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Title of review article: Pregnancy and malaria: the perfect storm

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Abstract (200 words max.):

Malaria in pregnancy continues to exert a toll on pregnant women and their offspring. The burden of *Plasmodium falciparum* infection is especially large in Africa, and new data show lasting effects of maternal infection on the infant's neurocognitive development. Elsewhere, *P. vivax* infection causes relapsing infections that are challenging to prevent. Infection in first trimester of pregnancy is an area of increasing focus, and its adverse effects on pregnancy outcome are increasingly recognised. Improving insecticide-treated bed net use and early antenatal attendance could bring many benefits because first-trimester infection is common and frequently acquired prior to conception. Although newer rapid diagnostic tests still have limited sensitivity, they may be useful in detection of early pregnancy malaria for treatment.

Artemisinin-based combination therapies are efficacious in later pregnancy but have yet to be recommended in first trimester because of limited safety data. In Africa, intermittent preventive treatment in pregnancy (IPTp) with monthly sulfadoxine-pyrimethamine (SP) improves pregnancy outcomes, but SP resistance is worsening. The alternative, IPTp with dihydroartemisinin-piperaquine, has greater antimalarial efficacy, but does not appear to improve pregnancy outcomes, because SP has poorly understood non-malarial benefits on birthweight.

We review current challenges and opportunities in prevention and treatment of malaria in pregnancy.

Text of review (2465words maximum)

Introduction:

Of 228 million cases of malaria that occurred globally in 2021, 95% were in sub-Saharan Africa. Here, *Plasmodium falciparum* malaria kills over 600,000 people annually [1]. Pregnant women are at particular risk because *P. falciparum*-infected erythrocytes accumulate in the placenta. These cells express the parasite protein VAR2CSA on their surface, which binds to chondroitin sulfate A (CSA) on placental cells. The consequences of placental malaria can include severe maternal anemia, miscarriage, stillbirth and perinatal mortality [2, 3], premature delivery, small for gestational age (SGA) and low birth weight (LBW; birth weight <2,500 g) [4], and altered risk of malaria in infancy [5]. Each year, ~900,000 babies are born with LBW attributable to malaria in pregnancy, and ~100,000 infants die. In high-transmission settings, the burden and consequences of malaria are generally worst in first pregnancy, when women lack immunity to VAR2CSA-expressing infected erythrocytes. In this article, we review recent findings regarding the epidemiology, pathogenesis, treatment and prevention of malaria in pregnancy, with a focus on *P. falciparum* and areas of moderate to high transmission (Figure 1).

Epidemiology

Several countries, notably in Asia and the Americas, have eliminated malaria this century, while others are decreasing their infection burdens [1]. As malaria transmission declines, LBW is estimated to fall by 1.48% (a 17% relative reduction), most notably in first time mothers [6].

Pregnant women may be a useful sentinel group for malaria surveillance to progress elimination efforts. In a low transmission setting, presence of antibody to VAR2CSA and other

malaria antigens was shown to distinguish between women who did and did not experience *P. falciparum* parasitaemia during pregnancy [7].

Diagnosis

Peripheral blood microscopy can miss placental malaria and low-density infections, and conventional rapid diagnostic tests (RDTs) are similarly insensitive [8]. The new ultrasensitive NxTek™ Eliminate Malaria Pf RDT (Abbott, Chicago, US), based on immunodetection of histidine-rich protein 2 (HRP2), was evaluated in 18 studies, including four in pregnant women. Overall, the new test was marginally more sensitive (56.1%, 95% confidence interval [CI] 46.9, 65.4%) than conventional HRP2-based RDTs (44.3%, 95% CI 32.6, 56.0%), using quantitative polymerase chain reaction (qPCR) as the reference [9]. In pregnancy, its performance was similar to that of conventional RDTs. Further advances in sensitivity will be needed for RDT-based screen-and-treat approaches to successfully identify most infected women. Ultrasensitive RDTs may have a role in screening in the first trimester of pregnancy where gains in sensitivity were most pronounced [10].

First trimester

There is a high malaria infection burden in the first trimester of pregnancy. In studies in Benin and DRC, over half of all infections detected occurred in the first trimester [11, 12]. Many first trimester infections originated before conception [13], and subpatent or asymptomatic infections often increase in density in pregnant women. Addressing first trimester infections remains a challenge, because in much of Africa early antenatal attendance is rare [14], and preconception interventions for malaria are absent. Recent studies show that insecticide-treated bed nets (ITNs) and detection and treatment of infection early in pregnancy may translate into substantial gains for the prevention adverse pregnancy outcomes [11, 15, 16].

Placental malaria

In a secondary analysis of trial data, primigravid women with asymptomatic infections in early pregnancy had an increased risk of placental malaria (adjusted odds ratio [aOR] 12.19, 95% CI 5.23, 28.43), whereas for multigravid women infection later in pregnancy was associated with placental malaria [17]. Placental malaria infection and associated inflammatory responses can affect placental angiogenesis by disrupting the angiopoietin-Tie2 axis and interfering with fetal growth and contributing to LBW and stillbirths [18, 19].

