Malaria in pregnancy

*In search of tools for improved prevention*

Ruizendaal, E.

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Chapter 9. Discussion
9.1 Community-based screening and treatment of malaria in pregnancy

The aim of the research described in this thesis was to contribute to the improvement of prevention of placental malaria (PM) and PM-related morbidity caused by *Plasmodium falciparum*. A first objective to reach this goal was to increase the access to adequate malaria care for pregnant women. Health care to mothers is normally given at antenatal care visits (ANC), during which the general health of the mother and child is assessed and any required treatment or vaccinations are given. Furthermore, intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP) is offered at the ANC. However, due to several constraints, partly cultural but also logistical, pregnant women (in particular primigravidae and adolescents) may visit the ANC late, seldom, or not at all during pregnancy.1–3 In children, access to health care was also one of the bottlenecks for case management of malaria, which led to the implementation of community case management of malaria (CCMm): instead of having to travel the relatively long distance to the health clinic, febrile children could now visit a community health worker (CHW) in their own village for malaria diagnosis and treatment. This intervention was more or less copied for pregnant women (chapter three), but instead of providing case management, the CHW offered screening of malaria in pregnancy. The review of CCMm (chapter two) identified the successes and failures of the CCMm intervention, so that potential barriers for implementation of a community based intervention for pregnancy malaria could be foreseen. Several lessons were drawn from the literature review (chapter two) and from the evaluation of the intervention in pregnant women (chapter four).

First of all, it was shown that community health workers (CHW) deployed for CCMm are capable of performing rapid diagnostic tests (RDT) to detect a malaria infection with high sensitivity and moderate to high specificity. The malaria screening intervention in pregnant women confirmed the notion that CHWs are capable of performing RDTs in a correct manner. However, as expected, the RDT sensitivity was lower (81.5%) when used for screening largely asymptomatic pregnant women compared with testing mainly symptomatic children (sensitivity ranging from 83.2% - 97.9%), as parasite densities in the latter group are generally higher. Although missed malaria diagnoses were frequently of low parasite density, it has previously been shown that these infections may also lead to malaria-related morbidity in pregnant women,4 hence all efforts should be made to optimize malaria diagnosis.

The moderate specificity of RDTs in some studies on CCMm was discussed as being potentially problematic in febrile children. In case of a false positive RDT result the CHW may assume that malaria is the cause of illness while there actually is an alternative underlying disease, such as pneumonia, requiring treatment. For preg-
nant women, the observed RDT specificity was high, although it did decrease with advancing gestational age, which is possibly related to HRPII antigen persistence. These false positive RDT results may contribute to unnecessary treatment, compromising cost-effectiveness of the intervention. Furthermore, there is the feared risk of enhancing drug resistance. Recent anti-malarial treatment should therefore be an important reason not to rely on a positive RDT result.

Both in CCMm and for screening of malaria during pregnancy the adherence to positive RDT results was excellent. However, in CMMm interventions there was some overtreatment of children with negative RDTs. As pregnant women usually have little symptoms and are more reluctant to take (anti-malarial) medication during pregnancy, it was expected that the adherence to negative RDT results would be better in pregnant women. Indeed, evaluation of the intervention in pregnant women did not reveal issues of non-adherence, both for positive and negative RDT test results.

Some of the bottlenecks of CCMm found in chapter three were not assessed in the evaluation of malaria screening in pregnant women described in chapter four. For example, it was not possible to assess the issue of inadequate stock supply regularly mentioned for CMMm, as the study team assured sufficient supplies in the trial on screening and treatment of malaria in pregnancy. However, a functioning supply chain is an essential part of the potential success of the intervention once it would be implemented. Furthermore, CHW motivation and (financial) incentives, work load and supervision are other extremely important issues for sustainable implementation of the intervention. These issues have been studied in the current trial, however, these results were not available at the time of writing.

