Malaria in pregnancy in Asia Pacific region:

A literature review from an area of mixed infections with *P.vivax* and *P.falciparum*

BACKGROUND WORKING PAPER

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Table of content

Introduction

More than half of all pregnancies at risk for malaria occur in areas where *P.vivax* is endemic and these are generally areas of low *P.falciparum* transmission where women have little acquired immunity against malaria [1-3]. Malaria infection in pregnancy (MIP) can have major effects on pregnant women, the developing fetus and the infant (double trouble) [4, 5]. For the mother MIP can rapidly develop in serious illness, severe anaemia and maternal death; for the unborn child it increases the risk of spontaneous abortion, stillbirth, preterm labour (PTL), intra uterine growth restriction (IUGR), congenital malaria; postnatal infant death and possibly long term effects (Barker hypothesis). Interventions to control MIP will benefit mothers and infants; indirectly because of the strong association between low birth weight (LBW) and child survival and directly as MIP was shown to be an independent risk factor for early infant mortality in Thailand[6] . The Millennium Development Goal 5 (improve maternal health) remains at the top of the global health agenda and every attempt to reduce the number and severity of malaria infections in pregnancies is valuable. The interventions for control of *P.falciparum* malaria during pregnancy recommended by World Health Organisation (WHO) Roll Back Malaria (RBM) are mainly based on studies conducted in sub-Saharan Africa, where *P.falciparum* is the dominant specie, the transmission is stable and *Anopheles gambiae* is the main vector [7]. The main components of this control strategy are: personal protection with insecticide impregnated bednets (ITNs), intermittent preventive treatment during pregnancy (IPTp) and case management of anaemia and malaria illness with effective antimalarial drugs[7].

Most countries in the Asia Pacific region (APR) have been successful in reducing the burden of malaria and some countries in these regions even have included elimination of malaria on their programme. However, specific MIP treatment guidelines or prevention strategies are lacking or just being deployed in several of these countries[8, 9]. Generally, maternal and child health are not evenly distributed and MIP is not often seen as a major health problem like in the African continent[9, 10]. However, pregnant women are increasingly recognized as a vulnerable population[11], but the morbidity and mortality are essentially unknown, and may be higher than previously estimated[1, 12, 13]. Since a single episode of malaria can be harmful to the mother and fetus and has a negative impact on birthweight[14, 15], each episode of malaria parasitaemia in a pregnant woman is deleterious and should be prevented or detected early and treated effectively. Furthermore, the vectors show a greater diversity of behaviours[12, 16, 17]. An important challenge in combating malaria in APR is the co-existence of *P.vivax*. Although the effects of *P.vivax* infection in pregnancy are recognized, treatment and prevention policies are focused on *P.falciparum*; e.g. there is no policy for the management of chloroquine (CQ) resistant parasites, except in Indonesia

and parts of Melanesia[18]. Recent emergence of resistance to artemisinins in *P.falciparum* [19], substandard and counterfeit drugs [20], difficult to reach cross border migrants and ethnic minorities and chloroquine resistance in *P.vivax* may further complicate the strategies to reduce the impacts of malaria [17].

In some of the APR countries studies have taken place on the epidemiology, clinical presentation, consequences, treatment and prevention of *P.falciparum* and *P.vivax* in pregnancy and the results may be valuable for other countries with changing transmission settings. There has been no systematic review of these projects. In this working paper we summarize the published and available unpublished literature on MIP in the APR, with a special attention to *P.vivax* malaria to assist with the debates at the coming meeting.

Methods

A Medline (PubMed) investigation was performed with the search terms "malaria" AND "pregnancy" by country on 10 January 2011. Each of the following countries was included: Bangladesh, Bhutan, Burma/Myanmar, Cambodia, China, India, Indonesia, Lao(s), Malaysia, Nepal, Republic of Korea, Papua New Guinea, Philippines, Sri Lanka, Solomon Islands, Thailand, Timor-Leste, Vanuatu, and Vietnam. These 20 countries are the territories in the APR that have malaria transmission[21]. The list of these counties was derived from the WHO South East Asia regions (SEAR), http://www.searo.who.int/ (n=10) and Western Pacific Regions (WPR), http://www.wpro.who.int (n=10). The analysis was restricted to English language articles. The "Malaria in Pregnancy Consortium library"[22], WHO website and regional websites [23, 24], World Malaria Report [25] and "ClinicalTrials.gov"[26] were scrutinized for additional MIP studies from these countries. We identified national malaria treatment and prevention policies for pregnant women on the websites of each ministry of health. If needed, WHO country representatives from all countries were approached by email to send all available literature from the National Malaria Programs pertaining to malaria in pregnancy. All abstracts were read by 2 authors and full text was obtained from all relevant articles. Predefined tables were completed for all articles; proportion of infected women, treatment and prevention guidelines, efficacy of *P.falciparum* and *P.vivax* treatments, effect of malaria in pregnancy on anaemia, birth outcomes, and maternal mortality.

Results

The PubMed search resulted in 412 hits published between 1965 and 2011. We excluded 300 articles: reviews of published data (n=34), articles that did not provide MIP data (n=80), data from outside APR (n= 17), articles not related to pregnancy (n=72), laboratory studies based articles (n=33), double citations (n=50) and articles not in English (n=14). The results are reported here from the 112 selected articles (Figure1 and Supplementary table S1). Only 3 of the 20 APR countries with malaria transmission provided 86% (96/112) of the published original studies or case reports on epidemiology, treatment or prevention of MIP: India (n=30 [12, 13, 16, 27-54]), Papua New Guinea (n=20 [55-75]) and Thailand (n=46 [6, 14, 15, 76-116]). The remaining articles were from Burma/Myanmar (n=3 [117-119]), , Indonesia (n=2 [120, 121]), Lao PDR (n=1 [122]), Malaysia (n=2[123, 124]), Nepal (n=2 [125]), Solomon Islands (n=4 [126-129]), Sri Lanka (n=2 [130, 131]), and Vanuatu (n=1[132]) (Figure 2 and Table S1). During the extensive search including tracking of citations we found an additional twelve articles[1, 133-143]. We included data from 6 unpublished studies: Bangladesh (Faiz et al.), India (Singh et al.), Indonesia (Syafruddin et al.), PNG (Stanisic et al.), Thailand (Boel et al, Rijken et al.).

Epidemiology

Malaria Transmission

Malaria transmission in APR is highly heterogeneous. In general, malaria transmission in APR is low, unstable, highly focal and seasonal. Nonetheless, of the total population ~23% live in areas of moderate or high *P.falciparum* malaria transmission (where reported case incidence is >1 per 1000 population per year): these are in regions in Bangladesh, Burma/Myanmar, India, Indonesia, and Papua New Guinea (Figure 3) [144, 145]**.** Fluctuations and seasonal differences in the intensity of malaria transmission lead to either unstable or epidemic prone malaria[146]. Korea, Indonesia, Burma/Myanmar, Nepal, Vietnam, the Philippines, Papua New Guinea (PNG) and India have all experienced malaria epidemics in the last decades [144]. All these variations have important consequences for the acquisition of natural immunity to malaria. If on average APR countries have low transmission (*P.falciparum* entomological inoculation rate (EIR) <1 infective bite a year), several of these countries have substantial areas with foci of (EIR)>10 infective bites a year, which indicates high transmission [146, 147]. Rural malaria accounts for the majority of cases, urban malaria is rare except in India[12].

Risk estimates for *P.vivax* are difficult to obtain, as climatic constrains on *P.vivax* transmission are less well defined, the accuracy of reporting *P.vivax* in mixed *P.falciparum* and *P.vivax* co-infections is poor and relapses from the liver stages cannot be distinguished from new infections[2, 148, 149]. In 2010 *P.vivax* endemicity was mapped showing the vast majority of the world population at risk for *P.vivax* live in APR [150].

Asia Pacific: numbers at risk

Calculation of the number of pregnant women at risk for malaria is based upon risk to the general population. More than 2.2 billion people are at risk in APR, which represents ~67% of the world population at risk of malaria[3, 144, 145, 150], of which 77.4 million women (61.8% of all pregnancies in malaria endemic areas) became pregnant in 2007 [1]. Recently the number of pregnant women at risk for malaria in APR were estimated and relevant data for this review is shown in Figure 4 [1]. The number of pregnancies at theoretical risk for malaria is overwhelmingly clustered in India and China. However, such risk estimates have to be refined and combined with clinical data to minimise biases, as the number of pregnant women actually exposed to malaria may be very different because of highly focal transmission in APR.

P.vivax is endemic in all countries with malaria in the APR, *P.falciparum* in all countries except the 2 Koreas (Figure 3)[144]. In APR there are extreme variations in malaria transmission even within each country, e.g. in Thailand malaria cases are concentrated along the international borders, in certain malaria foci[17, 24, 97, 151]. Within the same country some areas can be malaria free, whereas relatively close areas could have high transmission of malaria. Malaria elimination is on the agenda for several countries[144]. Finally *P.vivax* could re-emerge in areas where it was eliminated[152], or become more prevalent in areas where *P.falciparum* is controlled[87, 97].

Pregnancies at risk

The global distribution of pregnancies that occur within the global spatial limits of malaria transmission has been estimated [1]. Certainly not all the women at risk for malaria will experience a malaria infection. The actual number of infected pregnancies depends on the malaria transmission intensity at the specific spot [153], seasonality, and efficacy of preventive methods. Pregnancies that occur outside the malaria foci or transmission season may be at very low risk of exposure [1]. Pregnant women in all malaria endemic areas are at higher risk of *P.falciparum* and *P.vivax* malaria: pregnant women are more susceptible to infection than either before pregnancy or when compared with adult males [154], pregnant women are more likely to be bitten by malaria vectors [155, 156] and they are more likely to develop severe malaria [78].

