (Diagne et al. 2000; Ramharter et al. 2005). Immunological changes during pregnancy include changes in cell-mediated and humoral immunity (Jamieson et al. 2006; Robinson and Klein, 2012), which would presumably differentially affect susceptibility to *P. falciparum* and *P. vivax* due to underlying species differences in immunopathology.

### Immunity to *P. falciparum* and *P. vivax* in pregnancy

A variety of immunological changes occur during pregnancy, with changes in the nature of cytokine responses, a general suppression of cell-mediated immunity and increased humoral immunity (reviewed in Jamieson et al. 2006; Robinson and Klein, 2012). This shift is believed to reduce the

<table>
<thead>
<tr>
<th>Study/odds of infection compared to pregnancy</th>
<th>Country</th>
<th>Postpartum period</th>
<th>Magnitude (95% CI)</th>
</tr>
</thead>
</table>
| Bray and Anderson (1979)                    | The Gambia | At 1 mo. | N/A | N/A | Similar$^a$ | OR = 0·81 (0·41, 1·53)$^b$
| Brabin et al. (1990)                       | Papua New Guinea | Across 4 mos. | Increased$^a$ | IRR = 4·89 (1·92, 11·59)$^b$ | Increased$^a$ | IRR = 1·28 (0·78, 2·00)$^b$
| Steketee et al. (1996)                     | Malawi | At 2 mos. | N/A | N/A | Similar$^a$ | OR = 0·80 (0·72, 0·88)$^b$
| Fievet et al. (1997)                       | Cameroon | At 6 mos. | N/A | N/A | Decreased$^e$ | OR = 0·19 (0·05, 0·68)$^b$
| Diagne et al. (2000)                       | Senegal | Across 2 mos. | N/A | N/A | Increased$^a$ | IRR = 1·75 (0·75, 3·76)$^b$
| Green et al. (2007)                        | Kenya | At 2 mos. | N/A | N/A | Decreased$^a$ | OR = 0·20 (0·00, 1·80)$^b$
| Menendez et al. (2008)                     | Mozambique | At 2 mos. | N/A | N/A | Decreased$^a$ | OR = 0·36 (0·22, 0·58)$^b$
| Serra-Casas et al. (2011)                  | Mozambique | At 2 mos. | N/A | N/A | Decreased$^a$ | OR = 0·35 (0·19, 0·61)

| Risk/odds of clinical malaria compared to pregnancy | Senegal | Across 2 mos. | N/A | N/A | Increased$^f$ | IRR = 1·98 (0·84, 4·36)$^b$
| Risk/odds of infection compared to non-pregnant women | Senegal | Across 2 mos. | N/A | N/A | Increased$^a$ | OR = 0·36 (0·22, 0·58)$^b$
| Ramharter et al. (2005)                     | Gabon | Across 2·5 mos. | N/A | N/A | Increased$^a$ | IRR = 2·7 (1·0, 8·2)
| Boel et al. (2013)                          | Thailand | Across 3 mos. | Increased$^a$ | HR = 1·34 (1·05, 1·72) | Decreased$^a$ | HR = 0·39 (0·21, 0·72)

| Risk/odds of clinical malaria compared to non-pregnant women | Senegal | Across 2 mos. | N/A | N/A | Increased$^f$ | RR = 4·1 (1·8, 9·5)$^g$
| Ramharter et al. (2005)                     | Gabon | Across 2·5 mos. | N/A | N/A | Increased$^b$ | IRR = 9·8 (1·4, 42·0)

NB – ratios within 0·2 of 1 were considered similar to 1. All measures of association are unadjusted unless otherwise specified.

Abbreviations: mos., months; LM, light microscopy; OR, odds ratio; IRR, incidence rate ratio; RR, risk ratio; HR, hazard ratio.

$^a$ Detected by light microscopy.

$^b$ Calculated from data in the paper.

$^c$ Study restricted to primigravid women only.

$^d$ Asymptomatic infection.

$^e$ Detected by PCR.

$^f$ Clinical malaria defined as any case of fever or fever-related symptoms associated with a ratio of parasites to leucocytes that exceeds a pyrogenic threshold.

$^g$ Adjusted for exposure, parity, duration of residence in village and effects within study subjects.

