**Burden, pathology and costs of malaria in pregnancy: new developments for an old problem *Authors\**** *Prof Stephen J Rogerson PhD1#, Meghna Desai PhD2, Alfredo  Mayor PhD3,4, Elisa Sicuri PhD3,5, Steve M Taylor MD6,Anna M van Eijk PhD7*
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**Abstract**

Over the last ten years, our understanding of the burden, economic costs and consequences of malaria in pregnancy has deepened, while the prevalence of *Plasmodium falciparum* malaria has declined significantly in some areas. Studies outside of Africa have increased our knowledge of the burden, consequences and costs of *Plasmodium vivax* in pregnancy. Rapid diagnostic tests have performed poorly in detecting malaria in pregnant women, while PCR has revealed a high prevalence of low density infection, whose clinical importance remains unresolved. Erythrocytes infected with *P. falciparum* that express the surface protein VAR2CSA accumulate in the placenta, and VAR2CSA is an important target of protective immunity. A VAR2CSA vaccine has begun clinical trials, but sequence variation requires careful exploration. Health system and household costs still limit access to prevention and treatment services. Within the context of malaria elimination, pregnant women may be valuable sentinels for monitoring malaria transmission. This review summarises recent progress, and highlights unresolved issues relating to the burden of malaria in pregnancy.

**Introduction**

This review summarises progress in understanding of the epidemiology, burden, economic costs, pathogenesis, and diagnosis of malaria in pregnancy over the 10 years since Lancet Infectious Disease published a special issue on this topic. Readers are referred to the earlier reviews for comprehensive analyses of older literature.1,2 Looking forwards, we discuss how present efforts in malaria elimination may alter the burden and consequences of malaria in pregnancy, and how pregnant women may be used to monitor changing epidemiology of malaria across populations. Finally, we summarise important remaining research questions in this area. Our search strategy is outlined in Panel 1,and major advances over the last 10 years are summarised in Panel 2.

**Malaria in pregnancy: progress on epidemiology and burden of *P. falciparum***

In high malaria transmission areas such as sub-Saharan Africa, the risk of *Plasmodium falciparum* infection increases when women get pregnant, with potential adverse consequences for mother and child (Figure 1). Malaria prevalence is highest in the first and second trimester of pregnancy (AM van Eijk, personal communication),1 and the risk may not immediately return to pre-pregnancy levels after delivery.3 In these high transmission areas, defined as parasite prevalence in 2-9 year old children >10%, malaria in pregnancy is more common in younger compared to older pregnant women, in women in first or second pregnancy compared to later pregnancies, and in HIV-infected compared to uninfected women.1,4 Similar to the non-pregnant population, prevalence is affected by location (higher among rural populations), season, and use of malaria prevention.

Currently, malaria prevention and control in pregnant women in Africa rests on three pillars: insecticide treated nets (ITNs), intermittent preventive treatment (IPTp) with sulphadoxine-pyrimethamine, and effective case management of malarial illness and anaemia.5 However, coverage of these interventions is suboptimal: in 2014, only 35% slept under an ITN,6 and in 2015, only 31.5% of eligible women received three or more doses of IPTp. 7 The range of adverse outcomes among women and their newborns include well-described increased risks of maternal anaemia and low birthweight, and prematurity1 as documented in trials and observational studies.8 In a large study using African national survey data, the use of malaria prevention in pregnancy was associated with substantial reductions in neonatal mortality and low birthweight, agreeing with findings from an IPTp trial in Mozambique.9,10 In order to estimate the positive impact of prevention in Africa in 2015, Walker et al. developed a specific model of malaria in pregnancy which takes the unique feature of parity-specific patterns into account; using this model, it was estimated that, without pregnancy-specific interventions, 9.5 million pregnant women would have been exposed to infection, leading to 750 thousand low birthweight deliveries.11 However, with IPTp coverage (2 doses) estimated at 21.6% in 2015, potentially 128 thousand low birthweight deliveries could have been averted. 11