Table 1 and 2 describe the MIP studies from APR that have reported the point prevalence of malaria in pregnancy. The prevalence was mostly detected by malaria smear in cross sectional surveys: in the antenatal clinic (ANC) (Table 1) or at delivery (Table 2). Other methods used to detect parasites are described later in this review. In three cross sectional studies from India and one from Laos malaria smears (MS) were obtained from women with fever or a history of fever following the national guideline, likely showing higher prevalence of malaria than would have been found in asymptomatic women (point prevalence of malaria in these groups were 58% [44], 17% [42], 17%[41], and 23.5%[133], (Table 1 and 2).

When MS was used to detect malaria parasitaemia the median [range] proportion of pregnant women infected at the time of the cross sectional survey in the antenatal clinic and delivery room, excluding the above mentioned 4 studies, were: 16.7% [1.3-40.1] and 8.1% [1.7-18.7] respectively. The median [range] proportion of placenta parasitaemia was 10.9% [2.4-24.2]. As cross sectional surveys provide a point prevalence of malaria infection, these do not reflect the total burden of malaria in the pregnant women population and are very prone to bias due to use of self medication, season of screening and efficacy of the treatment used.

Pregnancy is a 40 weeks period of increased susceptibility and each episode of malaria has a potential negative impact on the mother and the fetus. The effects on the fetus are described in a separate paragraph below. To determine the true burden of malaria in pregnancy longitudinal follow up of pregnant women is preferable. Few (n=11) studies have followed the same women longitudinally during pregnancy, providing a cumulative proportion of malaria episodes during pregnancy (Table 3) [6, 14, 15, 36, 38, 95, 157]. Women attended the antenatal clinic weekly in Thailand and fortnightly in India. The median [range] proportion of women infected during pregnancy was 36.5% [6.0-64.0]%.

Specific high risk groups for malaria infection in pregnancy in low transmission areas are: young maternal age and second trimester of pregnancy, although women are infected in all trimesters [15, 36, 41, 70, 158]. Falciparum malaria is more common in primigravidae and secundigravidae[15, 29] than in multigravidae in most studies, whereas for *P.vivax* this is less clear [6, 14, 55, 62, 63, 70, 120, 128]. Interestingly the incidence of malaria in grand multigravidae (gravida above 8) was higher than in women with gravida 1-7 in Thailand [15].

In five studies in India pregnant women with fever or a history of fever (total n=974) had a significantly higher prevalence of malaria and significantly higher parasitaemia than non-pregnant women of child bearing age with fever or a history of fever in the same area and study period [41-44, 159].

Plasmodial species

Although the cumulative proportion of women with malaria during pregnancy on the Thai Burmese border (TBB) remained the same during 20 years, the incidence of malaria in the refugee camps has fallen from >3 per woman-year to less than 0.5 [87] and the distribution of malaria species changed dramatically (Table 3). In the early studies there was a predominance of falciparum malaria, whereas the recent studies show the majority of malaria infections are *P.vivax* [6, 14, 15, 95] (Boel and Rijken, unpublished). In the reviewed studies of APR *P. vivax* is responsible for median [range] 28.4% [5-100] of malaria infections at ANC. *P.ovale* and *P.malariae* were present in the antenatal clinic and at delivery in all study sites, but studies with PCR diagnosis suggest these species are likely to be underreported by microscopy[4, 12]. *P.knowlesi* is not reported in these pregnancy studies.

Pregnant women with *P.vivax* are less likely to present P.vivax relapses than non pregnant women[14]. A protective effect by *P.vivax* infection against subsequent episodes and severity of *P. falciparum* malaria was observed in Thailand[14, 78]. The protective effect of *P.vivax* may contribute to a lower incidence of fatal falciparum malaria in places where vivax and falciparum malaria co-exist [78]. This may have contributed to the increased parasitaemias observed in pregnant women,

who may have taken the recommended chloroquine prophylaxis before being screened in areas where *P.falciparum* was resistant but *P.vivax* sensitive to CQ [70].

Gametocytes

In India, pregnant women with a history of fever attending the ANC were more likely to carry gametocytes than non pregnant women of child bearing age from the same age [42]. There was no difference in gametocytes on admission in pregnant and non pregnant women of the same age category with severe malaria in a subgroup of patients from Burma/Myanmar in the SEAQUAMAT study [160] (Dondorp, unpublished data). Pregnant women are likely to carry gametocytes, but artemisinin combination therapies (ACTs) resulted in the lowest gametocyte rates post-treatment (data not shown but reviewed in McGready et al.[161]).

Clinical presentation

Most women in low and unstable malaria transmission areas have little acquired immunity against malaria parasites and consequently malaria infections are more frequently symptomatic[7]. Fever, headache, abdominal pain, body aches, nausea and vomiting are common reported symptoms [146]. Untreated, the infection can progress rapidly to become severe (sometimes in less than 7 days) and the occurrence of severe or cerebral malaria is not exceptional [146].

Diagnosis

The most common method to detect malaria parasites is malaria smear (MS) (Table 1-3). Malaria smear requires equipment and materials and its sensitivity and specificity is highly dependent on the skills of the technician and the quality of equipment and reagents. Rapid diagnostic tests (RDTs) are practical as they do not require extensive training, good infrastructure, or electricity but generally do not have the sensitivity needed in pregnancy[37, 162]. Although higher-priced PCR is used for genotyping and detection of malaria parasites and is more sensitive than microscopy[162]. In four of the reviewed studies MS and RDTs were used. Studies carried out from Jharkhand and Chhattisgarh states in India revealed that blood smears were positive in 1.3% and 1.2% of pregnant women at ANC clinics while an additional 0.5% and 0.1% women had positive RDTs. An RDT used for placenta blood nearly doubled the amount of detected malaria in placentas compared to MS in a study site in India (Table 2)[37]; this may be explained by the long elimination of the protein Histidine-rich protein 2 (HRP 2) detected by the RDT "Paracheck Pf" and may not conclusively demonstrate the presence of acute placental malaria.

An experienced and well equipped microscopist can detect 15 parasites per µL of blood (which still corresponds to a total biomass of 10^8 parasites)[162]. However, in field situations equipment may not be ideal and experienced microscopists overloaded with work. Sometimes the absence of good technical skills may result in misleading interpretation of parasite species and under estimation of parasite density. In India at present, the average efficiency of microscopy may not be more than 60% in many microscopy centres (National Vector Borne Disease Control Programme, India). In APR there is no published literature on PCR diagnostic evaluation in pregnancy, but there is unpublished data available. PCR detected more malaria than MS in PNG at enrolment in the study and at delivery (Table 1 and 2; Stanisic, unpublished). In the Solomon islands PCR detected more *P.falciparum* in a random selection of MS negative slides (Appleyard, unpublished) and in 75% of the MS vivax detected cases [128]. About 20-30% of women that were MS or RDT negative for *P. vivax* or *P. falciparum* both in India (Madhya Pradesh and Chhattisgarh) were infected as detected by PCR (Singh, unpublished data).

The placenta studies from Thailand (Table 2) are highly selective: they do not include all pregnant women but only those who had malaria in pregnancy[90] or were selected because they had malaria in the last month of pregnancy[104]. In these 2 prospective studies where all (100%) women had a confirmed malaria infection in pregnancy, only 6.9% (12/173)[104] and 4.4% (7/149)[90] of women had positive placental MS and all of these had concurrent maternal peripheral parasites detected. Detection of malaria in maternal peripheral blood by weekly screening and prompt treatment regardless of symptoms can explain the low proportion of infected placenta.

The sites that used ACTs in pregnancy at the time of the study (TBB and Indonesia) had less placentas positive MS compared to peripheral positive maternal MS at delivery than the sites that used CQ and/or SP (India and PNG) (Table 2 and Figure 5) where *P. falciparum* resistance to CQ and SP was reported to be high. Despite differences in transmission this may reflect effective clearance of parasites from the maternal and placental blood by the more effective ACTs.

Symptoms

Theoretically all malaria infections could become symptomatic if left untreated in areas with low acquired malaria immunity. Recognition of symptoms in pregnant women attending the ANC needs careful history taking by health care workers and is often not done properly[28]. In the studies from APR reported here there is no clear definition what is a symptomatic malaria episode; some authors use fever or a history of fever, others include symptoms such as headache. Obviously, the frequency of screening has an impact on symptoms, as the incubation period after an infectious bite is 7-30 days.

Self treatment with anti pyrexia or antimalarials has also an impact on symptoms. Taking all these factors into account, 30.6% [15.8%-51.2%] of malaria positive women who were screened once during pregnancy had symptoms. The corresponding figure for pregnant women who were found malaria positive at delivery is 38% [0%-64%]. These data should be interpreted carefully and not necessarily used for comparisons because the women who come to the clinic or for delivery to the hospital may not be representative for the whole population of pregnant women. The parasitaemic women without symptoms may have used anti pyretic or antimalarial self medication, have a very low parasite counts or may have some background immunity.