Antibody immunity

Pregnant women acquire antibodies against VAR2CSA, which can block binding of infected erythrocytes to CSA or opsonise them for clearance by phagocytic cells. Whether these antibodies mediate protection from placental malaria has been harder to demonstrate [20]. Using a "systems serology" approach for in-depth profiling of targets and features of antibody to VAR2CSA, seven antibody features predicted protection against placental malaria, and these features were mainly functional antibodies that block CSA binding or opsonise infected erythrocytes [21]. Complement-fixing, IgG1 and/or IgG3 antibodies may also be associated with protection from placental malaria or improved birth weight [22, 23], and antibody glycosylation [24] appears important.

Vaccines for malaria in pregnancy

Two early-phase trials of pregnancy malaria vaccines yielded disappointing results. The vaccines incorporated sequences from the VAR2CSA protein implicated in placental binding

[25, 26]. They elicited antibody against the homologous VAR2CSA variant that blocked CSA binding but showed little or no recognition of other variants. Studies have shown how the VAR2CSA protein is folded to create one, or possibly two, conserved binding regions for CSA [27-29]. These binding regions are highly conserved, while adjacent polymorphic and flexible regions may be the main targets for antibodies. Despite this, recent work using different VAR2CSA variants to affinity purify antibody from immune sera does show the existence of cross-reactive antibodies recognising multiple variants [30]. Future vaccine design may need to take the conformation of VAR2CSA into account and/or incorporate a more substantial proportion of this large, complex protein.

A second protein, termed PfCSA-L (L for ligand) was shown to bind to both VAR2CSA and CSA [31]. Given it is surface-exposed and invariant, it could be an alternative target for therapeutics to block placental malaria.

A degree of protection from malaria in pregnancy may also be achieved by non-VAR2CSA vaccines such as RTS,S which was approved in 2021 by the World Health Organization (WHO) for young children. In young children, combining RTS,S with regular antimalarial treatment was more effective than either strategy alone [32], and this might be a future strategy for malaria in pregnancy.

Placental malaria and fetal neurodevelopment

Placental malaria may affect the developing fetus's brain [33-36]. In Malawian children, malaria infection or associated inflammation during pregnancy were associated with neurodevelopmental delay, including delayed language development [35]. In Benin, maternal malaria was associated with impaired gross motor skills at one year; and impaired cognitive processing capabilities at six years [33]. In Brazil, educational attainment appeared particularly

affected by exposure in first trimester of pregnancy [36]. Together, these studies illustrate the significant impact of malaria in pregnancy on the child's future brain development. Whether malaria in pregnancy increases future risk of cardiometabolic disease [37] can only be addressed in extended cohort studies.

Risk of malaria in infancy

The effect of maternal infection on the risk of malaria in infancy is difficult to study, because mother and baby share similar exposure risks. Meta-analysis demonstrated associations of maternal infection with parasitaemia (adjusted Hazard Ratio [HR] 1.46, 95% CI 1.07, 2.00) and clinical malaria in children (adjusted HR 1.31, 95% CI 0.96, 1.79) [38]. Infant sex appears to modify this risk. In Uganda, malaria incidence in infancy was higher in male, but not female, infants of women with severe placental malaria (adjusted incidence rate ratio [IRR] 2.17, 95% CI 1.45, 3.25) [5].

Malaria in pregnancy may alter fetal immune responses, leading to tolerance of infection. Malaria in early pregnancy was shown to increase maternal microchimerism, the trafficking of maternal cells to the fetus. This can increase the production of fetal regulatory T cells, which induce tolerance against alloantigens [39]. In Brazil, maternal *P. vivax* infection at delivery was associated with an increased incidence of *P. vivax* infection in young children (IRR 2.58, 95% CI 1.41, 4.73) [40].

Vivax in pregnancy

Although *P. vivax*-infected erythrocytes do not sequester in the placenta, vivax malaria has been associated with maternal anemia and low birth weight. In Brazil, *P. vivax* in the first trimester of pregnancy was associated with premature birth (aOR 8.12, 95% CI 2.69, 24.54) and reduced head circumference (aOR 3.58, 95% CI 1.29, 9.97) [41]. *P. vivax* was also

associated with placental monocyte infiltrates and dysregulation of angiopoietin-2 and complement C5a production, processes previously reported in *P. falciparum* malaria.

Interactions between malaria and other risk factors.

Women at risk of malaria infection often have other risk factors for poor pregnancy outcome, such as genitourinary tract infections or nutrient deficiencies. Iron deficiency is highly prevalent in many malaria-endemic settings, but supplementation might increase the risk of adverse pregnancy outcomes [42]. In Papua New Guinea, iron deficient women were reported to have higher birthweight babies. In a second, larger study, women receiving a single course of sulfadoxine-pyrimethamine (SP) and chloroquine who were iron deficient had less SGA and higher birthweights than iron replete women [43]. However, among women receiving multiple courses of SP and azithromycin, these associations were not seen. Additionally, placental malaria infection could affect placental development, and may predispose to development of pre-eclampsia. On the Thai Myanmar border, peripheral falciparum but not vivax parasitaemia increased the odds of pre-eclampsia or eclampsia (aOR 2.61, 95% CI 1.01, 6.79) in primigravid women, and the odds of gestational hypertension in multigravid women (aOR 2.59, 95% CI 1.59, 4.23) [44].