Understanding of the impact of malaria in pregnancy on fetal growth has been facilitated by increased use of obstetric ultrasound in cohort studies, providing accurate estimation of gestational age, sometimes combined with Doppler studies. Using such approaches in longitudinal studies, malaria in the first trimester is now recognised as an important risk factor for miscarriage, fetal growth restriction, low birthweight and maternal anaemia in Africa12,13 and Asia.14,15 In studies from Benin, the Democratic Republic of Congo (DRC), Malawi, Thailand and Brazil, malaria infections in early pregnancy, in late pregnancy, and throughout gestation have each been associated with reduced fetal growth,14,16-20 which worsens with repeated infections.16-18 This fetal growth restriction can occur either immediately or with a delay after malaria infection,16,20,21 and it may be parity dependent: in Tanzania malaria infection was only associated with decreased fetal growth among primi- and secundigravidae.21 In the DRC, malaria in the first half of pregnancy was associated with decreased umbilical artery resistance in the late third trimester and fetal growth restriction among primigravidae, suggesting that parasitaemia in early pregnancy interferes with the development of the fetal circulation.22

**Malaria in pregnancy, the fetus, and the growing child**

In addition to the adverse impact of maternal malaria on newborn birthweight, it can also affect other measures of infant health. Maternal malaria can affect transplacental transfer of antibodies to the fetus, and thus the infant’s resulting level of antibodies to pathogens such as tetanus and measles.2 Maternal malaria has been associated with an increased risk of congenital malaria,23,24 infant malaria,25-29 infant anaemia1,30 and other febrile illnesses.28,31 It may reduce the response to vaccination in infants,32 and a significant increase in systolic blood pressure was documented among infants exposed to maternal malaria 33 In Uganda and The Gambia, infants born to mothers with malaria in pregnancy gained less height and weight in the first year of life.28,34

In epidemiological studies it is difficult to independently evaluate the effects of maternal malaria exposure on infant susceptibility to malaria, because mothers and their infants typically share similar exposure by living in the same household and frequently sleeping under the same net, but some studies have controlled for exposure. 29 Exposure to malaria in utero early in pregnancy may tolerize the infant’s immune system, whereas later in pregnancy it may prime the infant’s immune responses.35 These exposures appear to affect immune responses through early life, and could alter risks of severe and uncomplicated disease 27,29 by affecting regulation of infection in the young child.

**Malaria in pregnancy: *P. vivax***

Studies in Guatemala, Colombia, Brazil, Papua New Guinea, and Indonesia, as well as a review on malaria in pregnancy in Asia, have provided information on the burden of infection outside of Africa, including the importance of *P. vivax* malaria and mixed infections 36-38. By microscopy, prevalence of any malaria infection varied greatly from very low (<1% in regions in Brazil, India, and Guatemala), to 10-20% in some regions in Papua New Guinea and Indonesia.36,38,39 *P. vivax* frequently causes anaemia, and has been associated with reductions in infant birthweight37,38,40 and preterm delivery,38 and with an effect on fetal growth, including lower fetal head diameters in Thailand and lower birthweight in the Brazilian Amazon.14,20 In addition, severe disease and maternal and fetal deaths due to *P. vivax* have been reported.38,41 Submicroscopic and asymptomatic malaria infections occur even in areas of low transmission, but their importance still needs further investigation (Figure S1).41

**Detection of malaria in pregnancy**

The major options for detection of malaria infection in pregnant women remain light microscopy, rapid immunochromatographic diagnostic tests (RDTs), or polymerase chain reaction (PCR); in placental specimens, histopathology can also identify parasites and resulting inflammatory responses. Microscopy requires expertise and equipment and is only moderately sensitive, and alternative methods have strengths and weaknesses. Histology, which can reveal both current, active infections and past infections, is costly and its use is restricted to research settings. Loop-mediated isothermal amplification (LAMP) has been used to diagnose placental infections, 42 and has similar sensitivity to qPCR in pregnant women. 43

The use of PCR has improved species identification and has permitted studies of low-density parasitaemia. PCR is highly sensitive, but is time-consuming and requires specialized laboratories. Parallel parasite detection by PCR and either an RDT or light microscopy identifies many women with PCR-positive but RDT/microscopy-negative infections. These “subpatent” infections generally have parasite densities that fall between the limits of detection for traditional methods and for molecular assays. Among 20 studies with information, prevalence of submicroscopic infection ranged from 2-55%. When comparing the ratio of microscopy to PCR prevalence, the mean ratio was 0.46 (95% 0.35-0.57) among pregnant women (Figure S1, 9 studies) whereas this was 0.51 (95% CI 0.45-0.57) in 65 studies among mainly non-pregnant populations.44.