Although *P.vivax* has a lower pyrogenic density than *P.falciparum* fewer women infected with *P.vivax* presented with symptoms[95, 120], making *P.vivax* infected women less likely to seek treatment. This may reflect a more rapid development of maternal immunity against *P.vivax* as observed in children. Even though the point prevalence of (symptomatic) MIP can be low, malaria is still responsible for a substantial proportion of serious illness requiring hospital admission for pregnant women[29]. In India the proportion of malaria infected women at ANC

enrolment was 1.8% (43/2382), whereas 19.2% of the hospital admissions of pregnant women in the study period were malaria related[29]. This suggest that malaria, especially when caused by *P. falciparum*, is responsible for a substantial portion of serious illness requiring hospital admission for pregnant women in this region and may reflect late detection or inefficient treatment. During an epidemic in India 274 women were screened every 25 ± 5 days, 60% of the parasitaemic episodes detected were associated with symptoms (fever, headache, joint pains) and the proportion of infections that were symptomatic was identical in all parity groups[36].

Primigravidae, women with fever or history of fever, residence in rural areas and ethnicity are significantly associated with peripheral parasitaemia[29, 120]. Women with a history of malaria infection during pregnancy are at increased risk for another episode of MIP[120]. Persistent parasitaemia throughout pregnancy have been described in India and PNG[38, 70].

Anemia

The anaemia burden in pregnancy in Asia Pacific is huge: around 75% of the women attending the ANC in India[29, 36], Nepal[125], PNG[61] or on the TBB[6] developed anaemia at some stage of pregnancy. Malaria induced red blood cell destruction aggravates an underlying nutritional anaemia, intestinal parasitation and/or red cell genetic abnormalities, such as haemoglobinopathies [146, 163]. In low transmission areas mild anaemia predominates whereas in areas of high transmission 5-10% of pregnant women might develop severe anaemia [6, 15, 61, 65, 158]. Both falciparum and vivax malaria worsen anaemia, and reduce serum ferritin, but *P.falciparum* has a stronger effect than *P.vivax* [14, 30, 120, 125].

As expected all studies showed a relationship between malaria in pregnancy and anemia at delivery. Even asymptomatic malaria episodes result in anemia[120]. Multigravidae are more anaemic than primigravidae [6, 15, 62, 75, 120]. Maternal (severe) anaemia during pregnancy increases the risk for PTL[55, 120], stillbirth and abortion[56, 75], reduces birthweight[15, 61] and was an independent risk for infant death in early studies in Thailand[76, 157], but not in a more recent study[6]. This may be explained by the multi factorial causes of anaemia in Thailand, and co-deficiency in vitamin B1 in the infant, which was a major cause of infant mortality[164]. Data from Thailand suggests that there is an increased risk of *P. vivax* malaria associated with recent start of haematinic supplementation (iron and folate) [109].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is common in APR, but its interaction with the risk of malaria in pregnant women and anaemia is unknown. The genetic traits of Southeast Asian ovalocytosis and α-Thalassemia have been examined in relation to malaria in

pregnancy in two studies on the North Coast of Papua New Guinea. Although Southeast Asian ovalocytosis and α-thalassaemia protect young Papua New Guinean children against cerebral malaria[165, 166], neither trait appears to alter the manifestations of malaria in pregnancy[62, 64, 65]. Parasite prevalence and density and pregnancy outcome did not differ between women with and without these traits, with the exception of lower mean haemoglobin levels in women with α-thalassaemia than in controls, which appeared not to affect pregnancy outcomes.

Pregnant women are more susceptible to thrombocytopenia, the risk of low platelets in *P.falciparum* and *P.vivax* infections is greatest in the first malaria infection in pregnancy and most women experience low platelet counts (below 50,000/μL)[30, 93]. Prompt antimalarial treatment can normalise platelet counts within a week[93]. Malaria induced thrombocytopenia and anaemia may be related to a higher risk of post partum haemorrhage[58].

Co-morbidities

A relation between maternal malaria and pre-eclampsia is suggested from studies from high endemic areas Senegal, Kenya and Tanzania [167-169], but as far as we know no such reports are available from APR, except in one report from 1935 in an epidemic situation[134]. The burden of malaria has been exacerbated by the introduction of HIV, which increases the susceptibility to MIP, reduces the efficacy of IPTp and complicates the use of antimalarials because of potential drug interactions[170]. We could find no study on the interaction between malaria and HIV in APR. HIV prevalence is low[171] or not reported in MIP studies from Asia Pacific.

Recent studies from APR report an association with lower rates of *P.falciparum* or *P.vivax* infection in women co-infected with *A. lumbricoides* [89, 172, 173], but hookworm infestation was associated with an increased risk of *P.falciparum* [89]. If *A. lumbricoides* co-infection does indeed attenuate malaria, then mass deworming policies [174-177] may reduce a potential protective benefit. On the other hand, reported hookworm associations with malaria[89], LBW[89, 178, 179] and anaemia [180-183] suggesting that hookworm should be treated in pregnancy. An integrated approach to malaria and helminth control has been promoted for pregnant women [184], but local prevalence and intensity of geohelminths, malaria, and anaemia severity should be taken into account [89]. About 10% of women with malaria had rickettsial co-infection in a cohort study on the TBB[185]; this was associated with increased morbidity.

Severe malaria and mortality

In areas with low and seasonal patterns of malaria transmission a state of immunity is not attained by adulthood and severe disease may occur at all ages[15, 78]. Detailed malaria-attributable maternal

mortality rates (MMR) are rarely reported. However, in three districts in India 23% (22/95) of maternal deaths were attributed to malaria (total MMR 722 per 100000 live births) between 2004 and 2006[136]. In this report malaria was the most common cause of maternal death during the ante-partum period (48%; 11/23) and malaria was responsible for 23% (6/26) of post partum maternal deaths. In western Thailand 1.7% (5/300) of all pregnant women died of malaria in a single year before the introduction of malaria control programmes for pregnant women[15].

Syndromes that are relatively rare in childhood, e.g. acute renal failure, pulmonary oedema and severe jaundice are common manifestations of severe malaria in adults[57, 78]. In these settings women are reported to die during pregnancy or just after delivery from cerebral malaria, renal failure, hepatic impairment, severe anaemia, hypoglycaemia (worse with quinine treatment), uncontrollable post partum haemorrhage or adult respiratory distress syndrome [15, 35, 57, 134, 135, 137].

Pregnant women are three times more at risk for severe malaria than non pregnant women[78, 159]. In eight studies that reported details of severe malaria in pregnant women (total patients n=227) the maternal mortality was median [range] 39 [8 -100]%[35, 43, 52, 57, 135, 138, 160, 186]. This wide range is related to the broad definition of severe malaria: the lowest mortality was reported in pregnant women when the diagnosis of severe malaria was mainly based on hypoglycaemia[135], whereas all women with renal failure died[57]. In an autopsy study in 277 women in India, 10% of maternal mortality cases were due to infectious diseases of which tuberculosis, malaria or leptospirosis were the most common[47]. Severe *P.vivax* malaria in pregnancy is related to very poor pregnancy outcomes and even maternal mortality [30, 39, 143]. An "action for survival" program of dedicated care for pregnant women with malaria reduced the mortality dramatically in a regional hospital in Thailand where malaria was the most common cause of maternal death during the 1980s[110]. The early detection and treatment programme on the TBB has eliminated maternal death and made severe malaria in pregnant women a rarity among the women that follow the weekly screening[15].

Impact of MIP on the fetus and infant

Effect on pregnancy outcome

The median [range] reduction in birth weight in the reviewed studies was 150 [62-780] grams for *P.falciparum* and 108 [107-390] grams for *P.vivax* malaria[6, 14, 15, 29, 36, 37, 41, 44, 55, 62, 120]. This effect of birth weight reduction was seen for *P.falciparum* mainly in primigravidae, but for *P.vivax* also in multigravidae[14]. Reduction of birth weight occurred even in pregnancies with a single episode of *P.vivax* or *P.falciparum* malaria[14, 15, 104]. Both symptomatic and asymptomatic malaria episodes increased the risk of LBW, although symptomatic malaria infections in pregnancy may have a larger impact [15, 120]. Symptomatic malaria infection close to delivery increases the risk of PTL, and together with severe anaemia and primigravidity represents one of the major risk factors of low birth weight in malaria endemic settings [6, 120, 137]. However malaria also reduces birth weight independently of nutritional anemia[61]. McGregor showed an exponential fall in risk ratio for LBW in primigravidae following reduction in malaria transmission in the Solomon Islands[126, 187].

The question of how malaria reduces birth weight does not find an answer in this review, in particular the effect of *P.vivax* which has not been demonstrated to cyto-adhere in the placenta like falciparum; LBW alone is not be a reliable indicator, other information such as parents anthropometric data, gestational age, newborn length and head circumference are required[188]. Reported birth weights are subjective to many factors, such as accuracy in gestational age estimation, day of weight, parity, maternal height, body mass index, socioeconomic status of the family, number of antenatal clinic visits, ethnicity, pregnancy or medical conditions [55, 139, 188].

Gestational age estimation is notoriously difficult in resource poor settings; ultrasound dating for example, the gold standard for gestational age estimation and population specific fetal size charts to diagnose IUGR were not available in these studies[188].

Fetal distress (measured by cardiotocography or meconium staining of the amniotic fluid) is reported to be an important feature of symptomatic falciparum malaria and severe anaemia, before and during labour[75, 135]. Stillbirth and miscarriage/spontaneous abortion are consequences of *P.falciparum, P.vivax* and severe anemia[56, 61, 75]. In areas where women come late to ANCs or just attend for delivery, miscarriage rates are likely to be underestimated. In an intense antenatal malaria screening and prompt treatment program at the TBB *P.vivax* infection was not associated with PTL, miscarriage or stillbirth[14], whereas among 25 unwell Indian pregnant women, admitted in a hospital because of *P.vivax,* more than half of the pregnancies ended with abortion, fetal death or PTL [30]. This stresses the significance of early detection and treatment of MIP.