Malaria treatment and prevention

The WHO recommends a three-pronged strategy for the treatment and prevention of malaria in pregnancy in sub-Saharan Africa, including prompt case management with effective drugs, use of ITNs throughout pregnancy and three or more doses of monthly intermittent preventive treatment in pregnancy (IPTp) with SP, an antifolate drug combination that can only be started in the second trimester [1]. As highlighted above, malaria in first trimester contributes

significantly to the burden of malaria in pregnancy. The detection and safe treatment of such infections remain significant problems.

Malaria treatment

Artemisinin-based combination treatments (ACTs) are endorsed by WHO for the treatment of uncomplicated malaria in second and third trimesters. In an individual patient data meta-analysis, artemether-lumefantrine had the lowest efficacy in pregnancy, suggesting dose adjustment may be required [45]. In a trial of ACTs in an area of Thailand with vivax co-endemicity and increasing ACT resistance, dihydroartemisinin-piperaquine (DHA-PQ) was more efficacious than artesunate-mefloquine or artemether lumefantrine and better tolerated than the former. Falciparum recrudescence was associated with Kelch13 drug resistance mutations, and most women with *P. vivax* experienced relapses during pregnancy [46].

Treatment of malaria in first trimester remains contentious. Exposure of rats, rabbits and monkeys to ACTs in early pregnancy has resulted in cardiovascular malformations and fetal loss [47]. Collecting data on early pregnancy exposures is challenging, especially during periods of critical organogenesis in early pregnancy, before many women know they are pregnant [47]. A systematic review found low rates of miscarriage, stillbirth and congenital anomalies associated with ACT use later in pregnancy [48]. Treatment failure for ACTs is less common than for quinine with or without clindamycin, the current WHO policy for first trimester, and WHO is currently reviewing its recommendations.

Malaria prevention: intermittent preventive treatment

Malaria prevention relies on ITNs and, in sub-Saharan Africa, IPTp with SP. SP has been shown to markedly reduce LBW, but uptake of IPTp remains suboptimal [49] and was affected

by the Covid-19 pandemic [50]. Resistance to SP is mediated by mutations in the dihydrofolate reductase (*dhfr*) and dihydropteroate synthase (*dhps*) genes. Five *dhfr* or *dhps* mutations are very common in Eastern, Southern and Central Africa, where they decrease SP's antimalarial efficacy, and lower grade resistance is reported in West Africa [51]. A sixth mutant, *dhps* A581G, conveys high-grade resistance to SP and appears to be increasing in prevalence. In Tanzania and Malawi, infection with parasites with the A581G mutation was associated with substantial decreases in birthweight compared to women with no malaria, or to women infected with parasites that lacked the mutation [52, 53].

SP resistance has led to the search for alternative drugs or combinations. While mefloquine proved a better antimalarial, it was poorly tolerated. Recent interest has focused on DHA-PQ. DHA is highly potent and PQ has a long half-life, so the combination can both clear existing infections and prevent new ones between antenatal visits. Although PQ has been associated with prolongation of the corrected QT interval (QTc), recent studies of monthly dosing with fixed dose DHA-PQ (120/960mg daily for three days) showed no increased risk of QTc prolongation following repeated courses [54]), and good protection from malaria infection [55].

A mediation analysis compared pregnancy outcomes in three trials in which women received IPTp with SP or DHA-PQ [56]. Women receiving DHA-PQ had substantially lower risk of placental malaria (risk ratio [RR] 0.64, 95% CI 0.39, 1.04). However, mean birthweights were higher in SP recipients (mean difference 69 g, 95% CI 26, 112). SP had a more substantial non-malarial effect on birthweight than DHA-PQ (mean difference 87 g, 95% CI 43, 131), and this outweighed the malaria-mediated effect of DHA-PQ on birthweight (8 g, -9, 26). A new study suggests that SP's effect on birthweight might be mediated through improved maternal

gestational weight gain [57]. This appeared to occur by preventing infection with certain pathogenic *Escherichia coli* types, most notably enteroaggregative *E. coli*. [57]. SP might also modify the maternal microbiome or decrease maternal inflammation to improve birthweight. In a recent trial from Tanzania, DHA-PQ had superior efficacy for malaria prevention compared to SP-IPTp but had limited impacts on preventing adverse pregnancy outcomes apart from LBW [58]. DHA-PQ is highly cost-effective in high transmission settings with high SP resistance [59]. Further trials comparing IPTp with DHA-PQ with IPTp-SP are due to report. It is not presently clear if and where DHA-PQ should replace SP for IPTp, and more data are required on non-malarial risk factors affecting birthweight that may be modified by SP. On the other hand, trials of DHA-PQ in HIV-infected women (in whom SP is contra-indicated, and burden of malaria in pregnancy is increased) hold promise [60]. Future trials may combine SP and DHA-PQ for IPTp in HIV-negative women.