Although subpatent infections detected by PCR but not by RDT or microscopy are common in many holoendemic areas, they are inconsistently associated with clinical outcomes. Infections detected by PCR and not microscopy at antenatal enrollment were strongly associated with an increased risk of low birthweight or prematurity in Benin,45 whereas infections detected by PCR but not by RDT were not associated with poor infant outcomes in Malawi,46 47 Ghana,48 or India.49 Submicroscopic infections detected antenatally or at delivery may be associated with a mild increase in the prevalence of maternal anaemia at delivery (Figure S2). Therefore, it remains unclear whether, and to what extent, either *P. falciparum* or *P. vivax*  infections detected solely by PCR adversely affect maternal and infant outcomes; a large individual participant data analysis to examine this further is under preparation. In addition, more sensitive diagnostics are under development that have the potential to increase detection of malaria parasites. Whether deployment of these new assays can improve pregnancy outcomes and translate into a public health impact remains unknown.

RDTs are most sensitive for parasite densities above 200/μl for *P. falciparum*, and are less sensitive for other species. Many pregnant women have peripheral blood parasite densities below this threshold, but may also have placental infections. This has led some groups to propose host biomarkers for occult placental infection.50 The low sensitivity of current RDTs may have contributed to the low efficacy of intermittent screening and treatment compared to IPTp. 6,51 A further consideration is the emergence of parasite lines that lack histidine rich protein 2,52 the principal protein used in *P. falciparum* RDTs. Nevertheless, as parasite prevalence is generally highest on first presentation at antenatal clinic, these relatively insensitive tests could be a useful screening tool when pregnant women are first seen

In antenatal specimens, compared to parasite detection by a nested PCR method, the sensitivity of microscopy in a research study varied between 40-70%, while that of commercial RDTs varied from 42-75%.53 At delivery, peripheral or placental blood testing by microscopy or by RDT may not detect histopathologically-evident placental malaria.53-56 Owing to this, two studies have applied latent class analysis to such samples in order to quantify the operating characteristics of detection methods independent of any reference standard. This analysis suggested that either PCR of placental specimens or RDT of peripheral specimens may have sufficient sensitivity for routine diagnosis of placental malaria.57,58

**Malaria and maternal nutrition**

Malaria and poor maternal nutrition frequently co-exist, and there are over 0.9 million babies born with low birthweight due to malaria and an estimated 0·8 million infant deaths related to maternal undernutrition each year.59,60 In the DRC cohort discussed above, and in another study in Kenya, poor maternal nutritional status appeared to exacerbate the deleterious effect of malaria on fetal growth.17,22,61 Risk factors often overlap, and the rainy season is a period of both high malaria risk and food insecurity. With the frequent overlap between malaria and nutrition, strategies to reduce both these risk factors are needed. 62 To examine this further, a large study combining data from 14,635 pregnancies from 13 studies conducted in Africa and the Western Pacific from 1996-2015 showed an increased risk of low birthweight when malaria and malnutrition were present, but not a synergistic effect; one in three pregnant women had malaria and/or poor nutition 63.