$^h$ Clinical malaria defined as asexual *P. falciparum* parasitemia with >100 parasites μL$^{-1}$ of blood, fever (current or within the previous 24 h), or presence of other symptoms associated with malaria.
chance of foetal rejection and increase the maternal transfer of antibodies to the foetus. These broader immunological changes are also likely to contribute to an altered susceptibility to both \textit{Plasmodium} spp. during pregnancy in addition to the availability of the placenta as a sequestration site.

The broadly suppressed cell-mediated immunological state that exists during pregnancy should dampen the effectiveness of T cells on both \textit{P. falciparum} and \textit{P. vivax}. However, few studies have investigated the impact of an altered cell-mediated response on \textit{Plasmodium} spp. infection during pregnancy. CD8 T cell levels are higher in the inflammatory infiltrate in chronically \textit{P. falciparum} infected placentae compared to uninfected placentae, past infections, acute infections and placentae from non-exposed women (Ordí \textit{et al.} 2001). This observation was supported by another study which found greater frequencies of CD8 T cells producing IFN-alpha and TNF-alpha in \textit{P. falciparum} infected placentae compared to uninfected placentae (Diouf \textit{et al.} 2007). Less is known about the role of T cells at the placenta during \textit{P. vivax} infections. An increased presence of mononuclear cells in the placenta was detected in instances of \textit{P. vivax} and \textit{P. falciparum} infections compared to no infection, with similar numbers of mononuclear cells in \textit{P. vivax} and \textit{P. falciparum} infections (Souza \textit{et al.} 2013).

Another important impact an altered cell-mediated immune response may have in pregnancy is an altered ability to control liver stage infection and \textit{P. vivax} relapse. Though direct human evidence is lacking, cell-mediated immunity is thought to be particularly important for pre-erythrocytic immunity on the basis of animal models (reviewed in Doll and Harty, 2014). However, what constitutes an adequate immune response against clinical relapses of \textit{P. vivax} is unknown as is the risk of relapses during the altered immunological state of pregnancy.

The humoral immune response is a crucial component of naturally acquired immunity and antibody responses to both \textit{P. falciparum} and \textit{P. vivax} antigens are important biomarkers of exposure and protective immunity in meta-analyses of non-pregnant populations (Fowkes \textit{et al.} 2010; Cutts \textit{et al.} 2014). Numerous studies have demonstrated the important role of anti-\textit{Pf}VAR2CSA humoral immunity in \textit{P. falciparum} infections during pregnancy (reviewed in Duffy, 2007; Hviid and Salanti, 2007; Rogerson, 2010; Ataide \textit{et al.} 2013). Antibodies reactive against recombinant \textit{Pf}VAR2CSA, and to the surface of erythrocytes infected with \textit{P. falciparum} placental isolates and \textit{P. falciparum} lines selected by their adhesion to CSA increase with gravidity (reviewed in Ataide \textit{et al.} 2013), indicating that immunity to \textit{Pf}VAR2CSA is acquired or boosted progressively with successive pregnancies, and is associated with parasite clearance and reduced odds of placental infection (Guitard \textit{et al.} 2008; Feng \textit{et al.} 2009; Tutterrow \textit{et al.} 2012a, b). There is currently no complementary evidence for \textit{P. vivax}. The risk of \textit{P. vivax} also tends to decline with gravidity (Table 4), rendering the existence of \textit{P. vivax} antigens that are upregulated in pregnancy and important as immune targets a viable hypothesis. However, in the absence of pregnancy-specific \textit{P. vivax} isolates or antigens, the gravidity effect may also be explained by a broader acquisition and boosting of immunity towards \textit{Pv}-1Es and merozoite antigens during exposure to \textit{P. vivax} during pregnancy or merely a reflection of immune acquisition with age. Additional mechanisms that influence susceptibility to both species during pregnancies are increased cortisol concentrations (Vleugels \textit{et al.} 1989; Bouyou-Akotet \textit{et al.} 2005) and reduced NK cell activity (Bouyou-Akotet \textit{et al.} 2004) particularly in primigravid pregnancies.