Intermittent Screening and Treatment

An alternative to IPTp is testing pregnant women for malaria at each antenatal visit and treating infected women with a highly effective antimalarial. This strategy relies on highly sensitive point-of-care tests, and RDTs still miss a substantial fraction of infections, in particular placental infections. In a meta-analysis of four trials of intermittent screening and treatment (IST) compared to IPTp [61], malaria infection by microscopy was not decreased by IST, and subpatent infections were more common (RR 1.31, 95% CI 1.05 to 1.62). Although adverse pregnancy outcomes did not differ by arm, subpatent malaria infections were associated with lower birth weights and premature delivery [61]. More sensitive diagnostic tests are required to support any future IST strategy, and this approach is not currently endorsed by WHO.

Conclusion

The burden of malaria in pregnancy remains substantial, particularly in sub-Saharan Africa, with devastating short- and long-term consequences for maternal and infant health. Ongoing challenges include the prevention, identification and management of infections in the first trimester of pregnancy, and the development of new preventive strategies in light of the spread of high-grade resistance to SP, the mainstay of IPTp. Future preventive strategies might include combining DHA-PQ with SP for IPTp; next-generation vaccines; and more sensitive RDTs to screen women in early pregnancy and clear infections before they damage the placenta and the developing fetus.

Key points:

(3-5 key points/sentences that summarize your article)

- Many women carry low density infections into pregnancy, which may increase in density, persist, and affect the growth and development of the fetus.
- Intermittent preventive treatment with DHA-PQ offers substantially better malaria prevention than IPTp with SP, but does not seem to result in better fetal outcomes.
- New evidence shows that malaria in pregnancy can affect infant neurocognitive development, and subsequent educational attainment.
- A first generation of pregnancy specific malaria vaccines did not generate strong antibody responses to all variants, and new formulations may be required.

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Conflict of interest

The authors have no conflicts of interest to declare.

Figure legends

Figure 1. Timeline of pregnancy from before pregnancy to delivery, illustrating some newly recognised or newly emphasised impacts of malaria in pregnancy (yellow backgrounds). Current interventions are highlighted in blue, and interventions to be further developed or evaluated in red. These include preconception vaccination and use of insecticide treated nets. Screening and treatment may offer greatest benefit in first trimester. Surveillance for disease burden and potentially as a sentinel of transmission is relevant throughout pregnancy. Such surveillance should include ongoing monitoring of drug safety.

References and recommended reading

1. World Health Organization. World Malaria Report. Geneva: World Health Organizaiton, **2021**.

2. Mahamar A, Andemel N, Swihart B, et al. Malaria Infection Is Common and Associated With Perinatal Mortality and Preterm Delivery Despite Widespread Use of Chemoprevention in Mali: An Observational Study 2010 to 2014. Clin Infect Dis **2021**; 73:1355-61.

*An observation cohort study highlighted that the risk of adverse birth outcomes due to malaria in pregnancy (defined as peripheral parasitaemia detected by light microscopy or qPCR) is not abrogated in women who receive at least two doses of IPTp-SP.

3. Seijas-Chavez JA, Nolan MS, Lynn MK, et al. Causal effects on low Apgar at 5-min and stillbirth in a malaria maternal-fetal health outcome investigation: a large perinatal surveillance study in the Brazilian Amazon. Malar J **2021**; 20:444.

*Epidemiological and modelling study using surveillance data from delivery to determine relationships between *P. falciparum* and *P. vivax* malaria and adverse birth outcomes.

4. Ategeka J, Kakuru A, Kajubi R, et al. Relationships Between Measures of Malaria at Delivery and Adverse Birth Outcomes in a High-Transmission Area of Uganda. J Infect Dis **2020**; 222:863-70.

5. Kakuru A, Roh ME, Kajubi R, et al. Infant sex modifies associations between placental malaria and risk of malaria in infancy. Malar J **2020**; 19:449.

6. Heng S, O'Meara WP, Simmons RA, Small DS. Relationship between changing malaria burden and low birth weight in sub-Saharan Africa: A difference-in-differences study via a pair-of-pairs approach. Elife **2021**; 10.

*Novel approach to modelling the impact of the decline of *P. falciparum* transmission on the prevention of low birth weight drawing on annual malaria prevalence means and Demographic and Health Survey data from sub-Saharan Africa.

7. Dharmaratne A, Dini S, O'Flaherty K, et al. Quantification of the dynamics of antibody response to malaria to inform sero-surveillance in pregnant women. Malar J **2022**; 21:75.

8. Unwin VT, Ahmed R, Noviyanti R, et al. Use of a highly-sensitive rapid diagnostic test to screen for malaria in pregnancy in Indonesia. Malar J **2020**; 19:28.

9. Slater HC, Ding XC, Knudson S, et al. Performance and utility of more highly sensitive malaria rapid diagnostic tests. BMC Infect Dis **2022**; 22:121.

* A systematic review comparing the sensitivity of a highly sensitive HRP2-based RDT to conventional HRP2-based RDTs shows little improvement in sensitivity in pregnant women.

10. Briand V, Cottrell G, Tuike Ndam N, et al. Prevalence and clinical impact of malaria infections detected with a highly sensitive HRP2 rapid diagnostic test in Beninese pregnant women. Malar J **2020**; 19:188.