Congenital malaria

Congenital malaria occurs when malaria parasites cross the placenta either during pregnancy [121] or delivery[96]. It is usually defined as the presence of asexual forms of malaria parasites in the peripheral blood within the first 7 days of life [189], however cases up to several weeks postpartum have been described. Congenital malaria is a potentially serious complication of maternal malaria, but symptoms usually appear only after 10-30 days of age [96, 121, 189]. Table 4 shows the prevalence of congenital malaria in studies from Asia Pacific. In a series of 27 congenital malaria cases the average (mean ± SD) interval from the malaria episode in mothers to their delivery was 16.4 ± 6.8 weeks and 85% of the cases was a *P.vivax* infection, and all mothers and nearly all newborns were asymptomatic [96]. However *P.falciparum* and *P.vivax* congenital malaria can be a severe disease[96, 121]. In Timika (Papua, Indonesia), of 967 neonates admitted to the hospital 9% (87) had malaria, with P. vivax accounted for 48% of the infections. Severe anaemia and respiratory distress characterizes severe manifestation of malaria in these neonates, which quickly resolves following early diagnosis, prompt malaria treatment and adequate supportive therapy[190]. All sick neonates in malaria endemic regions should have a malaria smear[121] and all babies in such areas whose mothers had fever or malaria peri-partum should be followed closely. There are no WHO criteria for diagnosis and treatment of severe malaria in neonates.

MIP and infant survival

MIP has a direct impact on infant survival. In Thailand maternal infection within the week before delivery was the only risk factor for infant death in the first 3 months of life[6]. The infant mortality in the offspring of women who were anaemic at delivery was significantly higher than in the offspring of women who were not anaemic, independent of gravidy, LBW or prematurity[76, 157], but as explained above this may be explained by the multi factorial cause of anaemia, including vitamin deficiency. In PNG a surprisingly large group of stunted children in a specific age group was found in an malaria epidemic area[191]. The timing of the epidemic was such that most of these stunted children were in utero or newborns during the malaria epidemic. Severe maternal illness and death was reported from the epidemic, which affected the growing foetus. The effects of adverse intrauterine environmental factors on nutritional status, child development and the placental/fetal epigenome need to be studied[192].

Treatment

The management of MIP has been complicated by the emergence of antimalarial drug resistance[120, 161]. Recently, most countries in APR updated their national guidelines on MIP to

WHO recommendations of ACTs in second and third trimester. Table 5 shows the efficacy trials of antimalarials in pregnancy for *P.falciparum* and *P.vivax*. The majority of the treatment trials come from 1 site on the TBB.

Vivax malaria and other non falciparum malaria

Unlike *P.falciparum, P.vivax* develops liver stages (hypnozoites) causing recurrent blood stage infections (relapses), gametocytes appear early, *P.vivax* transmission occurs at low parasite densities already and *P.vivax* has a preference for infecting reticulocytes (young red blood cells) [148]. As a consequence vivax malaria usually does not result in high parasite burdens like *P.falciparum* which invades red blood cells of all ages. Primaquine, the only drug against liver stages is contraindicated in pregnancy and lactating women because of the susceptibility of fetal red blood cells to haemolysis and the inability to routinely assess G6PD status of a fetus in utero [193]. Cytoadherence and/or sequestration of *P. vivax*-infected RBCs has been described recently[194], but it is less widespread and of lesser magnitude than that with *P. falciparum* [148] and the relevance to adhesion in the placenta is unknown.

Ten years ago chloroquine (CQ) had day 28 cure rates of more than 95% in 111 pregnant women in the first trimester with vivax malaria in Thailand and in 2 patients from PNG[60, 108] (Table 5). Currently *P.vivax* resistance to CQ has been reported in the general population in several parts of APR [195]. At present only Indonesia, Solomon islands and Vanuatu have changed their national treatment for *P.vivax* to ACTs, due to high prevalence of CQ resistant parasites[196]. CQ showed no effect against *P.falciparum* in pregnant women in India during a malaria epidemic in 1997-1998[36]. No recent data of CQ efficacy in pregnancy is available, but CQ resistant vivax malaria in a pregnant woman is reported on the TBB[197]. Chloroquine remains the drug of choice for uncomplicated *P.knowlesi, P.malariae* and *P.ovale* [116].

Falciparum malaria

In a small pharmacokinetic study in PNG 13 women were treated with the combination SP+CQ, which showed a low cure rate of 62%[59, 60] (Table 5). The average cure rate of quinine monotherapy (6 studies, 802 patients) was 74.2%, probably due to resistance and poor adherence to 7 days of therapy. When clindamycin was added to quinine and the treatment supervised (1 study, 65 patients) the cure rate improved significantly to 100%[103]. Mefloquine monotherapy (1 study, 194 patients) showed a cure rate of 72%, but in combination with artesunate the cure rate reached 100%[79, 81, 101]. Artemisinin combination therapies (Dihydroartemisinin piperaquine (DHAPPQ), Artesunate Clindamycin (AC), artemether-lumefantrine (AL), artesunate-

atovaquone-proguanil (AAP)) showed all cure rates above 90%, except for AL. In a study on the TBB 125 pregnant women treated with AL for 3 days the cure rate was only 87%, inferior to seven days of artesunate monotherpy[90]. Quinine and clindamycin resulted in low failure rates on the Thai-Burmese border but the gametocyte carriage rate post-treatment in women who did not have them on admission was 13-fold higher than with a 7-day course of artesunate monotherapy[161].

There has been no treatment study for severe malaria in pregnant women. However, in line with the striking effect of intravenous artesunate in the treatment of adults[198] and children, this drug should be used in pregnant women with severe malaria.

In practise health workers providing malaria drug in the field may not prescribe correct doses[122] or are afraid to give drugs to pregnant women because of concerns of potential teratogenic effects or abortion[122, 129]. Recommendations on the regimens to use for the treatment of complicated or uncomplicated malaria during pregnancy are notably absent in the field settings [28] but WHO guidelines do recommend ACTs (uncomplicated) and artesunate (severe). A major disconnect has been identified between routine antenatal practices and known strategies to prevent and treat malaria in pregnancy [28]. DHAPPQ showed to be effective in Indonesia for both *P.falciparum* and *P.vivax* [120]. The main difficulty remains the treatment in the first trimester.

Pharmacokinetics of antimalarials

Most 62% (13/21) of all pharmacokinetic studies of antimalarials in pregnancy have been carried out in APR. A wide range of drugs have been studied including quinine (Q)[199], mefloquine (MFQ) [86, 113], chloroquine (CQ) [60, 200], sulphadoxine-pyrimethamine (SP) [59], artemether-lumefantrine (AL) [94, 99], proguanil[107, 201], artesunate[100]-atovaquone-proguanil[106] and azithromycin[202] compared to Q[203, 204], CQ[205, 206] and SP[207, 208] and artesunate [209] in Africa, with one study on atovaquone-proguanil in Zambia and Thailand[114]. Most report reduced drug concentrations in pregnancy and the need for dose alterations. Given the pharmacokinetic derived half life of the longer acting antimalarials, if IPT is to be used, monthly treatment doses would be required[210].

Prevention

Prevention of malaria in pregnancy is not a frequently highlighted objective in national guidelines for malaria in the SEAR and WPR countries. Long lasting insecticide treated bednets (LLITN) are distributed in all countries, but recent studies showed low availability or utilisation of ITNs among pregnant women[28, 118, 128]. Case management is available in all countries, but in reality blood smears were only obtained from pregnant women when fever or other malarial symptoms were present, if checked at all by health workers[28]. PNG is the only country with an IPTp policy. Chemoprophylaxis in pregnancy has been studied with different result for different species.

Interestingly implementing an effective ACT (e.g. mefloquine artesunate) in the general population on the TBB reduced the incidence of *P.falciparum* in the pregnant women population dramatically [87] and is seen as the best preventive method implemented so far in this community. Here we report the data about efficacy of malaria prevention in pregnancy.

Vector control

Vector control measures aiming at total population coverage benefit pregnant women. In Africa, but also in the APR, ITNs and IRS have been shown to reduce malaria transmission effectively[211]. If population-based vector control is a well-documented intervention, very few studies have examined the impact of transmission reduction measures targeting pregnant women in the APR. In the only study of bednets which randomised women to ITNs or untreated nets on the TBB, fewer women in the ITN group experienced peripheral parasitaemia than untreated nets, but this was not significant[76, 212]. The parasite density and frequency of anaemia was lower in the pregnant women with an ITN. There was no effect on birth weight or premature delivery, but there were significantly less fetal losses in the ITN group[76]. In India most women reported to have untreated bed nets in their homes, but very few had ITNs (3.3% 79/2386)[29]. Free ITNs for pregnant women were not distributed despite government policy, primigravidae have less bednets and CQ chemoprophylaxis coverage low in Solomon Islands[128, 129]. The species of mosquito vectors that contribute to malaria transmission in most APR countries exhibit exophilic and exophagic behaviour, which means they spend most of the time outdoors, prefer to bite outdoors and are most active in the early evening when most people are still active or dawn (crepuscular vectors) [25, 213, 214]. Several studies report that in communities priority to sleep under the ITN is given to young children[129, 130, 215].