There is little data available on antibodies to merozoite antigens during pregnancy (including orthologues expressed in both \textit{P. falciparum} and \textit{P. vivax}, e.g. AMA1, MSP119). Pregnant women in endemic settings have typically acquired protective immunity to these antigens during childhood; this immunity would likely contribute to a protective effect in pregnancy by reducing parasitaemia, which would have a knock-on protective effect on the burden of placental infection. Evidence to support this is limited, however some studies have found ad hoc associations with particular merozoite antigens (e.g. \textit{PfMSP1-19} and \textit{PfAMA-1}) with improved birth outcomes in women exposed to \textit{P. falciparum} (Taylor \textit{et al.} 2004; Mayor \textit{et al.} 2013). Results must be interpreted with caution, given the lack of similar associations with other non-pregnancy specific antigens in the same studies (\textit{PfCSP}, \textit{PfLSA1}, \textit{PfRESA}, \textit{PfDBLγ}, \textit{PfDBLα}, \textit{PfMSP1-19}, \textit{PfAMA1 PfEBA175}). Furthermore, \textit{P. falciparum} merozoite responses (and \textit{P. vivax} responses in co-endemic areas) are often highly correlated with \textit{PfVAR2CSA} (Fowkes \textit{et al.} 2012) so associations observed can serve as a proxy for higher levels of other protective responses.

Alternatively, in the absence of \textit{P. vivax}-specific mechanisms, the gravidity effect could be indirect. It has been hypothesized that relapses of \textit{P. vivax} infections are triggered by fever, notably by other malaria infections (reviewed in Shanks and White, 2013). If this were the case then one would expect \textit{P. falciparum} erythrocytic immunity (both cell-mediated and humoral), to indirectly protect against \textit{P. vivax} relapse by protecting against febrile symptoms. This indirect mechanism could explain the decreased risk of \textit{P. vivax} with increasing gravidity in co-endemic regions in the absence of more direct immunological mechanisms.

Cross-species immunity also provides an alternative explanation for the gravidity effect of \textit{P. vivax}.
There is little reliable human data on cross-species immunity. An experimental infection of a non-pregnant individual with \textit{P. vivax} showed that antibodies induced by \textit{P. vivax}, are capable of recognizing \textit{P. falciparum} schizont extract and may be able to inhibit \textit{P. falciparum} growth in vitro (Nagao et al. 2008). How this translates vice versa or in pregnancy is unknown but may explain the interaction in disease severity between the two species in Thailand where \textit{P. vivax} infection reduced the severity and number of \textit{P. falciparum} episodes during pregnancy (Luxemburger et al. 1997; Nosten et al. 1999). Evidence also suggests that high-density blood stage infections may be able to inhibit liver stage infections through an increase in hepcidin levels (reviewed in Portugal et al. 2011). Mechanisms of \textit{Plasmodium} species-transcending immunity are poorly defined in humans and require further elucidation to determine their role in pregnancy and postpartum.

There is a relatively scarce amount of literature regarding the role of non-IgG antibodies in \textit{P. falciparum} and \textit{P. vivax} infection during pregnancy and postpartum which is not surprising given that IgG is considered to be the key immunoglobulin for naturally acquired immunity against malaria (Doolan et al. 2009). IgM is typically observed in the primary response to infection and numerous \textit{P. falciparum} and \textit{P. vivax} antigens elicit IgM responses (Cutts et al. 2014). IgM has been shown to bind non-specifically to \textit{Pf}VAR2CSA a feature which may have evolved as an immune evasion mechanism (Creasey et al. 2003; Elliott et al. 2005; Rasti et al. 2006; Semblat et al. 2006; Barfod et al. 2011). The binding of IgM to \textit{Pf}VAR2CSA has been shown to interfere with specific IgG recognition and opsonic phagocytosis of IE infected with pregnancy-specific isolates ((Barfod et al. 2011) but not other non-pregnancy specific \textit{Pf}EMP-1s (Stevenson et al. 2014). IgM has also been implicated in rosetting and strengthening \textit{Pf}-IE erythrocyte interactions (Stevenson et al. 2014) however rosetting is rare in \textit{P. falciparum} placental isolates (Maubert et al. 1998; Rogerson et al. 2000). There is currently no data on the role of IgM in \textit{P. vivax} rosetting. Further investigation of the role of IgM in \textit{P. falciparum} and \textit{P. vivax} infections is warranted.