Despite the adequate performance of CHWs in screening pregnant women for malaria, preliminary analyses of the trial have shown no effect of the intervention on (placental) malaria at delivery, nor at secondary outcomes of low birth weight or maternal haemoglobin levels. This apparent lack of an effect can be related to: I. the intrinsic limitation of RDTs resulting in a suboptimal sensitivity when used for screening pregnant women; II. an adequate uptake of IPTp-SP during this study period; and III. current adequate effectiveness of IPTp-SP (chapter five). Despite an apparent lack of effects on primary and secondary outcome measure, a definitive positive outcome of the intervention is the frequency of contact between pregnant women and health care providers. The World Health Organization (WHO) has estimated that a minimum of eight health care contacts improves perinatal outcomes and is beneficial for the pregnancy experience of women. The number of health care contacts for women in intervention villages were on average almost three home visits and four visits to the ANC, totalling seven health care contacts. In control villages, this was limited to three to four ANC visits.
Furthermore, although there was no effect of the malaria screening and treatment on placental malaria or morbidity, more sensitive diagnostics that may become available in the future may favour community screening of malaria in pregnant women. Moreover, even though CHWs were only trained in malaria care, the quality of care they provided holds promise for extending or adapting the intervention to prevent, treat or signal other pregnancy-related health issues. In some areas, CHWs are already involved in antenatal care, although this is mostly in the form of counselling on nutrition, ANC attendance and hospital delivery. In these areas it has been suggested that CHWs may also be trained in identifying women with preeclampsia, one of the major pregnancy complications.\textsuperscript{15,16} Furthermore, CHWs could screen for anaemia during pregnancy, which can also be caused by other conditions than malaria, such as undernutrition or helminth infections\textsuperscript{10,11}, or they could assist in distributing iron and folic acid supplementation to prevent anaemia during pregnancy as recommended by the WHO.\textsuperscript{7} Also, the IPTp-SP currently given at ANC visits, could be provided by the CHW, thereby increasing the access to IPTp-SP and improving the dosing frequency as has been shown previously.\textsuperscript{12,13}\textsuperscript{1} Reduced ANC attendance is probably one of the major fears of transferring responsibilities of maternal care, such as IPTp-SP, to CHWs. In one of the studies on community provision of IPTp-SP a worrisome trend of simultaneous decreased ANC attendance was indeed seen.\textsuperscript{12} In contrast, in another study, IPTp-SP uptake at health facilities increased in areas where IPTp-SP was also distributed at community level.\textsuperscript{13} Also in the current intervention there was no negative effect on ANC attendance as pregnant women living in villages in which home screening for malaria was performed, had similar or slightly higher ANC attendance than women living in control villages. Therefore, transferring tasks to CHWs does not necessarily result in decreased ANC attendance, but it remains something that needs to be considered and monitored.

9.2 Resistance against sulfadoxine-pyrimethamine

Resistance against SP is emerging in sub-Saharan Africa.\textsuperscript{14–17} Nevertheless, in the described study area of Nanoro, Burkina Faso, it was shown that, although the triple \textit{dhfr} mutation was highly prevalent, the quintuple mutant that harbours mutations in both \textit{dhfr} codons (N51, C59, S108) and \textit{dhps} codons (A437, K540) is still rarely seen (chapter five). The minimal presence of quintuple mutants and sextuple mutants (quintuple mutant plus an additional mutation in \textit{dhps} codon A581) explains the continued efficacy of IPTp-SP in preventing low birth weight in the study area, and might be one of the reasons why the additional screening and treatment intervention for malaria in pregnancy was not beneficial in this setting. However, as IPTp-SP does seem to have reduced efficacy in areas where the sextuple mutant parasite is common, such as in parts of East Africa, it would be interesting to study whether the community screen and treat intervention may have a beneficial effect in these areas.\textsuperscript{18–24}
It is unclear if and how fast quintuple and sextuple mutant parasites may conquer West Africa, which means that regular monitoring of SP resistance and potential revision of prevention strategies are still needed in the future. There are some alarming signals that the prevalence of dhfr mutations can change rather rapidly. In Bourasso (Burkina Faso), a village 163 km West of our study site, the triple dhfr mutation was hardly present in the year 2000 (~2%), while the prevalence had increased to 35.3% in 2009 and to 55.0% in 2011. In the current study performed in 2015 in Nanoro, triple dhfr mutations were present in 73.9% of samples collected from the general population and the prevalence of dhfr mutations increased during pregnancy. It is most likely that this number will increase further in coming years, given that even higher prevalences of triple dhfr mutations, nearly reaching 100%, are found in pregnant and non-pregnant populations in the neighbouring countries Mali and Benin.25–27 It is more challenging to predict a possible spread of the dhps K540 mutation, or more importantly the quintuple or sextuple mutation. Rapid increases in prevalence of quintuple mutants have been observed in East Africa, however, these mutants emerged when SP was still used as first-line treatment of malaria.28,29 In contrast, the more recent appearance of quintuple mutants in West Africa occurs in a period of much lower drug pressure, as SP is only used for IPTp-SP, intermittent preventive treatment of infants (IPTi-SP) or seasonal chemoprevention (SMC) but not for case management. In fact, for all three strategies the actual selective pressure for SP resistant parasites is being debated, with some showing evidence of selective pressure21,26,30–35 while others do not.15,27,36–39 In the current study we could not confirm an association between dhfr or dhps mutations and IPTp-SP doses. Rather it seems that selection of SP resistant parasites is not simply related to SP exposure only, but is impacted by other factors such as transmission intensity and possibly immunity. Thus, emergence of quintuple or sextuple mutant P. falciparum parasites may be slower in West Africa compared with East Africa, but the continued use of SP in preventive strategies will likely result in (super-) resistant parasites in time.

