Epidemiology and burden of malaria in pregnancy

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We reviewed evidence of the clinical implications and burden of malaria in pregnancy. Most studies come from sub-Saharan Africa, where approximately 25 million pregnant women are at risk of *Plasmodium falciparum* infection every year, and one in four women have evidence of placental infection at the time of delivery. *P falciparum* infections during pregnancy in Africa rarely result in fever and therefore remain undetected and untreated. Meta-analyses of intervention trials suggest that successful prevention of these infections reduces the risk of severe maternal anaemia by 38%, low birthweight by 43%, and perinatal mortality by 27% among paucigravidae. Low birthweight associated with malaria in pregnancy is estimated to result in 100 000 infant deaths in Africa each year. Although paucigravidae are most affected by malaria, the consequences for infants born to multigravid women in Africa may be greater than previously appreciated. This is because HIV increases the risk of malaria and its adverse effects, particularly in multigravidae, and recent observational studies show that placental infection almost doubles the risk of malaria infection and morbidity in infants born to multigravidae. Outside Africa, malaria infection rates in pregnant women are much lower but are more likely to cause severe disease, preterm births, and fetal loss. *Plasmodium vivax* is common in Asia and the Americas and, unlike *P falciparum*, does not cytoadhere in the placenta, yet, is associated with maternal anaemia and low birthweight. The effect of infection in the first trimester, and the longer term effects of malaria beyond infancy, are largely unknown and may be substantial. Better estimates are also needed of the effects of malaria in pregnancy outside Africa, and on maternal morbidity and mortality in Africa. Global risk maps will allow better estimation of potential impact of successful control of malaria in pregnancy.

Introduction

"So long as Woman has walked the earth, malaria may have stalked her";[1] however, the problem of malaria in pregnancy was not described until the early 20th century.[2,3] This was followed by almost four decades of descriptive studies in sub-Saharan Africa that focused on the frequency of *Plasmodium falciparum* placental infection and its adverse effects.[4–9] In the past two decades, many comprehensive reviews have highlighted various aspects of malaria in pregnancy and its effect on maternal, newborn, and infant health. In this review, we compile these estimates across the spectrum of disease manifestations, including what is known in low and unstable transmission areas within and outside of sub-Saharan Africa and of species other than *P falciparum*. We used data from review articles, and included new data that were recently published if it provided important new information or insights.

Our aim is to identify gaps in knowledge of the epidemiology and burden of malaria in pregnancy globally, and to chart a course for gathering requisite knowledge to fill those gaps both through special studies and routine data-gathering exercises such as monitoring, surveillance, and evaluation.

Risk of infection: peripheral and placental parasitaemia

Stable transmission in Africa

A myriad of studies have reported on the prevalence of peripheral and placental parasitaemia in areas of stable endemic malaria transmission in Africa. Data from Africa before 1980 have been summarised in a review by Brabin and colleagues.[10] In another review of 20 studies from eight countries in Africa done between 1985 and 2000, the median prevalence of maternal malaria infection (defined as peripheral or placental infection) in all gravidae was 27·8%.[11] A similar estimate of 26% was obtained for placental malaria (range 5–52%) in a subsequent review of 11 studies done since 1980.[12] Thus, approximately one in four pregnant women in areas of stable transmission in Africa have evidence of infection with malaria at the time of delivery. These are minimum estimates because they are based on single-point prevalence data, and do not take into account women who have had malaria before or after the time of the point estimate. Additionally, these estimates are based on data from light microscopy and thus under-represent the low-grade submicroscopic parasitaemia that can be detected by more sensitive methods such as PCR[13] and placental histology.[14]