The functional roles IgG antibodies require for protection against \textit{P. falciparum} and \textit{P. vivax} infection are fairly poorly defined. The predominant isotypes found against \textit{P. falciparum} placental isolates are IgG1 and IgG3, the dominant isotypes against most malarial antigens (Elliott et al. 2005; Megnekou et al. 2005; Stanisic et al. 2009; Richards et al. 2010), which can function through adhesion-inhibition/invasion-inhibition, phagocytosis, antibody-dependent cell-mediated cytotoxicity and/or complement fixation. Anti-\textit{Pf}VAR2CSA IgG can inhibit adhesion by interfering with the binding of \textit{Pf}-IEs and CSA or recombinant \textit{Pf}VAR2CSA to CSA (Ricke et al. 2000; Barfod et al. 2010; Khunrae et al. 2010). Opsonic phagocytosis against CSA-binding parasite isolates have been identified in sera from pregnant women (Keen et al. 2007; Tippett et al. 2007; Feng et al. 2009; Ataide et al. 2010, 2011; Barfod et al. 2010). There is little information at present on the contribution of anti-\textit{Pf}VAR2CSA IgG to antibody-mediated complement activity, with some indications that excessive innate complement binding is detrimental (Conroy et al. 2009, 2013; Khattab et al. 2013). Antibody-mediated immune functions against a range of \textit{P. falciparum} targets are present during pregnancy (Teo et al. 2014), but whether altered immunology during pregnancy alters their magnitude as compared to non-pregnant individuals is unknown. Studies on \textit{Pv}-IE are severely hindered by the inability to culture \textit{P. vivax} long-term in vitro.

In non-pregnant populations, clinical immunity is thought to develop more rapidly to \textit{P. vivax} than \textit{P. falciparum} as indicated from parasitological data from syphils malarialotherapy patients (Collins and Jeffery, 1999a; Collins et al. 2004) and from malaria endemic areas whereby the prevalence of \textit{P. vivax} infection and clinical episodes peaks at younger ages compared to \textit{P. falciparum} (Maitland et al. 1996; Smith et al. 2001; Mueller et al. 2009; Lin et al. 2010). It is hypothesized that this is due to a reduced immune threshold required to achieve protection against \textit{P. vivax} compared to \textit{P. falciparum} or the ability of \textit{P. vivax} to relapse giving rise to a higher molecular force of infection (Koepfl et al. 2013). Species-specific differences in the rate of immune acquisition have yet to be reconciled in pregnancy but longitudinal studies show that antibody responses to both \textit{P. falciparum} and \textit{P. vivax} antigens during longitudinal studies show that antibody responses to both \textit{P. falciparum} and \textit{P. vivax} antigens during pregnancy are similarly dynamic in response to species-specific \textit{Plasmodium} spp. exposure (Aitken et al. 2010; Fowkes et al. 2012; Ampomah et al. 2014b), lending support to the notion that regular exposure is required to maintain malarial immunity. Interestingly, a recent longitudinal study of antibodies in pregnancy found that antibodies to \textit{P. vivax} (\textit{Pv}AMA1) were not boosted with successive infections in pregnancy, in contrast with \textit{P. falciparum} antibodies which were boosted with each exposure (including the homologue \textit{Pf}AMA1) (Fowkes et al. 2012). This may indicate a difference in immunological memory or recall response between the two species or the much lower parasitemia densities in \textit{P. vivax} infections are less efficient in boosting responses. The implications of this lack of boosting for immunity and increased risk of \textit{P. vivax} in pregnancy and the postpartum period (observed in the same study area) are unknown and further studies are necessary. Furthermore an understanding of antibody dynamics...
Table 7. Epidemiological observations of *P. falciparum* and *P. vivax* during pregnancy and postpartum and proposed mechanisms