11. Koladjo BF, Yovo E, Accrombessi M, et al. Malaria in the first trimester of pregnancy and fetal growth: results from a Beninese pre-conceptional cohort. J Infect Dis **2022**. Online ahead of print.

*Observational study showing that 40% of *P. falciparum* infections during pregnancy were detected in first trimester of pregnancy.

12. Leuba SI, Westreich D, Bose CL, et al. Predictors of Plasmodium falciparum infection in the first trimester among nulliparous women from Kenya, Zambia, and the Democratic Republic of the Congo. J Infect Dis **2021**. Online ahead of print.

* Up to two-thirds of women had *P. falciparum* infection detected by qPCR in first trimester of pregnancy.

13. Jafari-Guemouri S, Courtois L, Mama A, et al. A Genotyping Study in Benin Comparing the Carriage of Plasmodium falciparum Infections Before Pregnancy and in Early Pregnancy: Story of a Persistent Infection. Clin Infect Dis **2021**; 73:e355-e61.

** Samples taken from women infected with *P. falciparum* infection before conception and at first visit subsequent to conception were genotyped. Almost half the infections acquired pre-conceptually persisted into first trimester, with identical parasite genotypes present at the two time-points, suggesting interventions to prevent malaria before conception are needed.

14. Apanga PA, Kumbeni MT, Chanase MW. The Association Between Early Antenatal Care and Intermittent Preventive Treatment of Malaria in Pregnancy in Sub-Saharan Africa: Effect Modification by Planned Pregnancy Status. Ann Glob Health **2022**; 88:4.

*This study shows that women with planned pregnancies and those attending antenatal care early are more likely to receive the recommended three courses of IPTp.

15. Roh ME, Oundo B, Dorsey G, et al. A quasi-experimental study estimating the impact of long-lasting insecticidal nets with and without piperonyl butoxide on pregnancy outcomes. Malar J **2022**; 21:5.

*Using data from before and after ITN distribution campaigns, the authors found ITN distribution decreased rates of stillbirth, and these effects were greatest in women who were protected for most or all their pregnancy.

16. Roberts SA, Brabin L, Tinto H, Gies S, Diallo S, Brabin B. Seasonal patterns of malaria, genital infection, nutritional and iron status in non-pregnant and pregnant adolescents in Burkina Faso: a secondary analysis of trial data. BMC Public Health **2021**; 21:1764.

17. Tran EE, Cheeks ML, Kakuru A, et al. The impact of gravidity, symptomatology and timing of infection on placental malaria. Malar J **2020**; 19:227.

18. Singh PP, Bhandari S, Sharma RK, Singh N, Bharti PK. Association of Angiopoietin Dysregulation in Placental Malaria with Adverse Birth Outcomes. Dis Markers **2020**; 2020:6163487.

19. Tran V, Weckman AM, Crowley VM, et al. The Angiopoietin-Tie2 axis contributes to placental vascular disruption and adverse birth outcomes in malaria in pregnancy. EBioMedicine **2021**; 73:103683.

20. Cutts JC, Agius PA, Zaw L, et al. Pregnancy-specific malarial immunity and risk of malaria in pregnancy and adverse birth outcomes: a systematic review. BMC Med **2020**; 18:14.

*Systematic review of studies of immunity to malaria in pregnancy and risks of placental malaria and low birth weight. Broadly antibodies correlated with infection and overall did not protect from low birth weight.

21. Aitken EH, Damelang T, Ortega-Pajares A, et al. Developing a multivariate prediction model of antibody features associated with protection of malaria-infected pregnant women from placental malaria. Elife **2021**; 10.

*The authors identify specific features of an antibody repose to VAR2CSA that may protect from placental malaria in Papua New Guinean women.

22. Opi DH, Boyle MJ, McLean ARD, et al. Reduced risk of placental parasitemia associated with complement fixation on Plasmodium falciparum by antibodies among pregnant women. BMC Med **2021**; 19:201.

*Antibodies to VAR2CSA that can fix complement were associated with protection from placental malaria. Antibodies with specific functions may be good correlates of protection.

23. Tornyigah B, d'Almeida T, Escriou G, et al. Plasmodium falciparum VAR2CSA-Specific IgG Subclass Responses Reflect Protection Against Low Birth Weight and Pregnancy-Associated Malaria. Front Immunol **2021**; 12:610305.

24. Larsen MD, Lopez-Perez M, Dickson EK, et al. Afucosylated Plasmodium falciparum-specific IgG is induced by infection but not by subunit vaccination. Nat Commun **2021**; 12:5838.

*Naturally acquired antibody to VAR2CSA and to another PfEMP1 often lacked fucose, whereas vaccine-induced antibodies did not. These afucosylated antibodies caused greater activation of NK cells, with implications for immune response.

25. Mordmuller B, Sulyok M, Egger-Adam D, et al. First-in-human, Randomized, Double-blind Clinical Trial of Differentially Adjuvanted PAMVAC, A Vaccine Candidate to Prevent Pregnancy-associated Malaria. Clin Infect Dis **2019**; 69:1509-16.

26. Sirima SB, Richert L, Chene A, et al. PRIMVAC vaccine adjuvanted with Alhydrogel or GLA-SE to prevent placental malaria: a first-in-human, randomised, double-blind, placebo-controlled study. Lancet Infect Dis **2020**; 20:585-97.