Repellent with DET (N,N-Diethyl-meta-toluamide) is safe in pregnancy, can reduce exposure to insect bites and showed a reduction in the incidence of *P.falciparum* in pregnant women [77, 83, 85],

but this was not significant possibly due to low malaria transmission and small sample size. The popularity of the combination of thanaka (a popular local cosmetic in Thailand) and DET and compliance of this product suggests it could be evaluated in other areas of low (but not very low) transmission where control of malaria in pregnancy is hampered by multidrug-resistant parasite strains[85]. The role of indoor residual spraying in the prevention of MIP has not been evaluated in APR.

Chemoprophylaxis and IPT

A retrospective analysis of CQ chemoprophylaxis in pregnant women from PNG showed that CQ did not reduce placental or maternal peripheral blood infection at delivery in an area where CQ resistance was high [55]. In a double blind RCT of CQ chemoprophylaxis on the TBB CQ prophylaxis prevented *P. vivax* episodes[95], but had no impact on *P.falciparum* episodes in pregnancy. Mefloquine chemoprophylaxis gave 86% protection against *P.falciparum* and complete protection against *P.vivax* infection in a double-blind, placebo-controlled study on the TBB conducted when MFQ was still fully effective [157]. In PNG the prevalence of placental and maternal peripheral blood parasitaemia and density of parasitaemia was not different in women who did or did not take CQ chemoprophylaxis during pregnancy, but Hb concentration after delivery was higher in women who took CQ[55]. Weekly chloroquine prophylaxis showed poor parasite clearance despite good compliance in a longitudinal study in PNG[70]. A low proportion of pregnant women were using CQ chemoprophylaxis in India, PNG and Solomon Islands[29, 128, 216].
The only IPTp study available from APR is a pharmacokinetic report of CQ-SP (CQ 3 tablets daily for 3 days and SP single dose) in pregnant women: it prevented all vivax episodes but 5/13 women had another *P.falciparum* infection within 28 days[59, 60].

Intermittent screening and treatment

The rationale behind this preventive strategy is to screen pregnant women frequently in order to detect and treat any malaria parasitaemia in an early stage with an effective drug. Since the implementation of early detection and treatment by weekly screening of pregnant women on the TBB severe malaria and mortality among the women that attended weekly was eliminated[15]. Sensitive methods of parasite detection are required with this method, such as intensive training and ongoing quality control of microscopists. Consequently its main limitations are the logistic constraints and the costs. There is no data available about effectiveness and safety of programs that screen less frequently.

Discussion

Although considerable effort in malaria control has resulted in a marked declining of number of malaria deaths in the general population [24], MIP is often not recognised as a priority in APR. This may be due the paucity of data on the burden of MIP in this area. Not all national treatment guidelines reflect WHO treatment recommendation, health providers do not follow treatment guidelines[122] and prevention strategies have no focus on pregnant women[45].

In recent population at risk calculations a significant proportion of the world pregnancies at risk for malaria live in Asia Pacific, mainly India and China. However, the majority of pregnant women will not be infected as malaria transmission is generally low, highly focal and often seasonal. Specific foci within the APR have high transmission of malaria. This makes the prevention of MIP complex, but essential as potential malaria outbreaks could threaten a large number of pregnancies in APR.

The MIP evidence available from APR is presented in this review, but a limitation is that most of the articles came from three countries and may not reflect the situation in all 20 countries. This may due to the fact that not all national medical journals are found on PubMed.

Pregnancy is a 40 weeks long period, where recrudescent malaria infections could be harboured until delivery causing double trouble. Even a single (asymptomatic) malaria infection in pregnancy is harmful for the mother and the baby. Prevalence surveys may show a relative low proportion of women at one time point, but due to the nature of pregnancy the clinical impact of a single infection is carried all the way through and potentially into the puerperal period and later infant life. The effect on firstborn babies is similar as in high endemic settings, but mothers have no or little immunity and are at higher risk of severe malaria and death. Malaria detection by cross sectional surveys at the ANC, in the delivery room, by placenta smears or histopathology do not reflect the true burden of MIP in low endemic areas or in areas where ACTs are used in pregnancy. Longitudinal follow up of each individual woman throughout pregnancy informs us about the impact of MIP on mothers and their children, as frequent peripheral malaria smears in migrant pregnant women on the TBB proved to be a more sensitive measure of MIP than placental histopathology [90, 104]. Inviting all women to come for ANC visit as soon as they are aware of their pregnancy and using a longitudinal follow up approach will inform about the true burden of MIP in APR and could be the tool to prevent severe malaria in pregnancy, but this is difficult to implement.

Although all gravidae are at risk for serious maternal and fetal complications of vivax and falciparum malaria, the highest prevalence of MIP is in primigravidae and in the second trimester, indicating that malaria prevention in malaria endemic areas should start early in pregnancy. All people living in malaria endemic areas, but especially adolescent- non pregnant - women should be targeted to be informed about the dangers of MIP and the what can be done to prevent it.

In Africa much effort has been put into IPTp SP and ITNs [212], next to case management. The focal nature of malaria transmission and multidrug resistance makes IPTp or chemoprophylaxis in APR difficult. The number of women in the single IPT study in APR is too small to conclude on effectiveness, but CQ and SP were lost to *P.falciparum* resistance in the general APR population many years ago. IPTp with a drug that does not completely eliminate and prevent infection can be harmful; e.g. IPTp SP (when SP resistance is present) may select for increased level of resistant parasites in the placenta[217]. Ideally the antimalarial for IPTp provides clearance of existing (asymptomatic) (placenta) *P.falciparum* and *P.vivax* infections (treatment effect) and being a slowly eliminated drug, preventing new infections (prophylactic effect)[210]. To realize this aim the antimalarial drug, timing and dosing should guarantee adequate suppressive drug levels throughout pregnancy[18, 210]. Pharmacokinetic studies suggest changing the dose of antimalarials in pregnancy, and when IPTp is considered monthly treatment doses of antimalarials may be required. The safety profile of any drug to be used for IPTp needs to be excellent, well tolerated, easy to use and affordable, as a large number of uninfected pregnanct women will be exposed to this drug [18]. DHAPPQ seems to be the most promising candidate.

The single study of MFQ in Asia showed good prophylaxis against vivax and falciparum malaria[157], but MFQ has fallen to resistance, and was never deployed in Thailand. CQ was effective in prevention of *P.vivax* in pregnancy, but had no effect on *P.falciparum* or birth outcomes [70, 95]. Most countries in APR have a policy of distribution of ITNs, but not specific for pregnancy. Protective efficacy of ITNs in APR is modest and not as convincing as studies in African pregnant women [76, 212], but studies are few. Most effects of ITNs can be expected with vector species that are highly endophagic, anthropophilic and bite mostly during the time when people are under the nets. In APR there are no species that consistently combine all these favourable characteristics[213]. In reality the number of pregnant women who use an ITN is low. Furthermore relapses of *P.vivax* or reappearance of inadequately treated infections are not prevented by ITNs.

This said, implementing an effective ACT (e.g. mefloquine artesunate) in the general population in Thailand reduced the incidence of *P.falciparum* in the pregnant women population by > 90% [87]. In SEAR most *P.falciparum* infections are seen in adult males, the persons who work in the forests where they get the infections [97, 98]. Introduction of ACTs in the community reduce malaria transmission by their anti gametocyte properties. Interventions against MIP should always be part of a strategy that includes the whole population.

When a malaria infection could not be prevented accurate diagnosis and prompt treatment with efficient drugs is required of any detected parasitaemia. However, a quantity of the *P.falciparum* and *P.vivax* infections in the APR studies are asymptomatic at the moment of detection. This reflects that there may be some sort of background immunity present in pregnant women in APR. Such infections are likely to remain undetected and untreated in the WHO strategy of case management of malaria illness, but are deleterious to the mother and the fetus. Routine screening of malaria parasites in the peripheral blood by MS, RDT or PCR, can detect asymptomatic parasitaemias. However, submicroscopic parasite densities (biomass less than 10^8 parasites) in the peripheral circulation and parasites sequestered in the placenta are missed by the current methods of detection, but could still lead to adverse effects in the mother and the baby. Furthermore regarding the low sensitivity of MS in field situations the actual rates of MIP infection may be much higher as shown by PCR data from non pregnant patients and unpublished work in pregnant women. There is need for improved diagnostics to measure the impact of MIP.

Multidrug resistant *P.falciparum* parasites have spread all over the world and CQ resistant *P.vivax* is spreading. WHO recommends –evidence based- ACTs to be first line treatment in second and third trimester of pregnancy. The aim of treatment is to effectively eliminate all parasites from the woman's peripheral and placental blood[161]. Several factors contribute to the poorer treatment responses during pregnancy; *P. falciparum* parasites sequester in the placenta and so the parasite burden is underestimated, antiparasitic immunity is compromised, and antimalarial drug concentrations are generally lower[90]. Interestingly AL is recently introduced as first line treatment in many APR countries without efficacy data in pregnancy, except in Thailand where it was less than 90%. Efficacy of AL in MIP needs to be carefully monitored and dose optimization is urgently needed[94]. Interestingly the simple 3-day regimen of DHAPPQ, its low price, fast clinical response, and post-treatment prophylactic effect offered substantial benefits over AL in the general population of Papua Indonesia[218]. This should be confirmed in pregnant women as soon as possible.

Quinine monotherapy, still recommended in APR countries, had unacceptable low cure rates in Thailand. Clindamycin should be added to Q for the treatment of first trimester infections in APR and women recommended to protect themselves from mosquito bites as this treatment in pregnant women may result in high gametocyte rates. This increased gametocyte carriage rate with Q (+/-C) is not fully recognized in current treatment guidelines.