Low, unstable, and seasonal transmission

Despite a growing awareness of the importance of malaria in pregnancy outside malaria endemic regions in sub-Saharan Africa, very few studies have reported on the epidemiology of *P falciparum* infection in areas of low, unstable, or seasonal transmission, or epidemic-prone areas of the world.[15] We identified 13 relevant studies that were done between 1986 and 2004 (table 1 and table 2).[16–28] The median prevalence of peripheral (at antenatal care clinics) and placental parasitaemia in low-transmission African settings was 13·7% and 6·7%, respectively. For low-transmission areas outside Africa, the respective estimates are 6·2 and 9·6%. Evidence from areas with highly seasonal transmission in Africa indicates that placental malaria infections are identified more frequently in the dry season than would be expected from the low incidence of infection during this low-transmission season, suggesting that infections acquired during the peak transmission season may persist in the placenta for several months.[29,30]

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	Study period	Country	Sample size	Type of study	Description of transmission area	Description of transmission
Nosten et al[16]	1986–1989	Thailand	1358 (antenatal clinic)	Prospective community-based	Forest area	Unstable
Luxemburger et al[17]	1993–1996	Thailand	1495 (antenatal clinic)	Prospective community-based	Forest area	1 infection per person per year
McGready et al[18]	1995–2002	Thailand	204 (delivery unit*)	Prospective community-based	Forest area	Low and seasonal
Cot et al[19]	1996–1997	Madagascar	1637	Prospective	Highland	Unstable
Ahmed et al[20]	1997	Sudan	550	Prospective	Peri-urban and urban agricultural scheme prone to waterborne disease	Mesoendemic
Hammerich et al[21]	1997–1999	Rwanda	319	Prospective malaria admissions	Highland	Unstable
Kasumba et al[22]	1998	Uganda	537	Cross-sectional	Highly seasonal, during dry season	..
Newman et al[23]	2000–2001	Ethiopia	713 (antenatal clinic); 833 (delivery unit); 228 (hospital surveillance)	Cross-sectional	Highland	Unstable
Elghazali et al[24]	2001–2002	Sudan	86 pregnant women, 89 controls	Prospective community-based	Agricultural village	Unstable, seasonal
Espinoza et al[25]	2001	Ecuador	80 malaria admissions	Retrospective malaria admissions	Urban, with 45% of patients from rural endemic areas	Mesoendemic
Singh et al[26]	2002–2004	India	799 (2 delivery units)	Cross-sectional hospital-based	Tribal, rural, urban	Seasonal
Adam et al[27]	2003–2004	Sudan	744 (antenatal clinic)	Cross-sectional	Agricultural	Unstable, seasonal
Nosten et al[28]	1986–1997	Thailand	9956 (antenatal clinic)	Prospective	Forest area	Unstable

..=not reported. *175 were malaria detected during antenatal care and 29 were not malaria detected during antenatal care.

Table 1: **Characteristics of studies on malaria during pregnancy in areas of low, seasonal, or unstable malaria transmission**

	Peripheral parasitaemia		Placental parasitaemia (delivery unit)	Fever during pregnancy	Anaemia during pregnancy	Malaria-associated maternal mortality	Low birthweight	Preterm delivery	Stillbirth
	Antenatal clinic	Delivery unit							
Nosten et al[16]	5·9%	..	..	..	31·2% (incidence; clinical diagnosis); PAF 12·4%	0%	..	..	3·2%
Luxemburger et al[17]	..	..	..	37%	77·2% (PCV <30%)	..	16%	11%	2·7%
McGready et al[18]	..	9·5%	6·5%	..	..	..	13·1%	7·6%	..
Cot et al[19]	..	..	8·1%	..	..	..	11·3%; PAF 15·6%	..	..
Ahmed et al[20]	..	58·9%	..	..	24·1% (Hb <90 g/L)	..	..	..	..
Hammerich et al[21]	..	..	..	..	..	60%	..	..	..
Kasumba et al[22]	..	8·6%	6·7%	..	7·3% (PCV <30%)	0%	9·3%	8·6%	4·3%
Newman et al[23]	1·8%	2·3%	2·5%	11·8%; PAF 7·8%	14·7% (Hb <110 g/L); PAF 5·8%	11% (hospital surveillance)	6·6%	5·4%; PAF 6·8%	3·0%; PAF 13%
Elghazali et al[24]	17·4%	..	..	..	8·1% (Hb <80 g/L); PAF 15·2%	..	..	4·6%	..
Espinoza et al[25]	..	..	..	..	..	1·3%	35%	25%	..
Singh et al[26]	..	6·1%*	12·6%*	30%*	..	..	..	..	..
Adam et al[27]	13·7%	..	..	..	..	..	..	..	..
Nosten et al[28]†	6·4%	..	..	..	77·3%	..	18·7%	..	..