Concerns that iron supplementation might increase the risk of malaria in pregnant women appear to be unfounded. A recent systematic review of this interaction identified mostly observational studies, in which antenatal iron supplementation was associated with a temporal increase in *P. vivax* infections without a clear effect on *P. falciparum* risk.64 However, the results of two randomized clinical trials of iron supplementation in pregnancy have been reassuring: in both studies, 60 mg of daily elemental iron did not increase malaria risk and was associated with increased birthweight in Kenya,65 and with improved haemoglobin in Tanzania.66

**Pathogenesis of malaria in pregnancy**

The increased susceptibility of pregnant women to malaria is due, at least in part, to the sequestration of malaria-infected erythrocytes (IEs) in the maternal blood spaces of the placenta. Placental sequestration is common in *P. falciparum*, and placental changes have been seen in some, but not all, studies of *P. vivax*.67-69 Neither a direct link between placental changes and adverse birth outcomes nor placental sequestration of IEs have been clearly demonstrated in *P. vivax*. Placental changes in other species are not reported.

In*P. falciparum*,sequestration is mediated by the parasite-derived protein VAR2CSA, expressed on the IE surface, binding to placental chondroitin sulphate A (CSA) on syndecan-1.70 This was elegantly demonstrated with a placental perfusion model 71 in which perfusion of malaria-infected cells into uninfected placentas resulted in binding of VAR2CSA-expressing parasite lines, but not of other lines. Such a binding phenotype has been observed even among parasites collected in first trimester, suggesting that circulating IEs express VAR2CSA and preferentially bind CSA from early in gestation.72,73 VAR2CSA is composed of multiple DBL (Duffy binding-like) domains and interdomain (ID) regions, among which DBL 2, 3, 5, and 6 have been associated with binding to CSA (reviewed in74). The length and sulphation of the CSA chain are critical,75 which may be relevant to development of strategies to block sequestration.

Placental sequestration can lead to placental inflammatory responses, most notably accumulation of monocytes in the placenta. This is especially likely in first-time mothers, who often experience high density infections. Placental inflammation has been associated with fetal growth restriction and maternal anaemia in African women,2 and with low birthweight in Papua New Guinea.39 Modelling studies suggest that, in the absence of IPTp, placental inflammation may begin in early pregnancy and persist for months, and that 63% of placental infections may have been initiated by the end of the first trimester.59 However, longitudinal genotyping of *P. falciparum* isolates during gestation in Cameroonian pregnant women showed that 77% of placental parasites were acquired ≥30 weeks in pregnancy,76 suggesting that data is still needed to confirm the model.

Severe malaria is an infrequent but definite contributor to maternal mortality in endemic areas of Africa.77 In maternal autopsy studies, massive sequestration of IE has been observed in organs including both the brain and the placenta.78 The simultaneous sequestration of IE in cerebral capillaries and the placenta in these fatal cases suggests that infections during pregnancy may consist of multiple parasite populations with diverse binding phenotypes.79-81

*P. falciparum* infection in early pregnancy may interfere with trophoblast invasion into the uterus. Using an in vitro model, plasma from malaria-infected women inhibited trophoblast migration.82 Effects on the development of the maternal placental circulation may contribute to reduced fetal growth rates reported from early to mid gestation, discussed above.16,17 Placental malaria can also affect development of the fetal circulation, possibly through activation of the complement cascade, leading to disordered placental angiogenesis.83 In mice, complement activation led to underdevelopment of the villous vascular tree.83 In humans, malaria leads to small placental size, which may be due to similar impairments of placental angiogenesis affecting villous growth and development.84

Malaria-associated placental inflammation has also been associated with disorders of amino acid and glucose transport85,86 and dysregulation of the insulin-like growth hormone axis,87 probably driven by increased cytokine release into the intervillous space.2 Inflammatory cytokines can alter the expression and distribution of nutrient transporter molecules and growth hormones, and it is likely that disordered placental physiology – rather than mechanical obstructions from IEs – drives many of these effects.