In areas where intensive control measures using ACTs have been implemented to eliminate malaria, the proportion of malaria due to *P.vivax* usually remains stable or increases when compared with *P.falciparum* [87]. As primaquine cannot be used in pregnancy, pregnant women are likely to remain the carriers of vivax malaria when eradication campaigns against vivax will take place in the future. CQ resistant vivax spreading in the general population in APR will have its impact in pregnant women as well. In areas where differentiating *P.falciparum*, *P.vivax* or mixed infections is not possible a single treatment across species with an ACT should be considered.
Ongoing MIP studies in e.g. Cambodia, India, Indonesia, Solomon Islands, PNG and Thailand will inform us about the burden of falciparum and vivax MIP, efficacy of prevention strategies and ACTs.

The frequent intermittent screening and early treatment (IST) programme for malaria infection in each woman at each antenatal clinic visit proved to be successful in reducing the devastating effects of MIP in Thailand [15]. This strategy could reduce the burden of MIP while limiting the potential for antimalarial resistance to develop and unnecessary drug exposure in pregnancy due to the widespread use of drugs for chemoprophylaxis or IPT. Any women with a proven malaria infection in pregnancy should be followed closely throughout the rest of pregnancy, as parasites are likely to recur[15, 90, 120]. The best feasible option in terms of frequency of screening, ideally weekly, has to be determined before this could be deployed in other countries. This could take place in the antenatal clinics, where midwifery or health worker staff are trained in early detection and treatment policy. As a minimum the recommended frequency of at least four antenatal care visits must include parasitological diagnosis and the frequency of these recommended visits may be reconsidered in malaria endemic areas where effective prevention MIP strategies do not exist.
Research on efficacy and effectiveness of IST should be given a high priority and national programs already implementing IST should ensure good routine monitoring and rapid publication of their data.

Conclusion

Large numbers of pregnancies are at risk for *P.vivax* and *P.falciparum* malaria in APR. However, malaria transmission in APR is low, unstable, highly focal and seasonal. A smaller number of women will be infected during pregnancy, but any asymptomatic parasitaemia, even a single infection, is harmful and can be fatal for the mother and the foetus. Therefore early detection and prompt treatment with an effective antimalarial drug should be available to all pregnant women in this region. ACTs should be first line treatment of MIP policy in APR for *P.falciparum* and probably *P.vivax* infections, as they result in rapid clearance of parasites and a reduction of placenta malaria. Intravenous artesunate should be the life saving treatment of choice in severe malaria. Since AL is introduced as first line treatment, its efficacy should be monitored carefully as a single study from APR showed a low cure rate, probably due to altered pharmacokinetics in pregnant women. DHA PPQ was safe and efficient in Thailand and Indonesia and should be confirmed in other areas as well. The treatment of first trimester infections remains difficult, safety data of ACTs in the first trimester is urgently needed. Quinine has low cure rates and resulted in high gametocyte carriage in pregnant women.

Currently, intensive (weekly) screening during pregnancy is the best available evidence at the moment in reducing the adverse outcomes of maternal malaria. The effectiveness of modified intermittent screening and treatment in areas with limited capacity and accessibility to health care should be defined. In addition, the suitability of IPT in pregnancy in low to moderate malaria transmission area should be carefully reviewed. Interventions against MIP should always be part of a strategy that includes the whole population, but adolescent women should be targeted with education about the risk of MIP and provided with methods to prevent MIP (e.g. vector control by LLITN). Given the varying level of malaria transmission within countries in APR, the National MIP programming in this region should apply a site-specific approach rather than a nationwide policy. More data is urgently needed on the epidemiology of MIP in the region and also more evidence is needed on which to base the policies for treatment and for prevention of MIP in APR.

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Tables

Table 1 Point prevalence of malaria in pregnancy in Asia Pacific Region in the antenatal clinic

Country	Screening method	Total women	% women with malaria	Total women with malaria	special group	Proportion of infections by species						
						Pf %	Pf (N)	Pv %	Pv (N)	Mix %	Mix (N)	Other species
PNG (1990)[70]	MS	620	29.0	180		94.4	170	5.0	9	n.a.	n.a.	Pm 1
PNG (1990)	MS	472	23.3	110		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
India (1993)[44]	MS	322	57.7	186	h.o.f.	60.2	112	37.6	70	2.2	4	none
India (1995)[42]	MS	831	17.4	145	h.o.f.	69.7	101	28.3	41	2.1	3	none
India (1999)[41]	MS	2127	17.2	365	h.o.f.	66.8	244	33.2	121	none	none	none
Nepal (2000)[125]	MS	288	19.8	57		0	0	100	0	none	none	none
Laos (2000)[133]	MS	68	23.5	16	h.o.f.	100	16	n.a.	n.a.	none	none	none
India (2004)[137]	MS	n.a.	n.a.	215		60.9	131	32.0	69	7.0	15	Po 1
Solomon (2008)[128]	MS	106	17.9	19		78.9	15	21.1	4	0	0	none
Solomon (2008)[128]	PCR	106	17.9	19		78.9	15	5.2	1	15.8	3	none
Indonesia (2008)[120]	MS	2984	22.4	669	ward	62.6	434	27.2	189	6.6	46	Pm 22, Po 2
India (2009)[29]	MS	2386	1.3	32		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	none
India (2009)[29]	RDT	2386	1.8	43		53.5	23	37.2	16	9.3	4	none
Burma (2010)[118]	RDT	850	11.8	100		100	100	n.a.	n.a.	n.a.	n.a.	n.a.
Bangladesh [n.p.]	MS	388	3.9	15		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
India [n.p.]	MS	2696	1.2	33		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	none
India [n.p.]	RDT	2696	1.3	35		82.8	29	17.2	6	none	none	none
PNG [n.p.]	MS	468	40.1	191		74.3	142	20.0	38	n.a.	n.a.	Po 11
PNG [n.p.]	PCR	468	65.6	307		70.7	217	n.a.	n.a.	n.a.	n.a.	Po 52
Indonesia [n.p.]	MS	1551	15.3	238		57.9	138	28.5	68	12.6	30	none
Indonesia [n.p.]	MS	1554	13.3	207		67.1	139	28.9	60	3.8	8	none

h.o.f. history of fever, MS malaria smear, n.a. not applicable, n.p. not published, Pf Plasmodium falciparum, Pm Plasmodium malariae, Po Plasmodium ovale, Pv Plasmodium vivax, PNG Papua New Guinea, RDT rapid diagnostic test

Table 2 Point prevalence of MIP in APR in the delivery room

Source	Site	Screening method		Total women	% women with malaria	Total women with malaria	Proportion of infections by species						
							Pf %	Pf (N)	Pv %	Pv (N)	Mix %	Mix (N)	Other species
India (1999)[41]*	Jabalpur	MS	M	2127	17.2	365	66.8	244	33.2	121	none	none	none
India (2003)[39]	Maihar	MS / RDT	P	182	29.1	53	92.4	49	1.9	1	5.7	3	none
India (2005)[37]	Mandla	MS	M	209	5.3	11	63.6	7	0	0	36.4	4	none
India (2005)[37]	Mandla	MS	P	209	14.4	30	86.7	26	0	0	13.3	4	none
India (2005)[37]	Mandla	RDT (PC)	P	209	26.8	56	100	56	n.a.	n.a.	n.a.	n.a.	n.a.
India (2005)[37]	Maihar	MS	M	590	6.9	41	70.7	29	24.4	10	4.9	2	none
India (2005)[37]	Maihar	MS	P	590	10.8	64	84.4	54	12.5	8	3.1	2	none
India (2005)[37]	Maihar	RDT (PH)	P	590	11.0	65	100	65	n.a.	n.a.	n.a.	n.a.	n.a.
India (2009)[29]	Jharkhand	MS / RDT	M	718	1.7	12	75.0	9	16.7	2	8.3	1	none
India (2009)[29]	Jharkhand	MS	P	712	1.4	10	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
India (2009)[29]	Jharkhand	RDT	P	712	2.4	17	70.6	12	11.8	2	17.6	3	none
India (n.p) Singh	Chhattisgarh	MS	M	1028	1.5	16	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
India (n.p) Singh	Chhattisgarh	RDT	M	1028	1.8	19	68.4	13	26.3	5	5.3	1	none
India (n.p) Singh	Chhattisgarh	MS	P	1027	1.7	17	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	none
India (n.p) Singh	Chhattisgarh	RDT	P	1027	3.3	33	54.5	18	36.4	12	9.1	3	none
Thailand (2008)[90#]	TBB	MS	M	169	4.7	8	62.5	5	1.8	3	0	0	0
Thailand (2008)[90#]	TBB	PCR	M	169	3.0	5	100	5	n.a.	n.a.	n.a.	n.a.	n.a.
Thailand (2008)[90#]	TBB	MS	P	156	4.5	7	85.7	6	14.3	1	0	0	0
Thailand (2008)[90#]	TBB	PCR	P	168	3.6	6	100	6	n.a.	n.a.	n.a.	n.a.	n.a.
Thailand (2004)[104#]	TBB	MS	M	175	10.9	19	63.2	12	36.8	7	0	0	Pm 2
Thailand (2004)[104#]	TBB	MS	P	173	6.9	12	91.6	11	8.3	1	0	0	0
Thailand (2004)[104#]	TBB	Histopath	P	174	21.3	37	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Sol Is (1983)[127]	Malaita	MS	M	180	7.8	14	85.7	12	14.3	2	none	none	none
Sol Is (1983)[127]	Malaita	MS	P	180	5.6	10	90.0	9	10	1	none	none	none
Vanuatu (1986)[132]	Malekula	MS	P	184	10.9	20	50.0	10	50	10	none	none	none
PNG (1992)[63]	East Sepik	MS	M	83	8.4	7	85.7	6	14.3	1	n.a.	n.a.	n.a.
PNG (1992)[63]	East Sepik	MS	P	83	19.3	16	100	16	0	0	n.a.	n.a.	n.a.
PNG (1998)[55]	Madang	MS	M	987	18.5	183	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
PNG (1998)[55]	Madang	MS	P	860	24.0	206	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
PNG (2006)[62]	Madang	MS	M	402	15.7	63	93.7	59	6.3	4	none	none	none
PNG (2006)[62]	Madang	MS	P	402	16.4	66	95.5	63	4.5	3	none	none	none
PNG (2006)[62]	Madang	Histopath	P	192	42.2	81	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
PNG (2007)[65]	Madang	MS	M	919	18.7	172	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
PNG (2007)[65]	Madang	MS	P	812	24.2	196	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
PNG [n.p.]	Madang	MS	M	331	7.6	25	80.0	20	20	5	0	0	nil
PNG [n.p.]	Madang	PCR	M	331	42.3	140	72.9	102	n.a.	n.a.	n.a.	n.a.	Po 4
Indonesia [n.p.]	Jayapura	MS	M	830	10.8	90	61.1	55	32.2	29	2.2	2	Po 4
Indonesia [n.p.]	Jayapura	MS	P	818	9.1	75	61.3	46	32	24	4	3	Po 2
Indonesia [n.p.]	Sumba	MS	M	981	11.4	112	64.2	72	31.2	35	4.4	5	none
Indonesia [n.p.]	Sumba	MS	P	974	11.2	109	62.3	68	33	36	4.5	5	none