Because of the resistance against SP and failing IPTp-SP in certain parts of sub-Saharan Africa, other drugs are currently also considered for use in IPTp. Recently, there has been an interest in dihydroartemisinin-piperaquine (DP), a drug combination that profits from the fast acting artemisinin compound and the long half-life of piperaquine.40 In two studies performed in East African countries, IPTp with DP was superior over IPTp-SP in reducing the number of malaria infections during pregnancy and at delivery, and reducing the prevalence of anaemia.41,42 Although there were no positive effects on birth weight in these studies, the promising results of IPTp-DP may offer an alternative for IPTp-SP in areas of high SP drug resistance.
9.3 Biomarkers for diagnosis of malaria in pregnancy

As mentioned, the lack of effect of the community screening and treatment of malaria in pregnancy may have been related to adequate uptake of IPTp-SP and sufficient sensitivity of *P. falciparum* parasites to SP in the study area. However, the suboptimal sensitivity of RDTs in detecting malaria infections may also have limited the potential benefits of the screening intervention, as women with malaria infections not detected by RDT do carry a high risk of malaria-related morbidity. As microscopy is often not better than RDTs in terms of sensitivity, screen and treat based strategies could benefit from other diagnostic methods. A study on biomarkers was performed to explore whether these can be used to support malaria diagnosis in pregnant women. The choice of biomarkers was based on a systematic review of previously published literature described in chapter six. After reviewing the literature, it already seemed unlikely that a single biomarker could be identified that would be sufficiently sensitive and specific for malaria in pregnancy. For this reason, a combination of (anti-)inflammatory cytokines, a vascular endothelial growth factor receptor associated with placental pathology, and markers of lipid metabolism were studied.

The study on biomarkers revealed that two (anti-)inflammatory markers were potentially useful as biomarkers to support malaria diagnosis. These were interleukin-10 (IL-10) and soluble tumour necrosis factor receptor II (sTNF-RII). The created model indicated a fair sensitivity and specificity (88.9%, 95%CI 45.7 – 98.7 and 83.3%, 95%CI 57.1-94.9 respectively) for diagnosing malaria infections in primigravidae. For secundi- and multigravidae the model performed less well. This is probably because primigravidae carry the highest parasite densities, which correlated with IL-10 and sTNF-RII levels. Likewise, the sensitivities of RDT and microscopy have also shown to depend on gravidity in malaria endemic areas due to differences in parasite densities, with the highest sensitivity observed in primigravidae. The biomarkers model is therefore unlikely to outperform RDT or microscopy in diagnosing infections of moderate to high parasite densities. However, host biomarkers for diagnosis of malaria in pregnancy are probably more useful for inclusion in a diagnostic decision tree, in which a biomarkers test is used if the RDT is negative, or if a woman has received recent treatment with a consequent high risk of a false positive RDT result. The model in its current format did identify some sub-microscopic infections, however, these analyses were based on very small numbers. Nevertheless, it was concluded that sensitivity for diagnosis of infections with low parasite densities needs improvement. Furthermore, as IL-10 and sTNF-RII are probably unspecific markers of infection, additional biomarkers may also be needed to improve specificity.