**Protective antibodies against malaria in pregnancy**

Protection against malaria in pregnancy, low birthweight and anaemia has been associated with development of antibodies to the surface of CSA-binding IEs,2 88 and the dominant target of such antibodies is VAR2CSA. By ELISA, IgG against DBL1-DBL2 is associated with protection against low birthweight,89 while depletion studies suggest antibodies that most efficiently block IE adhesion are directed against DBL2 and its flanking inter-domain (ID) regions and DBL4.90 Antibodies that block adhesion to CSA are associated with reduced risk of placental infection and preterm delivery,89 while antibodies that opsonise IE for clearance by phagocytic cells may protect from maternal anaemia (reviewed in 91). The acquisition of antibodies to components of VAR2CSA may be impaired by the receipt of IPTp, which is broadly recommended in malaria-endemic Africa.92

Sequence diversity within VAR2CSA has, until now, undermined efforts to define immunogenic and pathogenic motifs. Two recent studies have identified reproducible dimorphism in sequences encoding the ID1-DBL2 region from diverse parasite populations, which may differentially contribute to increase the risk of low birthweight.93,94 Two VAR2CSA-based vaccines are currently in early-stage clinical trials (NCT02647489 and NCT02658253, clinicaltrials.gov), but it remains unclear how VAR2CSA-based vaccines may need to be adapted to address VAR2CSA sequence diversity and to offer broad protection against placental malaria.93

**The economic burden of malaria in pregnancy**

The economic burden of malaria in pregnancy can be considered to include: (i) provider costs: the cost to the health system of providing prevention and treatment services; (ii) user costs: the cost to households of accessing these services; and (iii) broader economic impacts arising from several channels such as the reduced labour productivity of women who have experienced malaria in pregnancy and the short- and long-term consequences of low birthweight and other adverse newborn outcomes.

Limited resources constrain the management of malaria in pregnancy and hinder the achievement of optimal intervention coverage. From the perspective of healthcare providers, adequate management of malaria in pregnancy absorbs significant proportions of the total available budget. For example, in 2010, provider costs associated with the management of confirmed cases of malaria in pregnancy reported by a tertiary hospital in a low-endemic area of the Brazilian Amazonas constituted 1% of the monetary value of the total activities undertaken that year. 95 This is a remarkable proportion given that pregnant women are a sub-set of the total population at risk and the study area is characterized by low-transmission.

A number of studies have estimated unit costs associated with the provision of interventions in pregnancy (Table 1). Only a few studies evaluated costs of treatment, 95-97 whereas most studies reported either actual or projected costs of preventive interventions. 97-106 These costs differed according to delivery strategy and, in the case of IPTp, the drug used.

In many countries, public healthcare providers have required financial contributions from pregnant women (also known as cost-sharing). Such contributions may exacerbate barriers to access. Even when healthcare is free, pregnant women still incur high transportation and indirect costs, which by themselves can prevent women from seeking malaria prevention and treatment. Qualitative studies have largely identified direct patient cost to be a major barrier to management of malaria in pregnancy. 107-119 In quantitative studies, removing user fees significantly improved coverage of interventions,120 and improved IPTp delivery.121 There are concerns that women may not use nets that are provided free-of-charge, wasting resources 122 but on the other hand cost-sharing schemes for ITNs, some of which employ loans, discourage demand and reduce access for the poorest potential users. 123,124

A number of studies have estimated the costs incurred by pregnant women for both prevention and treatment, classifying these as direct costs (fees, drugs, ITNs transportation) or as indirect, opportunity costs 95,96,101,104,105,125 (Table 2). The highest costs, which were for treatment, were observed in a study from Brazil, arising from both its higher gross domestic product (reflected in high indirect costs) and the presence of *P. vivax* infection which, during pregnancy, requires additional interventions compared to *P. falciparum* to achieve radical cure.95 In order to offset these costs, and thereby improve coverage with ITNs in pregnant women, a number of strategies have been implemented. Vouchers have been distributed to incentivise ITN purchase and use. 105,126 Social marketing increased supply of nets as well coverage.127 From the provider perspective, social marketing was found to be more costly than procuring and selling nets in the private retail market, but also as costly as distributing free of charge to the community.104 Another strategy to increase IPTp and ITN coverage consists of delivering the interventions through community approaches.101,128,129 Such community interventions allow coverage to be increased by shifting delivery costs from women (transport and time to seek IPTp) to the provider. For example, when women were promised a box of personal medical supplies at the delivery facility, this increased adherence to IPTp and rates of institutional delivery by offsetting delivery costs. A complementary community-directed intervention in which volunteers delivered ITNs and IPTp as well as basic counseling services to pregnant women was effective and the additional costs generated were smaller compared to larger health campaigns.129