27. Bewley MC, Gautam L, Jagadeeshaprasad MG, Gowda DC, Flanagan JM. Molecular architecture and domain arrangement of the placental malaria protein VAR2CSA suggests a model for carbohydrate binding. J Biol Chem **2020**; 295:18589-603.

28. Ma R, Lian T, Huang R, et al. Structural basis for placental malaria mediated by Plasmodium falciparum VAR2CSA. Nat Microbiol **2021**; 6:380-91.

*Shows how VAR2CSA folds together to form two relatively conserved binding channels for CSA, which do not change on CSA binding.

29. Wang K, Dagil R, Lavstsen T, et al. Cryo-EM reveals the architecture of placental malaria VAR2CSA and provides molecular insight into chondroitin sulfate binding. Nat Commun **2021**; 12:2956.

*Identifies a major CSA binding groove formed when VAR2CSA folds, and illustrates the polymorphic residues outside the groove.

30. Doritchamou JYA, Renn JP, Jenkins B, et al. A single full-length VAR2CSA ectodomain variant purifies broadly neutralizing antibodies against placental malaria isolates. Elife **2022**; 11.

*Using one full-length VAR2CSA protein, it was possible to purify out antibody that recognised other variants. As plasma was absorbed against increasing numbers of variants, the activity against subsequent variants diminished.

31. Keitany GJ, Jenkins BJ, Obiakor HT, et al. An invariant protein that co-localizes with VAR2CSA on Plasmodium falciparum-infected red cells binds to chondroitin sulfate A. J Infect Dis **2021**. Online ahead of print.

32. Chandramohan D, Zongo I, Sagara I, et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. N Engl J Med **2021**; 385:1005-17.

*The combination of vaccination with RTS,S and monthly chemoprevention was superior to either intervention alone in young West African children.

33. Garrison A, Boivin MJ, Fievet N, et al. The Effects of Malaria in Pregnancy on Neurocognitive Development in Children at 1 and 6 Years of Age in Benin: A Prospective Mother-Child Cohort. Clin Infect Dis **2022**; 74:766-75.

**This study shows that children exposed to malaria in utero are more likely to have impaired motor and non-verbal intelligence on follow up to 6 years of age.

34. Lawford HLS, Nuamah MA, Liley HG, et al. Associations between malaria in pregnancy and neonatal neurological outcomes. Int J Infect Dis **2021**; 112:144-51.

35. Weckman AM, Conroy AL, Madanitsa M, et al. Neurocognitive outcomes in Malawian children exposed to malaria during pregnancy: An observational birth cohort study. PLoS Med **2021**; 18:e1003701.

**Maternal malaria and immune activation were both associated with delayed neurocognitive development over the first two years of life. Preventing or minimising maternal malaria may lead to improved child development.

36. Veras H. Wrong place, wrong time: The long-run effects of in-utero exposure to malaria on educational attainment. Econ Hum Biol **2022**; 44:101092.

*The study uses historical data from Brazil's malaria control campaigns and educational data to show that educational attainment is lower in children exposed in utero to malaria, an effect that was greater with first trimester exposure.

37. Grunnet LG, Bygbjerg IC, Mutabingwa TK, et al. Influence of placental and peripheral malaria exposure in fetal life on cardiometabolic traits in adult offspring. BMJ Open Diabetes Res Care **2022**; 10.

38. Park S, Nixon CE, Miller O, et al. Impact of Malaria in Pregnancy on Risk of Malaria in Young Children: Systematic Review and Meta-Analyses. J Infect Dis **2020**; 222:538-50.

39. Simon N, Shallat J, Houck J, et al. Peripheral Plasmodium falciparum Infection in Early Pregnancy Is Associated With Increased Maternal Microchimerism in the Offspring. J Infect Dis **2021**; 224:2105-12.

40. Pincelli A, Cardoso MA, Malta MB, et al. Low-level Plasmodium vivax exposure, maternal antibodies, and anemia in early childhood: Population-based birth cohort study in Amazonian Brazil. PLoS Negl Trop Dis **2021**; 15:e0009568.

**This is the first large study to report the effects of in utero exposure to *P. vivax* on the infant's risk of malaria. Exposed children were more likely to experience malaria in the second year of life, even after accounting for differences in malaria transmission.

41. Dombrowski JG, Barateiro A, Peixoto EPM, et al. Adverse pregnancy outcomes are associated with Plasmodium vivax malaria in a prospective cohort of women from the Brazilian Amazon. PLoS Negl Trop Dis **2021**; 15:e0009390.

*This study shows that *P. vivax* infections in first trmiester of pregnancy are associated with poor pregnancy outcomes including preterm delivery, and small head circumference, which may influence future congitive development.

42. Nti AM, Botchway F, Salifu H, et al. Effects of Iron Supplements on Heme Scavengers in Pregnancy. Am J Trop Med Hyg **2021**; 105:1163-72.

43. Unger HW, Laurita Longo V, Bleicher A, et al. The relationship between markers of antenatal iron stores and birth outcomes differs by malaria prevention regimen-a prospective cohort study. BMC Med **2021**; 19:236.