Since publication of the review in chapter six, several studies have confirmed a positive association of IL-10 levels in women with (placental) malaria infection by *P. falciparum*. The same applied for IL-10 and malaria in HIV-infected women, although this association was borderline significant. In one study IL-10 also cor-
related negatively with birth weight.\textsuperscript{46} Regarding sTNF-RII, significantly increased levels were found in the urine of malaria-infected women and these levels correlated with parasitemia.\textsuperscript{52} However, no new studies on malaria and sTNF-RII levels in peripheral blood were found after publication of the review. Other, newly mentioned, inflammatory cytokines showing significant associations with placental malaria were IL-17E, IL-27 and IL-28a.\textsuperscript{53}

Several other studies that appeared after the review described in \textit{chapter six}, have looked further into biomarkers other than (anti-) inflammatory cytokines. One study compared hormones (17β oestradiol and progesterone) and lipid fractions (triglyceride, total cholesterol, high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol) at delivery in women with placental malaria versus women without placental malaria.\textsuperscript{54} In particular the hormone progesterone is of interest, as significantly decreased levels were found in women with placental malaria. Furthermore, progesterone correlated negatively with parasitaemia, and positively with haemoglobin levels and birth weight.\textsuperscript{54}

The complement system has also previously been linked to malaria infection during pregnancy.\textsuperscript{55–57} Two recently published studies looked into biomarkers of the complement system. One study evaluated terminal complement complex (TCC) and found significantly lower levels of TCC in malaria infected women versus uninfected women.\textsuperscript{58} However in a previous study this association was inversed.\textsuperscript{57} The second study found significantly decreased levels of protein C, tissue factor pathway inhibitor and antithrombin-III in women with placental malaria infections compared with women without placental infection.\textsuperscript{59}

Impaired vascularization has been described as a feature of placental malaria.\textsuperscript{60} This has translated into an interest in biomarkers associated with angiogenesis and vascularization as described in \textit{chapter six}. One additional study after publication of the review on biomarkers (\textit{chapter six}) was identified that examined angiogenesis factors. In this study, a trend of decreased angiopoietin-1 levels and an increased ratio of angiopoietin receptor:angiopoietin-1 in women with \textit{P. falciparum} infections compared with uninfected women was found.\textsuperscript{61} Furthermore, there have been recent propositions to evaluate certain markers associated with preeclampsia for diagnosing pregnancy malaria, as the two entities share multiple pathophysiological features.\textsuperscript{52} Although one of the suggested markers in this review, sFlt-1, showed no associations with (placental) malaria in the study described in \textit{chapter seven}, others such as placental protein 13 or pregnancy-associated plasma protein A may be of interest for further study.

The above new findings offer new possibilities of biomarkers for malaria in pregnancy, while they also substantiate the high potential of IL-10 and sTNF-RII. As these are two (anti-)inflammatory markers, other biomarkers of main interest are progesterone, biomarkers of the complement system and biomarkers of angiogenesis.
9.4 Immunity and malaria transmission

The VAR2CSA (variant surface antigen 2-chondroitin sulphate A) antibody study described in chapter eight revealed that higher VAR2CSA IgG levels are associated with protection from high parasite densities and LBW, but not with protection from PM. This association with clinical immunity was mainly seen for women of higher gravidity. Unfortunately, it seemed that in primigravidae VAR2CSA antibodies could not be used as a marker for protection from high parasite densities or LBW.

The higher VAR2CSA antibody levels and the associated clinical immunity in women of higher gravidity versus primigravidae, suggests that regular monitoring of these antibodies can inform on changing immunity and vulnerability of the local population of pregnant women. In fact, monitoring these antibodies may be a tool to monitor changing malaria transmission, or the success of malaria prevention strategies, as IPTp-SP and bed net use have both been related to reduced acquisition of VAR2CSA antibodies. In the study described in chapter eight, there was no association between the number of IPTp-SP doses and the level of VAR2CSA antibodies at delivery, however the number of women with no or few doses of IPTp-SP may have been too small, or women may have already acquired antibodies before the first dose of IPTp-SP. Regular monitoring of VAR2CSA antibody levels over successive pregnancies in women with high versus low uptake of IPTp-SP doses might reveal whether sufficient VAR2CSA antibody responses are acquired, or whether the gravidity dependent gain of VAR2CSA antibody levels will eventually disappear in women with a high uptake of IPTp-SP.