Although the evidence base on the economic burden of malaria in pregnancy has expanded in recent years, there are still three main gaps to fill: (i) very little is known about the economic burden outside sub-Saharan Africa, where different *Plasmodium* species co-exist; (ii) the impact of malaria in pregnancy on indicators of economic development has never been investigated: for example, it is unknown how malaria in pregnancy impacts women’s employment and wages; and (iii) costs and consequences associated with malaria in pregnancy are underexplored: only a few studies have estimated, for example, cost associated with low birthweight in malaria endemic countries.130,131 Additional knowledge on (i), (ii) and (iii) may, respectively: guide decisions on optimal allocation of resources in areas where malaria control tools and strategies depend on *Plasmodium* species and where conditions to achieve elimination exist; inform economic growth, development and women’s empowerment strategies; further promote investments towards improvement of prevention and treatment of malaria in pregnancy.

**Malaria in pregnancy and the elimination agenda**

Variations in malaria transmission, whether geographic or temporal, result in variable exposure to infection, affecting the course of disease.132,133 Where malaria transmission has declined substantially, increases in parasite density134,135 and in malaria-related adverse impacts have been observed134,135. Taken together, these data suggest that measures that reduce malaria transmission, and thus reduce opportunities to acquire immunity, may lead to a change in both the burden and clinical spectrum of disease. For this reason, it becomes important to estimate changing trends134-136 and potential rises in the frequency of severe malaria syndromes,135 especially in areas with a high prevalence of HIV, which can impair the maintenance of effective immune responses. For malaria control programs, these rapid changes in immunity and susceptibility necessitate ongoing monitoring of the burden of malaria disease in at-risk populations, including pregnant women. This is especially critical in areas embarking on malaria elimination, as understanding the determinants and clinical consequences of malaria declines and resurgences, as well as the time-scales over which antimalarial immunity is gained and lost, has become a priority to prevent reinfection and resurgence of malaria infections.137

Antenatal malaria infections may undermine elimination efforts that rely on mass administration of ACTs. Trials based on mass drug administration with an antimalarial such as dihydroartemisinin-piperaquine (DHA-PPQ) are in progress in several African countries (ClinicalTrials.gov Identifier: NCT02329301). ACTs are yet to be approved by WHO for treatment of malaria in the first trimester of pregnancy, and there may be concerns over the use of DHA-PQ, in mass drug administration campaigns that could result in women in the first trimester receiving the drug who are not infected or at risk. Women in the first trimester need to be excluded from mass drug administration programs and instead managed according to a malaria RDT result. Given the low sensitivity of malaria RDTs,55 that IPTp with SP is contraindicated in first trimester, and that pregnant women frequently do not use ITNs59 and often carry gametocytes in their blood,138 there is a risk that undetected and untreated infections in this group can constitute a reservoir of malaria with the potential to sustain transmission during malaria elimination efforts. Recent modeling analysis suggests that pregnant women might constitute up to 23.9% of all infectious individuals following MDA to 90% of the non-pregnant population139. Further studies are needed to understand the impact of omitting pregnant women in MDA campaigns. Use of antimalarials that are known to be safe during pregnancy,such as chloroquine, may be an alternative in areas where the parasite population has regained susceptibility to the drug.140 Development of new anti-malarials for radical cure of *P. vivax* which are safe in pregnancy are also needed. In absence of these antimalarial alternatives, monitoring pregnant women in areas where malaria elimination activities are conducted can inform the risk of unsuccessful interruption of transmission due to undetected foci of malaria among pregnant women.