PAF=population attributable fraction; PCV=packed cell volume; Hb=haemoglobin; ..=not reported. *Estimates are median values for the two sites described in the study. †Only data on *Plasmodium vivax* inluded.

Table 2: **Effect of malaria during pregnancy in areas of low, seasonal, or unstable malaria transmission, by study**

Risk groups

In high-transmission areas, primigravidae are indisputably at greater risk of infection, whereas the gravidity effect is less marked in low-transmission areas,[16] and absent in areas with epidemic malaria.[23] Younger maternal age (especially adolescence) is also an independent risk factor for malaria in pregnancy (ie, young primigravidae and multigravidae are at greater risk of malaria and its adverse effects than older primigravidae or multigravidae, respectively).[25,31–34] This suggests that in addition to the parity-specific immunity that is acquired through consecutive pregnancies, age-associated immunity also plays an important part in controlling the infection during pregnancy in areas of high and stable transmission.
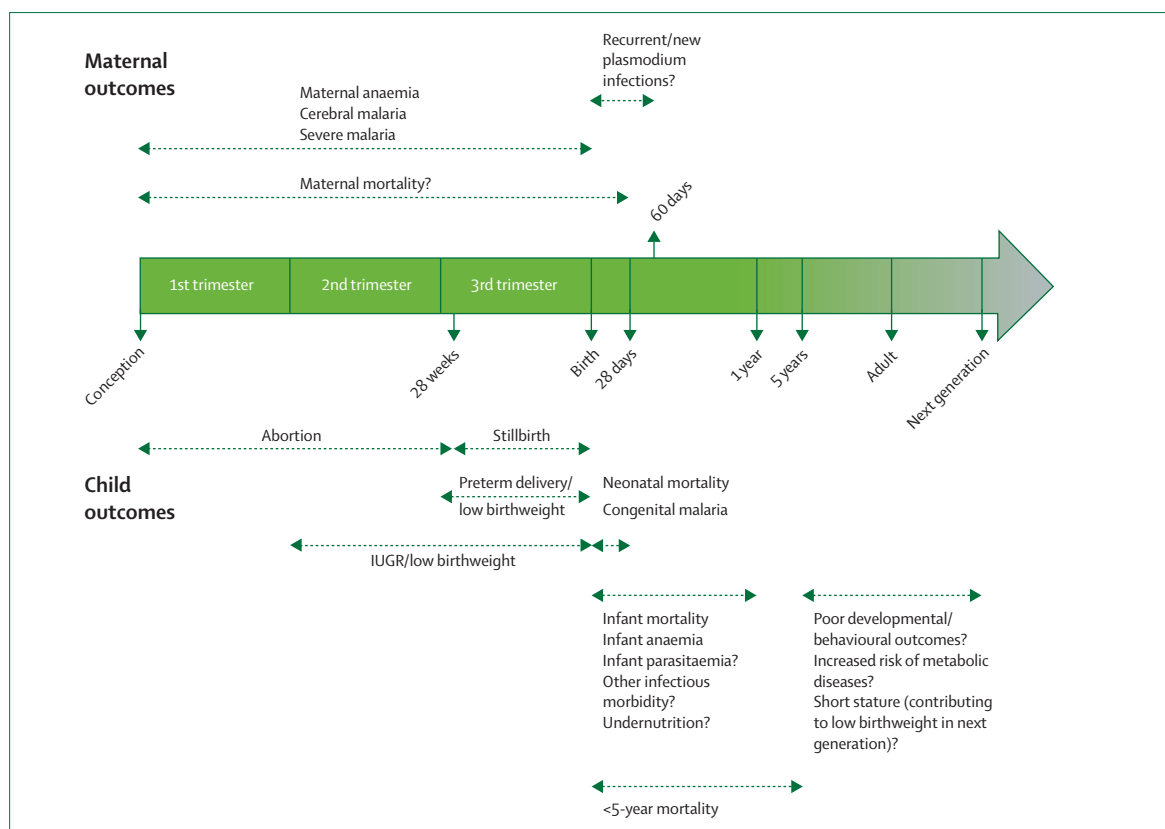
Figure 1: Effect of malaria in pregnancy on maternal, newborn, infant, and child health
Effect of malaria in pregnancy in the first trimester is unclear, and may result in early abortions. Exposure to antimalarials during this period may also increase the risk of abortion. Effect of malaria in pregnancy in the first year of life and through adulthood remains to be established. IUGR=intrauterine growth retardation.