* history of fever

All women had at least one malaria infection in pregnancy

M mother, MIP malaria infection in pregnancy, MS malaria smear, n.a. not applicable, n.p. not published, P placenta, PC Paracheck, PH ParaHIT*f*, Pf Plasmodium falciparum, Pm Plasmodium malariae, Po Plasmodium ovale, Pv Plasmodium vivax, PNG Papua New Guinea, RDT rapid diagnostic test, Sol Is Solomon Islands, TBB Thai Burmese border

Table 3 Cumulative proportion of MIP in APR

Source	Site	Freq malaria smear	Total women	% women with malaria	Total women with Malaria	Total malaria episodes	Proportion of infections by species						
							Pf %	Pf (N)	Pv %	Pv (N)	Mix %	Mix (N)	Other species
Thailand (1991)[15]	TBB	weekly	1358	37.2	505	888	80.2	712	17.1	152	2.7	24	none
Thailand (1994)[157]*	TBB	weekly	169	21.9	37	89	69.7	62	23.6	21	5.6	5	Pm 1
India (1998)[38]#	Mandla	Fortnightly	150	64.0	96	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Thailand (1999)[14]	TBB	weekly	9956	25.2	2509	2509	55.9	1402	25.3	634	18.8	473	none
India (2000)[34]	Orissa	Fortnightly	209	n.a.	n.a.	92	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Thailand (2001)[6]	TBB	weekly	1495	37.1	555	1096	44.8	491	52.0	570	3.1	34	none
India (2001)[36]^	Mandla	Fortnightly	274	55.1	151	237	85.2	202	11.4	27	3.4	8	None
Thailand (2007)[95]*	TBB	weekly	479	11.9	57	163	47.9	78	50.9	83	n.a.	n.a.	Pm 2
Thailand [n.p.]	TBB	weekly	824	38.7	319	772	22.5	174	76.7	592	0.52	4	Pm 1, Po 1
Thailand [n.p.]	TBB	weekly	100	36.0	36	97	10.3	10	87.6	85	2.1	2	none
India [n.p.]	Jabalpur	monthly	1742	6.0	105	119	73.9	88	26	31	none	none	none

* Placebo group in RCT, # pregnant women with history of fever, ^ during a malaria epidemic

h.o.f. history of fever, N number, n.a. not available, Pf Plasmodium falciparum, Pm Plasmodium malariae, Po Plasmodium ovale, Pv Plasmodium vivax , TBB Thai Burmese border

Table 4 Congenital Malaria in APR

Author/Sites	Study Method	Nr neonates tested	At birth		1 - ≤ 7 days		8 days - <1 month		1 - 3 months		Maternal Malaria	PD
			Pf	Pv	Pf	Pv	Pf	Pv	Pf	Pv		
South East Asian Region												
Sri Lanka (1982) [131]	CR	1	-	-	-	-	-	-	-	1 (S)	History of MIP	n.a.
India (1995)[140]	CR	1	-	-	-	-	-	-	-	1 (S)	h.o.f. in first trimester	n.a.
India (1998)[38]	Prosp	100	-	-	-	-	1 (S)	-	-	-	Peristent parasitaemia	None
Thailand (2004)[104]	Prosp	175	2 (S)	-	-	-	-	1 (S)	-	-	Placental malaria positive	None
Thailand (2006)[96]	Review	27	5 (AS)	20 (AS)			-	2 (S)	-	-	All mothers history of MIP	n.a.
India (2007)[32]	CR	1	-	-	-	-	-	-	-	1 (S)	Peripheral Pv and h.o.f.	None
Thailand (2007)[91]	Review	15	2(AS)	-	1(S)	-	3(S)	3 (S)	1 (S)	5 (1 AS)	h.o.f. except in 1 case	n.a.
India (2010)[141]	CR	1	-	-	-	-	-	1 (S)	-	-	History of MIP	n.a.
India (2010)[142]	CR	1	-	-	-	-	-	1 (S)	-	-	Peripheral Pf and Pv	None
India (2010)[46]	CR	1	-	-	-	-	-	1 (S)	-	-	History of MIP	n.a.
India (2010)[219]	CR	1	-	-	-	-	-	-	1 (S)	-	History of MIP	n.a.
Indonesia (2010)[121, 190]	CS	4884	29 (1S)	6*(AS)	-	-	-	-	-	-	29 PW parasitaemia	5 cases
Western Pacific Region												
Malaysia (1980)[123]	CR	1	-	-	-	-	-	-	1 (S)	-	Placental and peripheral Pf	None
Solomon Island (1983)[127]	CS	180	1(AS)	-	-	-	-	-	-	-	Peripheral Pf	None
PNG (1986)[73]	CR	1	-	-	-	-	-	1 (S)	-	-	Peripheral Pv	None
PNG (1988)[72]	CC	52	4 (AS)	-	-	-	-	-	-	-	Peripheral Pf	None

*also 1 ovale and 2 mixed (Pf and Pv)

AS asymptomatic; CC case control, CR case report, CS cross sectional, h.o.f. history of fever during pregnancy; n.a. not applicable, Pf Plasmodium falciparum, PD Parasite Discordance, PNG Papua New Guinea, Pros prospective study, Pv Plasmodium vivax, S symptomatic, TBB Thai Burmese border

Table 5 Efficacy studies of antimalarials in the Asia Pacific Region

Source	Year Study	Type	FU Days	drug	Size	Cure rate % *	Conclusion or concerns
P.falciparum							
Burma (1988)[119]	1985-86	RCT	7	AMQ	19	100%	Very short follow up
India (2001)[36]	1997-98	Obs	35	CQ	21	5 (0-13.9)	Efficacy <90%,
TBB (1991)[15]	1997-98	Obs	28	Q	405	77.5	Compliance of 7d treatment was poor
TBB (1998)[81]	1992-96	Obs	42	Q	93	77	Efficacy <90%
TBB (2000)[79]	1995-97	RCT	63	Q	43	67.0 (43.3-90.8)	Efficacy <90%, AE
TBB (2002)[108]	1995-2000	Obs	42	Q	209	71.3	Efficacy <90%, Q safe in 1st trim, AE↑
TBB (2002)[108]	2002	Obs	42	Q	25	56	Treatment of repeat Pf, Efficacy <90%
TBB (2005)[102]	2001-03	RCT	63	Q	41	63.4 (46.9 - 77.4)	Unsatisfactory treatment response, AE↑
Thailand (2001)[101]	1995-98	RCT	28	Q	29	100	Slower PCT and AE
TBB (2001)[103]	1997-2000	RCT	42	Q + C	65	100 (99.3-100)	More gametocytes, AE, cost
TBB (1998)[80]	1992-96	Obs	42	AS 7d	53	90.6 (81.6-99.6)	Efficacy <90%
TBB (1998)[81]	1991-96	Obs	42	M	194	72	Efficacy <90%
TBB (2000)[79]	1995-97	RCT	63	MAS	65	98.2 (94.7-100)	MAS effective, less gametocytes
Thailand (2001)[101]	1995-98	RCT	28	MAS	28	100	MAS less AE, short PCT, FCT
TBB (2003)[105]	2000-01	Obs	42	AAP	24	100	Expensive
TBB (2005)[102]	2001-03	RCT	63	AAP	39	94.9 (81.4 - 99.1)	Well-tolerated, effective, practical, but expensive
TBB (2008)[92]	2006-07	Obs	63	DHAPPQ	50	92.2 (76.9–97.4)	Well tolerated, effective, no evidence of toxicity
TBB (2008)[90]	2004-06	RCT	42	AS 7d	128	94.9 (91.0-98.8)	Well tolerated, effective, no evidence of toxicity
TBB (2008)[90]	2004-06	RCT	42	AL	125	86.8 (80.5-93.1)	Efficacy low; unsatisfactory for deployment in PW
TBB (2008)[90]	2004-06	Obs	42	AS + C	88	95.4 (90.3-100)	Highly efficacious in MDR-Pf (unpublished)
PNG (2009)[59]	2006	PK	28	SP + CQ	13	62	Small sample size
P.vivax							
TBB (2002)[108]	1995-2000	Obs	28	CQ	111	95.5	CQ safe in first trimester
PNG (2010)[60]	2006	PK	28	SP + CQ	2	100	Small sample size