Pregnant women might be used as a sentinel population to monitor malaria transmission with sufficient sensitivity to guide malaria elimination activities. Compared to other target populations (e.g. children), pregnant women are relatively easy to access because of their high rate of attendance to antenatal clinics in malaria endemic countries.141 Parasite prevalence and seroreactivity to parasite antigens at delivery correlate with measures of overall *P. falciparum* transmission,135 and parasite prevalence in pregnant women correlates with that in children in Africa.142 In Southern Mozambique, malaria hospital admissions followed similar trends to malaria prevalence among pregnant women,135 suggesting that detection of malaria parasites with highly sensitive diagnostic tests such as PCR in pregnant women at their first antenatal visit may be useful to assess malaria trends in the underlying community. In addition to the value of surveillance in pregnant women as a surrogate for parasite transmission in general populations,103 the distribution of molecular markers of parasite drug resistance in parasites collected from untreated African pregnant women closely resembled that observed in children or non-pregnant adults.143

Immunologically, sera collected from pregnant women may be used as a proxy for population-level exposure to *P. falciparum*. As transmission fell in Southern Mozambique, antimalarial IgG responses against VAR2CSA declined.135 Antibodies against VAR2CSA develop after exposure to placental parasites in a parity-dependent manner, increasing over successive pregnancies. They are affected by variables that influence the risk of exposure to *P. falciparum* such as season, household location,144 use of IPTp92,145 or ITNs.146 Measures of antibody during pregnancy integrate malaria exposure over time (a pregnancy) in which cumulative exposure to VAR2CSA can increase from zero to very high levels. However, the longevity of antibody responses againt VAR2CSA as well as the impact of *var2csa* diversity needs to be evaluated to assess the utility of such a serological approach. The use of pregnant women as a sentinel group for malaria transmission, and the use of antibodies against VAR2CSA as markers of cumulative exposure to *P. falciparum* during pregnancy147, although still needing further validation, may constitute a feasible alternative to generate sensitive metrics of malaria transmission intensity for malaria elimination.137

**Conclusion**

The global burden of malaria in pregnancy remains substantial. In sub-Saharan Africa, access to recommended ITNs and IPTp with SP and adherence to recommended policies remain poor, and there is an urgent need to identify programmatic bottlenecks and gaps for optimal coverage of preventive tools. Globally, there are challenges in the prompt diagnosis and treatment of malaria infections with both *P. vivax* and *P. falciparum*. Some of these challenges include the low sensitivity of diagnostic tests and restrictions on anti-malarial agents to be used for treatment, prevention and elimination in pregnant women, such as anti-relapse therapy for *P. vivax*. The identification of VAR2CSA as a major target of protective immunity against *P. falciparum* malaria in pregnancy has led to efforts to develop a pregnancy-specific malaria vaccine, but understanding of the importance of different genetic variants of this protein is still very limited. Studies are uncovering the relationship between the longevity of antimalarial immune responses, and the impact of waning immunity on malaria-related adverse outcomes in settings of declining malaria transmission. Such studies can help to tailor existing diagnostic and preventive tools to different transmission settings, and to guide appropriate clinical practice in situations of changing malaria transmission. Not only this, a deeper understanding of the biology of malaria infection in pregnancy will contribute to the development of new approaches for the successful implementation of malaria elimination strategies in order to achieve a malaria free world. A proposed future research agenda is outlined in Panel 3.

**Author Contributions**

SJR coordinated the manuscript scope and design. All other authors contributed equally to the manuscript. All authors drafted individual sections of the manuscript, and revised the final version critically for content. All authors read and approved the final version of the manuscript.

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**Conflict of interest:**

We declare that we have no conflicts of interest.

**Panel 1. Search strategy and selection criteria**

We examined literature on malaria in pregnancy published over the last 10 years as cumulated in the malaria in pregnancy library (MiPL; http://library.mip-consortium.org/). The keywords “Ultrasound” and “Doppler” were used to screen on publications on fetal growth and malaria. Using the terms stillbirths, perinatal death, and neonatal death, and infant we screened on articles on impact on the infant. For subpatent malaria in pregnancy, we screened on the key words polymerase chain reaction or submicroscopic or subpatent up to May 2016, and articles which presented data in a format which could be extracted and combined were included for Figure S1 and Figure S2. For diagnosis, we searched the MiPL and Pubmed using keywords “malaria”, “pregnancy,” and “diagnosis.” For pathophysiology, we searched the MiPL and Pubmed using keywords “placenta” and “plasmodium” or “malaria” For elimination, we searched publications using keywords “elimination”, “trends” with “malaria ” and “pregnancy”. For the economic burden we searched in PubMed using (malaria[Title/Abstract] AND (pregnan\*[Title/Abstract] OR gestat\*[Title/Abstract]) AND cost\*[Title/Abstract]). Original search on 03/08/2016. Two additional articles were taken from EconLit data base with no specific search criteria but with the aim of facilitating the interpretation of articles extracted from PubMed.