* This study shows that maternal iron deficiency is associated with a higher mean birth weight. This effect was modified by malaria prevention regimes and was not seen in women receiving multiple monthly courses of sulphadoxine-pyrimethamine plus azithromycin.

44. Harrington WE, Moore KA, Min AM, et al. Falciparum but not vivax malaria increases the risk of hypertensive disorders of pregnancy in women followed prospectively from the first trimester. BMC Med **2021**; 19:98.

** This is the largest study to date of the relationship between malaria and hypertensive disorders of pregnancy. *P. falciparum* but not *P. vivax* infection was associated with gestational hypertension, pre-eclampsia and eclampsia. This comprehensive study highlights the potential impacts of *P. falciparum* infection on implantation and placental development.

45. Saito M, Carrara VI, Gilder ME, et al. A randomized controlled trial of dihydroartemisinin-piperaquine, artesunate-mefloquine and extended artemether-lumefantrine treatments for malaria in pregnancy on the Thailand-Myanmar border. BMC Med **2021**; 19:132.

*This study shows that treatment of malaria in pregnancy in Thailand with dihydroartemisinin-piperaquine is more efficacious than the alternatives. *P. vivax* infection frequently relapses following treatment and chloroquine prophylaxis is recommended.

46. Saito M, Mansoor R, Kennon K, et al. Pregnancy outcomes and risk of placental malaria after artemisinin-based and quinine-based treatment for uncomplicated falciparum malaria in pregnancy: a WorldWide Antimalarial Resistance Network systematic review and individual patient data meta-analysis. BMC Med **2020**; 18:138.

47. Clark RL. Teratogen update: Malaria in pregnancy and the use of antimalarial drugs in the first trimester. Birth Defects Res **2020**; 112:1403-49.

48. Shibeshi W, Baye AM, Alemkere G, Engidawork E. Efficacy and Safety of Artemisinin-Based Combination Therapy for the Treatment of Uncomplicated Malaria in Pregnant Women: A Systematic Review and Meta-Analysis. Ther Clin Risk Manag **2021**; 17:1353-70.

*This systematic review shows that treatment failure is significantly less frequent with artemisinin-based combination treatments than for other treatments. There were no differences in rates of adverse pregnancy outcomes by treatment types.

49. Ameyaw EK, Njue C, Amoah RM, et al. Is improvement in indicators of women's empowerment associated with uptake of WHO recommended IPTp-SP levels in sub-Saharan Africa? A multilevel approach. BMJ Open **2021**; 11:e047606.

50. Burt JF, Ouma J, Lubyayi L, et al. Indirect effects of COVID-19 on maternal, neonatal, child, sexual and reproductive health services in Kampala, Uganda. BMJ Glob Health **2021**; 6.

51. Amimo F, Lambert B, Magit A, Sacarlal J, Hashizume M, Shibuya K. Plasmodium falciparum resistance to sulfadoxine-pyrimethamine in Africa: a systematic analysis of national trends. BMJ Glob Health **2020**; 5.

52. Hansson H, Minja DTR, Moeller SL, et al. Reduced Birth Weight Caused by Sextuple Drug-Resistant Plasmodium falciparum Infection in Early Second Trimester. J Infect Dis **2021**; 224:1605-13.

*This study indicates a significant negative impact of highly resistant *P. falciparum* parasites on birth weight.

53. Taylor SM, Levitt B, Freedman B, et al. Interactions Between Antenatal Sulfadoxine-Pyrimethamine, Drug-Resistant Plasmodium falciparum Parasites, and Delivery Outcomes in Malawi. J Infect Dis **2020**; 222:661-9.

* Like the previous study, this study indicates a significant negative impact of highly resistant *P. falciparum* parasites on birth weight.

54. Hughes E, Wallender E, Kajubi R, et al. Piperaquine induced QTc prolongation decreases with repeated monthly dihydroartemisinin-piperaquine dosing in pregnant Ugandan women. Clin Infect Dis **2021**. Online ahead of print.

*This paper allays concerns that QTc prolongation may be exacerbated in women receiving regular monthly dihydroartemisinin piperaquine. Despite the long half life of piperaquine, QTc prolongation decreased over multiple doses during pregnancy.

55. Chotsiri P, Gutman JR, Ahmed R, et al. Piperaquine Pharmacokinetics during Intermittent Preventive Treatment for Malaria in Pregnancy. Antimicrob Agents Chemother **2021**; 65:e01150-20.

56. Roh ME, Kuile FOT, Rerolle F, et al. Overall, anti-malarial, and non-malarial effect of intermittent preventive treatment during pregnancy with sulfadoxine-pyrimethamine on birthweight: a mediation analysis. Lancet Glob Health **2020**; 8:e942-e53.

57. Waltmann A, McQuade ETR, Chinkhumba J, et al. The positive effect of malaria IPTp-SP on birthweight is mediated by gestational weight gain but modifiable by maternal carriage of enteric pathogens. EBioMedicine **2022**; 77:103871.

**This study shows for the first time that the non-malarial effects of SP on birth weight may be mediated by changes in the maternal intenstinal flora. SP was associated with increased maternal weight gain, which appeared to be mediated by protection from gut colonisation with certain types of *E. coli*.