Apart from improved prevention of malaria in pregnancy by IPTp-SP and bed net use, immunity against pregnancy malaria might be influenced by the decreasing malaria transmission that has been observed over the past decade in sub-Saharan Africa. In Burkina Faso some studies reported a decline in malaria prevalence over the past years, although malaria incidence has been more or less stable according to a recent WHO country report. In a literature review Ataíde and colleagues propose that VAR2CSA antibody levels in primigravidae at the end of pregnancy may serve as a measure for local malaria transmission. They argue that VAR2CSA antibody levels in primigravidae are a good representative of recent malaria transmission, as they are not influenced by exposure in previous pregnancies as is the case for multigravidae. However, in our study population, even primigravidae with proven malaria infections did not show a significant increase in VAR2CSA IgG antibody levels over pregnancy. Perhaps this is related to early acquisition of antibodies (before first measurement in second trimester) or to the relatively high uptake of IPTp or correct case management, reducing the exposure time to . Irrespectively, VAR2CSA IgG levels at end of pregnancy in primigravidae may not be sufficiently informative.
To gain a better picture of local malaria transmission and acquisition of immunity, regular monitoring of VAR2CSA antibodies over successive pregnancies (and not only in primigravidae) might be more appropriate, as VAR2CSA antibody acquisition seems transmission dependent. In high transmission settings VAR2CSA antibody responses are dependent of gravidity as has been shown in chapter eight and in previous studies.\textsuperscript{71,72} In contrast, in an unstable transmission setting in Sudan, the VAR2CSA antibody response was not gravidity dependent.\textsuperscript{50} Furthermore, the pattern of VAR2CSA antibody acquisition changed in an area in Mozambique transitioning from high to low transmission: the clear parity dependent increase in VAR2CSA antibody levels seen in high transmission years was less pronounced during low transmission years.\textsuperscript{73} This matched the observation that during high transmission years, multigravidae showed significantly lower parasite densities than primigravidae, while this difference was lost during years of lower transmission.\textsuperscript{72} Furthermore, the reduction in antibody levels during low transmission years coincided with larger reductions in birth weight in women with placental malaria infections, suggesting that women were less protected from malaria related morbidity.\textsuperscript{73} Other indicators of immunity against PM, like opsonic IgG antibody levels, have shown to remain stable in years of low transmission in Papua New guinea, in contrast to total IgG.\textsuperscript{74} This suggests that IgG against VAR2CSA expressing parasites is a better marker of changes in malaria transmission than opsonic antibodies, but it could also mean that some immunity against malaria in pregnancy might remain intact.

IPTp strategies may become less cost-effective with decreasing malaria transmission: more women need to be treated to prevent a single case of placental malaria.\textsuperscript{75} Instead, screen and treat strategies may become increasingly important. Furthermore, if a reduction in transmission is indeed accompanied by reduced acquisition of VAR2CSA antibodies over successive pregnancies, it may in fact improve the performance of diagnostic tools for malaria in pregnancy. As was shown in the study from Mozambique, parasite densities in multigravidae become more similar to primigravidae in years of low malaria transmission.\textsuperscript{73} An increase in parasite density in pregnant women with declining transmission was also previously seen in Malawi.\textsuperscript{76} Higher average parasite densities would increase the sensitivity of RDTs and microscopy. Furthermore, biomarkers may become more discriminative in identifying pregnant women with malaria, as in the biomarkers study in chapter seven both IL-10 and sTNF-RII levels were positively associated with parasite density, and the biomarkers model performed best in primigravidae. In addition, it has been shown that cytokine responses to low parasite densities in children are much more pronounced in areas of low malaria transmission than in high endemic areas.\textsuperscript{77} The reduced cytokine response in high transmission areas suggests a certain level of parasite tolerance in these children. This is substantiated by the finding that in low endemic areas, the parasitaemia threshold for developing
clinical symptoms is also much lower than in high endemic areas. To conclude, VAR2CSA antibody levels in women of different gravidity might inform on malaria transmission, and a reduction in transmission will lead to a shift in the clinical picture of malaria in pregnancy (higher parasitaemia, more severe morbidity, and more equal risks of PM-related morbidity for primi- versus multigravidae). This will however also improve the possibilities of diagnosing malaria in pregnancy.