<table>
<thead>
<tr>
<th>Proposed species-transcending mechanisms</th>
<th>References</th>
<th>Proposed species-specific mechanisms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imunomodulation in pregnancy alters susceptibility</td>
<td>Bouyou-Akotet et al. (2005)</td>
<td><em>Plasmodium vivax</em> – placental sequestration, though evidence is minimal</td>
<td>(Carvalho et al. 2010; Chotivanich et al. 2012)</td>
</tr>
<tr>
<td>Altered hormonal profiles during pregnancy</td>
<td></td>
<td></td>
<td>Roberts et al. (1996)</td>
</tr>
<tr>
<td>Altered attractiveness to mosquitoes</td>
<td>Lindsay et al. (2000)</td>
<td><em>Plasmodium vivax</em> – altered immunity/hormones in pregnancy alters risk of relapse</td>
<td></td>
</tr>
<tr>
<td>Reduced risk of infection with increasing gravidity</td>
<td>Doolan et al. (2009)</td>
<td><em>Plasmodium falciparum</em> – humoral immunity to P/VAR2CSA acquired with gravidity</td>
<td>Fried et al. (1998)</td>
</tr>
<tr>
<td>Altered hormonal profiles with gravidity</td>
<td>Bouyou-Akotet et al. (2005)</td>
<td></td>
<td>Roberts et al. (1996)</td>
</tr>
<tr>
<td>Altered immunomodulation with gravidity</td>
<td>Riley et al. (1989)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered iron deficiency with gravidity</td>
<td>Ouedraogo et al. (2012)</td>
<td></td>
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<td>Infection with both species leads to adverse birth outcomes, more severe in <em>P. falciparum</em> than <em>P. vivax</em></td>
<td>Umbers et al. (2011)</td>
<td><em>Plasmodium falciparum</em> – sequestration at the placenta, leads to local pathology and immune response at the placenta</td>
<td>Umbers et al. (2011)</td>
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<tr>
<td>Systemic immune response to infection contributes to foetal growth restriction.</td>
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<tr>
<td>Anaemia</td>
<td>Friedman et al. (2009)</td>
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<tr>
<td>Altered risk postpartum</td>
<td>Boel et al. (2013)</td>
<td><em>P. falciparum</em> – increased susceptibility during pregnancy leads to increased immunity postpartum</td>
<td>This review</td>
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<tr>
<td>Behavioural changes postpartum alter level of exposure to vectors</td>
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<tr>
<td>Hormonal/immunological profile in transition from pregnancy to 'normal'</td>
<td>Diagne et al. (2000)</td>
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Postpartum would help elucidate how pregnancy-favoured antibodies are maintained in between pregnancies with apparent limited exposure to pregnancy-favoured antigens.

**Antibody responses postpartum and between pregnancies**

The strong link between gravidity and P/VAR2CSA antibodies suggests that antibody responses and immune memory are maintained between pregnancies and postpartum when exposure to P/VAR2CSA is low. This is at odds with the paradigm that frequent exposure is required to develop a long lasting antibody response to malaria and that, in the absence of repeated exposure, immunity is short lived (i.e. weeks) (Kinyanjui et al. 2003; Langhorne et al. 2008).

Antibodies are secreted by plasma cells, which can be either short-lived or long-lived (Manz et al. 2005). Mathematical modelling has demonstrated that separate populations of long and short lived cells can describe the rapid decay of antibodies observed immediately following exposure and the long-lived maintenance of a lower level of antibodies in African children (White et al. 2014). This is reflected in studies that have investigated antibody longevity. Estimates in individuals’ shortly after a drug treated acute episode of malaria typically find short *P. vivax* and *P. falciparum* antibody half-lives (6 to 52 days) (Soares et al. 1999; Kinyanjui et al. 2007) whereas studies investigating long-term decay of antibodies in uninfected individuals have estimated longer *P. vivax* and *P. falciparum* antibody half-lives in excess of 5 years (Drakeley et al. 2005; Wipasa et al. 2010). Additionally, antibodies have been detected in individuals who have not been exposed to either species in over 5 years (Luby et al. 1967; Druilhe et al. 1986; Braga et al. 1998; Wipasa et al. 2010; Moncunill et al. 2013; Ndungu et al. 2013).

Little is known about antibody longevity in pregnancy and postpartum. A study in a low
transmission co-endemic area of Thailand found that *P. vivax* and *P. falciparum* merozoite antibody response half-lives calculated during pregnancy were shorter than that calculated for *Pf*VAR2CSA responses and was longer in those who had been exposed (0.8–7.6 years for merozoite antigens vs 57.6–142 years for VAR2CSA (Fowkes et al. 2012)). While these estimates should not be directly extrapolated from pregnancy into the postpartum period, recent evidence from cohorts of pregnant and postpartum women provide further evidence for long-term antibody maintenance postpartum. A study in Mozambique found that women 1–2 months postpartum had a median level of antibodies against the surface of a placental parasite line (CS2) comparable (3.3% higher) to women at delivery (Mayor et al. 2012b). A study in Malawi found that at 6 months postpartum 72.3% of women were still seropositive for antibodies to CS2 surface antigens (Aitken et al. 2010). More than 40% of women in Ghana who had not been pregnant in 1–6 years remained seropositive to *Pf*VAR2CSA suggesting that there is some level of antibody response maintenance in the relative absence of exposure (Ampomah et al. 2014a, b). Importantly they also demonstrated that the level of *Pf*VAR2CSA specific IgG-secreting B cells did not depend on time since last pregnancy or number of pregnancies suggesting that *Pf*VAR2CSA B cell memory is stably maintained in the absence of exposure (Ampomah et al. 2014a).