58. Mlugu EM, Minzi O, Kamuhabwa AAR, Aklillu E. Effectiveness of Intermittent Preventive Treatment With Dihydroartemisinin-Piperaqunine Against Malaria in Pregnancy in Tanzania: A Randomized Controlled Trial. Clin Pharmacol Ther **2021**; 110:1478-89.

*This study found that IPTp with DHA-PQ was not only associated with lower malaria incidence, as previously described, but also with less low birth weight, than IPTp with SP.

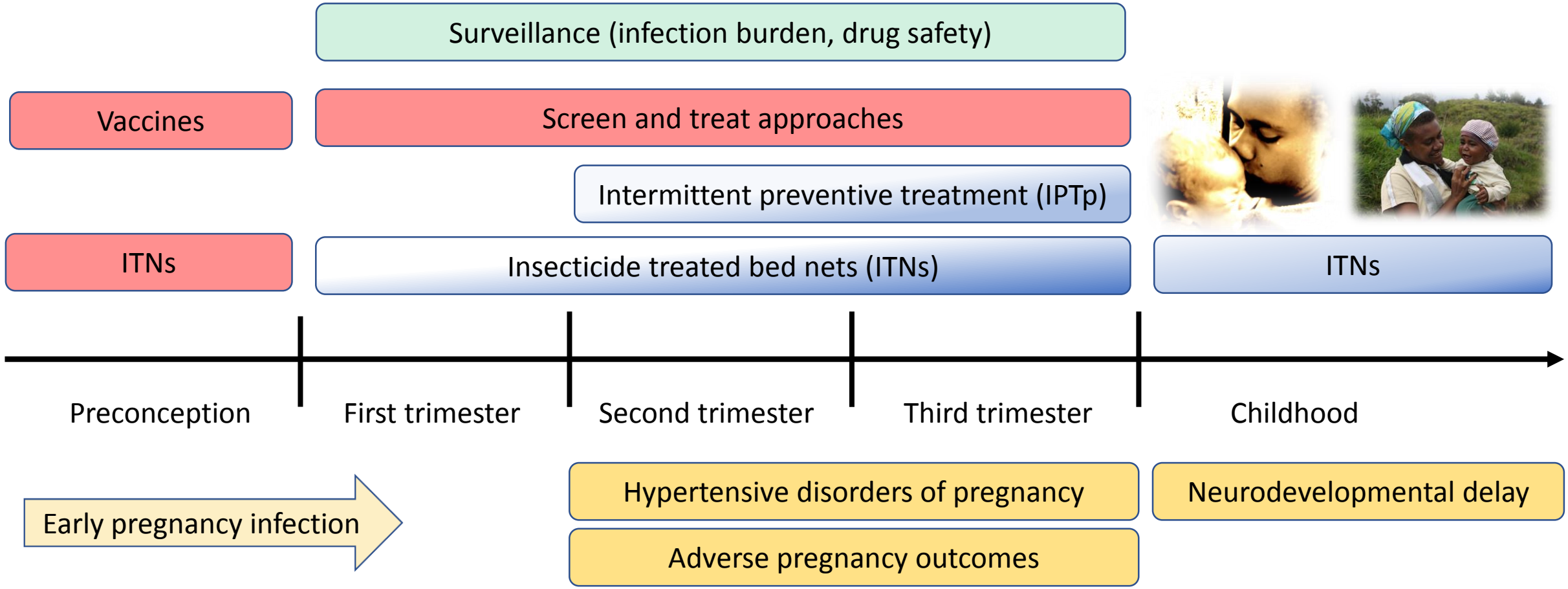
59. Fernandes S, Were V, Gutman J, et al. Cost-effectiveness of intermittent preventive treatment with dihydroartemisinin-piperaquine for malaria during pregnancy: an analysis using efficacy results from Uganda and Kenya, and pooled data. Lancet Glob Health **2020**; 8:e1512-e23.

60. Gonzalez R, Nhampossa T, Mombo-Ngoma G, et al. Evaluation of the safety and efficacy of dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in HIV-infected pregnant women: protocol of a multicentre, two-arm, randomised, placebo-controlled, superiority clinical trial (MAMAH project). BMJ Open **2021**; 11:e053197.

61. Gutman JR, Khairallah C, Stepniewska K, et al. Intermittent screening and treatment with artemisinin-combination therapy versus intermittent preventive treatment with sulphadoxine-pyrimethamine for malaria in pregnancy: a systematic review and individual participant data meta-analysis of randomised clinical trials. EClinicalMedicine **2021**; 41:101160.

*This systematic review found that, over five trials comparing IST to IPTp, IST was associated with higher risks of supatent malaria infection, preterm birth and low birth weight.

Figure


Surveillance (infection burden, drug safety)
Vaccines
Screen and treat approaches
Intermittent preventive treatment (IPTp)
ITNs
Insecticide treated bed nets (ITNs)
ITNs
Preconception
First trimester
Second trimester
Third trimester
Childhood
Early pregnancy infection
Hypertensive disorders of pregnancy
Adverse pregnancy outcomes
Neurodevelopmental delay