**Panel 2. Progress in the last 10 years for burden, pathogenesis and economics of malaria in pregnancy (previous table 1)**

Burden of malaria in pregnancy

* Declining prevalence of *P. falciparum* in parts of Africa
* Low prevalence of *P. vivax* in Asia and Latin America
* Modelling to demonstrate the high burden in Africa of low birthweight attributable to malaria
* Established importance of malaria in the first trimester
* Evidence generated indicating impact of malaria in pregnancy on infant health

Diagnosis

* Subpatent antenatal infections are common but their impacts on pregnancy outcomes remain unclear.
* Current rapid diagnostic tests lack sensitivity for diagnosis of placental malaria.

Malaria and nutrition

* In clinical trials, iron supplementation does not increase the risk of malaria in pregnancy
* Both malaria and poor nutrition associated with low birth weight

Malaria pathogenesis

* A vaccine based on VAR2CSA has entered phase I clinical trials.
* Placental malaria can interfere with placental development and function

Economics

* Malaria in pregnancy absorbs significant proportions of the total available healthcare budget
* Direct and indirect costs incurred by pregnant women for malaria prevention and treatment are high.
* Strategies to lower costs incurred (e.g., vouchers, social marketing and delivery through community approaches) are effective, but they need to be scaled up

Changing transmission

* Decreasing exposure to malaria parasites is associated with exacerbated impacts of malaria in infected women

**Panel 3: Knowledge gaps and research priorities (Previous table 4)**

* Are there long term consequences of malaria in pregnancy for offspring health?
* How do co-morbidities such as helminthiasis and HIV, and treatments such as ivermectin or ARVs, modify the effects of malaria in pregnancy?
* What are the timescales over which antimalarial immunity is gained and lost in situations of transitioning malaria epidemiology?
* What proportion of miscarriages and stillbirths are attributable to malaria in pregnancy in different epidemiological settings?
* Do subpatent antenatal malaria infections contribute to adverse pregnancy outcomes?
* Will deployment of more sensitive, next generation rapid diagnostic tests improve the detection of malaria in pregnancy including placental infections?
* Could combinations of malaria and nutrition interventions result in improved birth weights and decreased maternal anaemia?
* How does malaria in pregnancy affect the development of immunity in the fetus and infant?
* Can vaccines based on VAR2CSA or other antigens prevent malaria in pregnancy and its adverse consequences for offspring?
* Are antenatal women suitable as a sentinel population to monitor malaria transmission, control or elimination in the general population?
* Are parasite prevalence and antibody serology useful monitoring tools?
* How can pregnant women be effectively and safely integrated into malaria elimination efforts?
* How can antenatal malaria prevention be effectively extended to protect women in the first trimester?
* What is the economic burden of malaria in pregnancy in areas with co-existing Plasmodium species?
* How does malaria in pregnancy affect indicators of economic development?
* What are the costs and consequences associated with low birth weight due to malaria?

Tototo

**Figure1: Effect of malaria in pregnancy on maternal, newborn, infant and child health**

**Figure S1 Prevalence of submicroscopic malaria in pregnancy in 20 studies with information available in 15 countries, 1995-2013**

\* This study only included HIV-infected pregnant women

Note that studies are ordered by prevalence of malaria by microscopy.

**Figure S2: The association between microscopic or submicroscopic malaria and anaemia in 6 studies with information available in 5 African countries, 1995-2013**

\*This study only included HIV-infected pregnant women

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