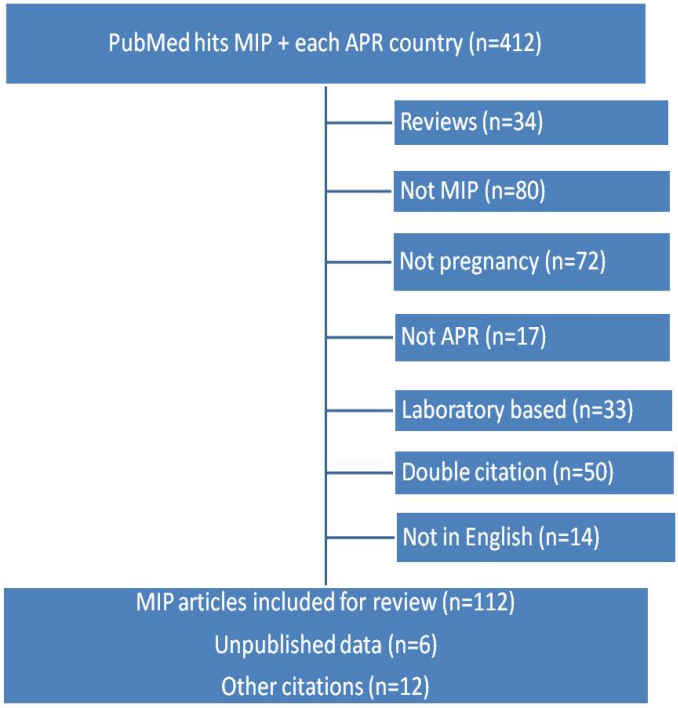
* (95%CI) if available

n.p. not published, obs observational, AMQ amodiaquine, As artesunate, AAP artesunate atovaquone proguanil, C clindamycin, CQ chloroquine, DHAPPQ dihydroartemisinin piperaquine, FCT fever clearance time; IPTp Intermittent Preventive Treatment in pregnancy, M mefloquine, PCT parasite clearance time; Pf *Plasmodium falciparum*, PK pharmacokinetic, PNG Papua New Guinea, Pv *Plasmodium vivax*, Q quinine, RCT randomized controlled trial, SP Sulfadoxine-pyrimethamine

Figures

Figure 1

Selection of articles

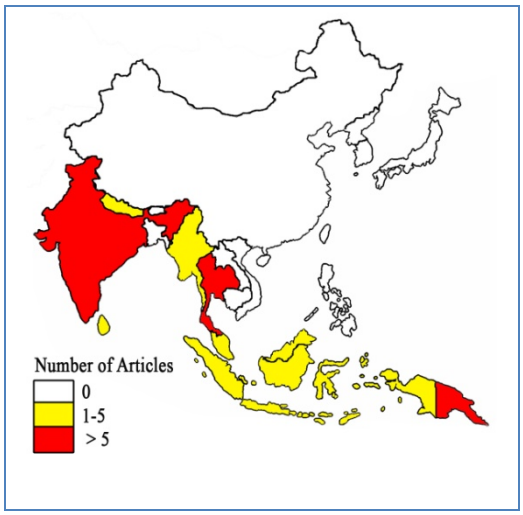


Abbreviations:

MIP Malaria in pregnancy, APR Asia Pacific Region

Figure 2

Distribution of articles included in the review



Solomon Islands and Vanuatu are not on this map but included 4 and 1 article respectively.

Figure 3

Transmission intensity in Asia Pacific Region (Data WMR 2010[25])

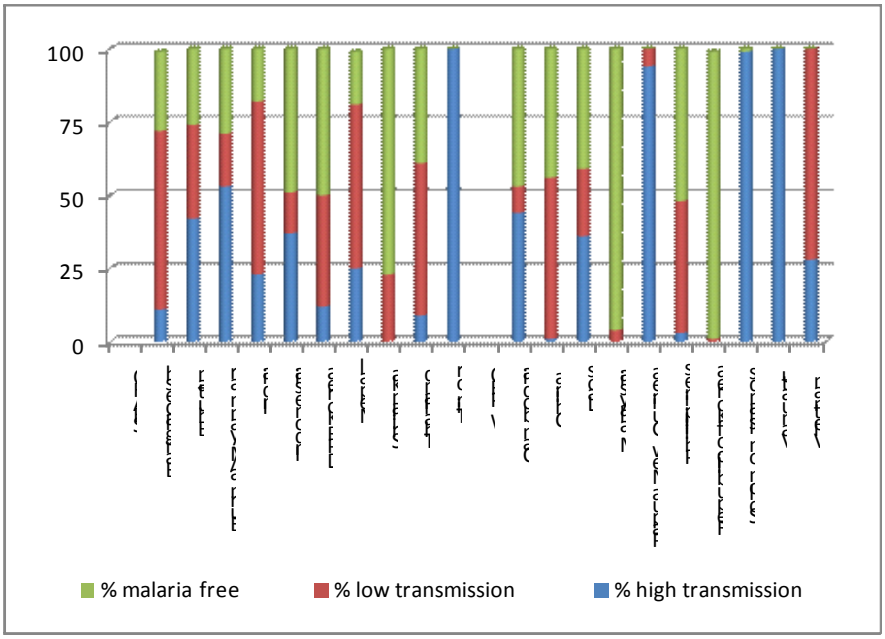


Figure 4

Pregnant women at risk for malaria in the Asia Pacific region (data Dellicour 2010[1]) (numbers are in *10^6).

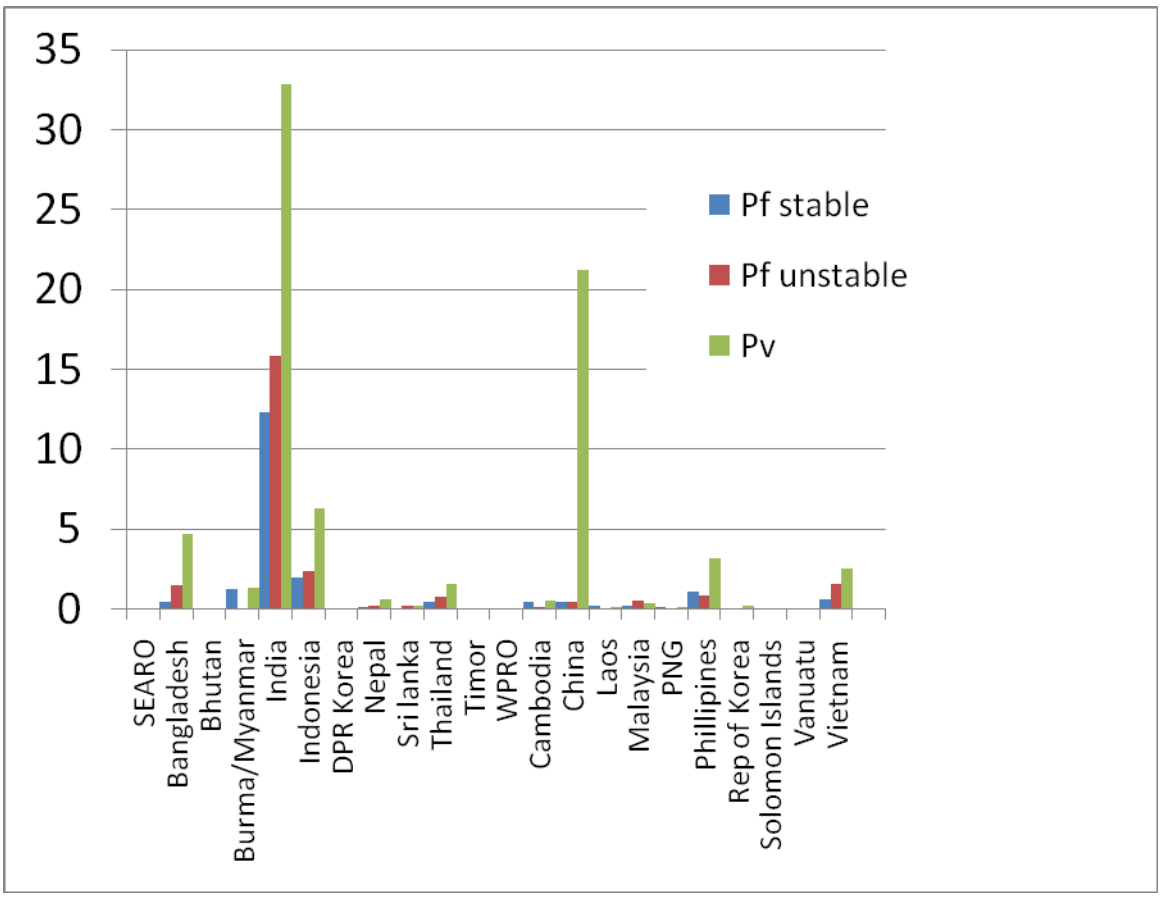


Figure 5

Proportion of mothers (M) and Placentas (P) infected with malaria parasites *P.falciparum* (pf) and *P.vivax* (pv) at delivery in areas where ACTs or CQ/SP were used to treat pregnant women with malaria