Explanations for an apparent increased longevity of *Pf*VAR2CSA responses are unclear, but could relate to a large sequestered parasite load providing a strong and sustained antigenic stimulus or be reflective of boosting as a result of undetected placental infection during pregnancy, or the greater immune longevity that appears to occur in adults. It is thought that there is limited or infrequent exposure to *Pf*VAR2CSA prior to the first pregnancy, in contrast to most malarial antigens, which are generally encountered throughout life. However, studies have shown that exposure to *Pf*VAR2CSA can be acquired in childhood (Beeson et al. 2007). This would influence subsequent response to *Pf*VAR2CSA in pregnancy such that antibody levels may be boosted more rapidly upon re-exposure and be better maintained. Younger individuals tend to have shorter half-lives than older individuals (Taylor et al. 1996; Akpogheneta et al. 2008) and the age of primary exposure to an antigen may affect the longevity of immune responses to that antigen. The detection of *Pf*VAR2CSA antibodies in women who have not been pregnant in years and the observed persistence of *Pf*VAR2CSA specific IgG-secreting B cells supports the hypothesis that *Pf*VAR2CSA antibodies acquired in earlier pregnancies are maintained to protect subsequent pregnancies against *P. falciparum*. However, further longitudinal studies of women followed after pregnancy are required to assess this.

Whether there are *P. vivax* antigens that are specifically upregulated in pregnancy and whether antibodies against *P.vivax* are maintained postpartum and throughout pregnancies is unknown. Furthermore, the extent to which the immunological changes that occur during pregnancy and postpartum influence the risk of *P. vivax* relapse is unclear. If cell-mediated immunity is important in controlling liver infection, as it is in mouse models (reviewed in Doll and Harty, 2014), then the dampening of cell-mediated immunity would have a greater impact on *P. vivax* than *P. falciparum* due to the former parasites relatively longer period of residence in the liver. More immunological research is needed to further understand how immunity relates to the differential risk of *P. falciparum* and *P. vivax* postpartum.

**Box I. Research priorities**

- **Further epidemiological studies on the risk of *P. vivax* by pregnancy status and gravidity in different populations.**
- **Elucidate the mechanisms by which *P. vivax* infection during pregnancy contributes to negative maternal and infant outcomes.**
- **Quantify the clinical relevance of putative in vivo *P. vivax* binding to the placenta.**
- **Conduct longitudinal studies in pregnant women that incorporate humoral, cellular and functional immunity against both *P. vivax* and *P. falciparum* to quantify their relative contributions towards protection against infection and its course.**
- **Determine the risk of *P. vivax* and *P. falciparum* postpartum in different settings, ideally with both pregnant and non-pregnant comparison groups.**
- **Elucidate the immunological mechanisms of altered risk postpartum.**
- **Investigate the modulating effect of pregnancy on cell-mediated immunity in a malaria context.**
- **Discover the mechanisms that underpin the cause of *P. vivax* relapse.**
- **Identify immune correlates of protection against *P. vivax* relapse.**
- **Determine the contribution of cross-species immunity in naturally exposed human populations.**
FUTURE DIRECTIONS

Immunological evidence has helped provide a convincing explanation for the unique epidemiology of *P. falciparum* in pregnancy. Many questions remain to be answered in relation to *P. vivax* during pregnancy and the risk of both species post-partum (Table 7 and Box 1). Currently the availability of both immunological and epidemiological evidence pertaining to *P. vivax* in pregnancy is limited and inconsistent. A more comprehensive understanding of the epidemiology of *P. vivax* in pregnancy will act as a primer for future studies on the immunology of *P. vivax* in pregnancy. Ideally, comprehensive longitudinal studies that incorporate measurements of multiple immunological mechanisms would be able to assess the relative contribution of each of these functions towards protection and the observed epidemiology. Whether delivery marks the end of a period of increased risk of malaria is debatable. The epidemiology of the postpartum period remains unclear, with the few studies conducted providing conflicting results. Further epidemiological studies are needed to explore the differential risk of *P. falciparum* and *P. vivax* in the postpartum period, preferably in tandem with immunological studies, which may be able to explain the mechanisms underlying the epidemiology.

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