The risk of maternal infection (assessed by finger-prick) is highest during the second trimester. The few studies that have addressed the risk in the early postpartum period show inconsistent results: some studies show an increased risk (rate ratio 2·7–4·1) of recurrent and new *P falciparum* malaria in the first 2–3 months post partum,[35–37] whereas other studies show a rapid clearance of peripheral parasitaemia within 2 days of delivery.[38] Little is known about the risk of infection in the first trimester; however, the susceptibility must increase in this period to explain peak prevalence in the second trimester. There is some evidence to suggest that pregnancy-induced changes in splenic function early in pregnancy predispose primigravidae to *P falciparum* as early as 8 weeks' gestation.[39] Recent evidence from rural Mozambique suggests that more than 20% of pregnant women attending a maternity clinic with symptoms suggestive of malaria are in their first trimester (Bardaji A, Centre for International Health, Hospital Clinic, University of Barcelona, Spain, personal communication).

Effects on maternal health
The clinical features of malaria infection during pregnancy vary by the degree of immunity that women

have acquired by the time they become pregnant, and thus by the epidemiological setting (figure 1).

Stable transmission in Africa
Few infections in healthy adults living in areas of high malaria transmission result in fever, and the same is true for semi-immune pregnant women. Although it is commonly assumed that most parasitaemic pregnant women are therefore symptomless, a study in Ghana suggested that pregnant women were more likely to complain of symptoms compatible with malaria if they were parasitaemic than if they were not, despite the absence of a recent history of fever.[40]

In Africa, 5–10% of pregnant women may develop severe anaemia (defined as haemoglobin <70 g/L or <80 g/L).[41–43] The proportion of severe anaemia among pregnant women of all gravidities that is attributable to malaria (population attributable fraction) is estimated to be 26% (table 3). Thus, depending on the relative contribution of other possible causes of anaemia and local epidemiological profiles, approximately one in four cases of severe anaemia may be prevented with adequate prevention of malaria in pregnancy.[45] The estimate is higher in paucigravidae (ie, women in their first or second pregnancies); meta-analysis of antimalarial prophylaxis trials or trials with intermittent