9.4 Future perspectives
The call for highly sensitive malaria diagnostics able to detect low parasite densities for screening purposes has been around for several years. The most sensitive diagnostic tests currently available are molecular based diagnostics. Molecular tests have thus far hardly been discussed in this thesis due to several limitations, e.g. they are frequently labour intensive, relatively expensive and they require cold chains and advanced equipment. Due to these limitations, molecular based tests are usually not field applicable. However, in recent years there has been an increasing effort to eliminate some of the limitations currently hampering the implementation of molecular diagnostics in the field. As a result, much progress has been made in developing molecular tests that are potentially useful for near point-of-care diagnosis in resource poor settings. For example, a direct on blood polymerase chain reaction (PCR) with an easy read-out based on nucleic acid lateral flow immunoassay (db-PCR-NALFIA) showed high sensitivity and specificity for detection of Plasmodium spp., with a limit of detection of 8 parasites/µL. Although this assay still requires a thermal cycler, new advances in solar powered and portable thermal cycler machines may enable use of such machines in resource poor settings. Another promising near point-of-care molecular test currently available is loop-mediated isothermal amplification (LAMP). Because LAMP is based on isothermal amplification of DNA there is no specific need for a thermal cycler machine and a simple water bath can be sufficient. LAMP assays developed for detection of P. falciparum have shown high sensitivity and moderate to high specificity in non-pregnant symptomatic patients. A recent study also evaluated the use of LAMP for detecting malaria during pregnancy in Ethiopia and showed a sensitivity of 100% and specificity of 93.5% compared with nested PCR. The limit of detection for LAMP assays currently seems to lie around 1-5 parasites/µL. A first attempt has also been made in using another promising isothermal molecular method, recombinase polymerase amplification (RPA), for detection of P. falciparum. In preliminary laboratory analyses, the detection limit of this assay was 4 parasites/µL, however, no field analyses have been performed thus far. Several other isothermal molecular methods have been developed that all have the potential of being near point-of-care tests. There is however a large variety in methods of DNA extraction (e.g. chemical lysis, boil and spin methods) and read-out systems (e.g. lateral flow devices, turbidity, fluorescence) used in
these assays.\textsuperscript{82–85,88} Although these DNA extraction and read-out methods are relatively simple, the different steps complicate the process, which still limits the field applicability of these molecular tests. Preferably, a simple integrated device for DNA extraction, amplification and read-out is developed for use of molecular methods in resource poor areas. Advances in this field have been made by Cordray \textit{et al.} who developed a device with integrated RPA and lateral flow detection,\textsuperscript{89} and by Yeh \textit{et al.} who developed a microfluidic chip with integrated sample preparation, RPA and fluorescence read-out.\textsuperscript{90}

Another field of research that could become of great importance for prevention of malaria in pregnancy in the future is vaccinology. The VAR2CSA variant surface antigen expressed by \textit{P. falciparum} parasites in the pregnant host, is an antigen of the \textit{Plasmodium falciparum} erythrocyte membrane protein 1 (PfEMP1) family of surface antigens. Although PfEMP1 surface antigens are known for their high heterogeneity, the VAR2CSA antigen is relatively conserved. This raises the potential for using the VAR2CSA antigen as a target in vaccines. A vaccine eliciting an adequate IgG response could prevent the accumulation of \textit{P. falciparum}-infected erythrocytes in the placenta, by blocking the binding of VAR2CSA with chondroitin sulphate A (CSA). To reach this goal, vaccine studies are currently not focusing on a vaccine based on the full-length VAR2CSA protein, as it was shown in mice that a full-length VAR2CSA immunogen elicits IgG antibodies that are only capable of preventing homologous \textit{P. falciparum} strains from adhesion to CSA.\textsuperscript{91} Therefore subdomains of the VAR2CSA antigen, which consists of 6 Duffy binding like domains (DBL), inter-domain regions and an intracellular part, have been studied for their potential use in vaccines. Currently, a subdomain considered as the CSA binding domain, ID1-DBL2x-ID2a, is of main interest for vaccine development as it has shown cross-inhibitory IgG antibodies.\textsuperscript{92} The vaccine development based on this subdomain is still in an early phase and it will have to be proven whether substantial IgG responses can be elicited with anti-adhesion activity against a broad variety of \textit{P. falciparum} strains and with sufficient longevity.\textsuperscript{93} If such a vaccine can be developed, this would mean women can be immunized before their first pregnancy, protecting both the pregnant women and their offspring from severe morbidity related to \textit{P. falciparum} infections.
References