	Review or individual study (period)	Study area	Gravidity	Severe anaemia*	Cerebral malaria*	Severe malaria*	Mortality†	Predominant species
Steketee et al[11]	Review (1985–2000)	Sub-Saharan Africa	All	PAF 3–15% (moderate to severe)	..	..	..	*P falciparum*
Singh et al[44]	Review (1911–2004)	India; Thailand, low transmission	All	India: 8·6–90·0%; Thailand: 31–43%‡	India: 7·0–76·0%	Thailand: 60%§	India: 7·0–66·6%; Thailand: 10–27%‡	*P falciparum, P vivax*
Guyatt et al[45]	Review (>30 years)	Sub-Saharan Africa	All	PAF 7·3% (cross-sectional studies); 26% (protective efficacy from prospective intervention trial)	..	..	..	*P falciparum*
Brabin et al[46]	Review	Endemic (Papua New Guinea and Africa)	Primi	PAF 18%	..	..	9 per 100 000 livebirths¶	*P falciparum*
Maitra et al[47]	Study	Gujarat, India	All	22·7%	..	..	3·4%	*P falciparum*
Brabin et al[48]	Review	Africa; low endemicity	All	..	..	..	Africa: 0·5–23% (hospital), 2·9–17·6% (community); low endemicity: 0·6–12·5% (hospital)	*P falciparum*

*Estimates are percentages of women among pregnant women with malaria, unless otherwise indicated. †Mortality estimates are percentages of women with malaria-related death among pregnant women with malaria, unless otherwise indicated. ‡Includes mostly hospital-based treatment studies and thus the estimates likely reflect impact of severe malaria on adverse outcomes. §The only study contributing to this estimate is that by Luxemburger et al,[17] with rate ratio of severe malaria of 3·0 (95% CI 1·4–6·2) in pregnant compared with non-pregnant women. ¶Severe malaria-anaemia-related deaths; this review gives an overall relative risk of maternal mortality in women with severe anaemia of 3·51 (95% CI 2·05–6·00). PAF=population attributable fraction; ..=not reported.

Table 3: Effect of malaria in pregnancy on maternal outcomes, by study

preventive treatment (IPT) suggest that successful prevention of malaria reduces the risk of severe anaemia by 38% (95% CI 22–50%).[49]

Despite decades of work on the epidemiology of malaria in pregnancy, good estimates of its effect on maternal mortality in Africa are scarce. The percentage of direct and indirect malaria-related maternal deaths range from 0·5% to 23·0% in hospital studies and from 2·9% to 17·6% in community-based studies.[48] One model estimates that in holoendemic malarious areas with a 5% prevalence of severe anaemia (haemoglobin <70 g/L), there would be nine maternal deaths related to severe malarial anaemia per 100 000 livebirths to primigravidae.[46]

Low, unstable, and seasonal transmission
A review of mostly treatment studies from south and southeast Asia attempted to quantify some of the burden of malaria in pregnancy in areas of varying endemicity in

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Figure 2: Symptoms of malaria in pregnancy in Asia
Malaria in pregnancy in many parts of Asia is very symptomatic. This pregnant woman of 5 months' gestation was vomiting because of malaria and was unable to tolerate oral antimalarial medication.

this region (table 3).[44] Infections in areas of low malaria transmission where women have little acquired immunity are generally believed to be much more likely to result in symptoms, severe disease, and death of the mother or fetus than in endemic Africa (figure 2). In one study in Thailand, 1·7% pregnant women died in a single year from malaria before the introduction of malaria control programmes specifically targeting pregnant women.[16] Single and pauci-symptomatic infection with *Plasmodium vivax* is also known to result in increased risk of maternal anaemia.[28] Surprisingly, the overall percentage of maternal deaths attributed to malaria from direct and indirect causes in low transmission areas outside of Africa (0·6–12·5%) is not substantially different from the estimate derived for high transmission areas (0·5–23·0%; table 3).[48]

Effects on birth outcome
Stable transmission in Africa
Malaria in pregnancy has an unequivocally devastating effect on the newborn infant (table 4). Low birthweight (defined as birthweight <2500 g) is associated with a marked increase in infant mortality.[11,30,50,52,53] In areas of high malaria transmission in Africa, the risk of low birthweight approximately doubles if women have placental malaria,[12] with the greatest effect in primigravidae.[54] The odds ratio of low birthweight associated with malaria is two to seven times higher in primigravid than multigravid women.[54] In sub-Saharan Africa, nearly 20% of low-birthweight deliveries are attributable to malaria in pregnancy, and this is 35% of preventable low birthweight in women of all pregnancy orders.[11,12] Among paucigravidae, effective prevention of malaria with chloroquine prophylaxis or IPT reduces the risk of low birthweight by as much as 43%.[49] Malaria-induced low birthweight is estimated to be responsible for between 62 000 and 363 000 infant deaths every year in

	Review or individual study (period)	Study area	Gravidity	Estimate type	Low birthweight (<2500 g)	Preterm delivery (<37 weeks' gestation at birth)	Intrauterine growth retardation (<10th percentile weight for gestational age)	Stillbirth*	Predominant species
Steketee et al[11]	Review (1985–2000)	Sub-Saharan Africa	All	PAF range	8–14%	8–36%	13–70%	..	P falciparum
Guyatt et al[12]	Review (1980–2003)	Sub-Saharan Africa	All	Median PAF (range)	19% (14–25%)	..	..	..	P falciparum
Singh et al[44]	Review (1911–2004)	India; Thailand, low transmission	All	% among pregnant women with malaria†	India: 5·4–89·0%	India: 4·2–60·0%; Thailand: 3·3–4·0%	..	India: 2·0–13·0%; Thailand: 3·2–13·3%	P falciparum, P vivax
Luxemburger et al[50]	Study (1993–1996)	Thailand, low transmission	All	PAF (95% CI)	20% (7–29%)	10% (6–12%)	..	..	P falciparum, P vivax
van Geertruyden et al[51]	Review (1948–2002)	Endemic (mostly Africa)	All	Odds ratio (95% CI)	..	..	..	2·19 (1·49–3·22)	P falciparum

*Complete expulsion or extraction from the mother of a product of conception, of at least 22 weeks gestation or 500 g, which after separation did not show any signs of life. †Includes mostly hospital-based treatment studies and thus the estimates likely to indicate the effect of severe malaria on adverse outcomes. PAF=population attributable fraction; ..=not reported.

Table 4: Effect of malaria in pregnancy on birth outcomes, by study

Africa, which translates to three to 17 deaths per 1000 livebirths.[53] Another estimate suggests that 11·4% of neonatal deaths and 5·7% of all infant deaths in malaria-endemic areas of Africa may be caused by malaria in pregnancy-associated low birthweight,[52] which translates to around 100 000 infant deaths.[12] Not surprisingly, this effect is greatest in infants born to primigravidae at 17·6% of neonatal deaths and 9·8% of infant deaths.[52]

The relative contribution of intrauterine growth retardation (IUGR) or preterm delivery in causing low birthweight varies by the level of malaria endemicity as well as other factors, such as access to prompt treatment and spread of HIV. In areas of high malaria transmission where women are exposed to a greater frequency of antenatal infections and may have acquired immunity to prevent most febrile episodes that cause preterm delivery, IUGR is likely to be the predominant cause of malaria-associated low birthweight (figure 3).[55] Malaria in pregnancy in these settings may be responsible for up to 70% of IUGR, whereas its contribution to preterm delivery, although still substantial, is relatively lower at up to 36%.[11]

Until recently, the link between placental malaria and stillbirths in endemic settings was unclear. However, a recent review of nine mainly hospital-based studies showed that placental malaria was associated with twice the risk (odds ratio 2·19) for stillbirth; although the review did not take into account the effect of gravidity, it is likely that the effect is stronger in paucigravidae.[51] Furthermore, systematic reviews of randomised controlled trials have shown that successful prevention of malaria in pregnancy among paucigravidae with antimalarial prophylaxis, IPT, or insecticide-treated bednets, result in substantial reductions in perinatal mortality (27%)[49] and spontaneous abortions and stillbirths (33%).[56]

Low, unstable, and seasonal transmission

P falciparum-associated low-birthweight deliveries are common in low-transmission settings outside Africa where preterm delivery is likely to be a more important contributing factor.[3,44] The median prevalence of stillbirths, premature delivery, and low-birthweight deliveries in low-transmission settings of Africa was 3·7%, 8·6%, and 9·3%, respectively (table 2). The corresponding figures for low-transmission settings outside of Africa are comparable: 3·0%, 11%, and 16%. The increased risk of low birthweight associated with placental parasitaemia ranged from 1·8 in Thailand to 4·3 in low-transmission sites in Africa, whereas the risk of stillbirths and preterm delivery, where studied, was reported to be four times higher among women with placental parasitaemia. Interestingly, despite the difference in aetiology and regardless of the number of episodes of parasitaemia, the magnitude of the reduction in birthweight in grams (which may range from 35–310 g)[4,7–9,23,28,57–59] and the population attributable fraction of malaria-related low birthweight are comparable in areas of low[50] and high[12] malaria transmission (table 4).[60]

Figure 3: Effect of malaria in pregnancy on low birthweight in Africa
A low-birthweight baby born to a woman with an infected placenta from Manhiça, Mozambique.

	Study area	Gravidity	Follow up	Infant anaemia (95% CI)	Infant parasitaemia (95% CI)
Van Eijk et al[62]	Kenya	All	4–23 weeks	RR 1·21 (1·04–1·40)	..
Cornet et al[63]	Cameroon	..	6 months	RR 3·6 (1·1–12·3)	..
Reed et al[64]	Malawi	..	2 months	RR 2·0 (1·3–3·0)	..
Le Cessie et al[65]	Malawi	All	6 and 12 months	Difference in haemoglobin (g/L): –24 (–64 to 15) at 6 months; –54 (–93 to –15) at 12 months	..
Slutsker et al[66]	Malawi	All	3 months	..	OR 1·1 (0·7–1·9)
Le Hesran et al[67]	Cameroon	All	2 years and 6 months	..	46·5% (PM+) vs 38·5% (PM–), p=0·6 at 2 years; ~36% (PM+) vs ~14% (PM–), p<0·05 at 6 months
Mutabingwa et al[68]	Tanzania	All	12 months	..	RR 1·41 (1·01–1·99)*

*This study reported a significant interaction between placental malaria and gravidity, where placental malaria in multigravidae was a strong risk factor for infant parasitaemia. Risk ratio (RR) or odds ratio (OR) is ratio of adverse outcome in women with malaria compared with those without malaria at the time of delivery. PM=placental malaria; ..=not reported.

Table 5: Effect of malaria in pregnancy on infant outcomes, by study

Effect on infant outcomes

The prevalence of fetal anaemia at birth is high in malaria-endemic areas, and the risk is associated with the presence of high-density parasitaemia in the mother at delivery.[61] Few studies report the effect of malaria in the pregnant mother on anaemia or malaria in the infant (table 5 and table 6). Some studies have now shown that the risk of all-cause anaemia is estimated to be three times higher among infants born to mothers with placental parasitaemia, even after adjusting for environmental and ecological confounders.[62–64] Recent evidence also indicates an association between placental malaria and diminished development of cellular and antibody responses to *P falciparum* epitopes in infants.[70,71] A birth cohort study from Tanzania reported a 41% increased risk of malaria infection in infants born to mothers with placental malaria, also after adjusting for potential confounding environmental and ecological factors.[68] This study shows that multigravidae are also at increased risk, implying that offspring of multigravid women with malaria may have greater clinical consequences than previously appreciated, even after adjusting for the effect of HIV on malaria in pregnancy, which is more pronounced in multigravidae.[72] These are important observations, because if placental malaria indeed affects infant morbidity in multigravidae, then the burden of malaria in pregnancy in Africa extends beyond that observed in paucigravidae, and the total burden may have been vastly underestimated. This is important to confirm in prospective studies. Placental malaria also reduces infant transplacental transfer of maternal antibodies and cellular immune responses in the infant to several other infectious diseases, including measles,[58,73] *Streptococcus pneumoniae*,[73] and tetanus.[74]

Congenital malaria in the indigenous populations of malaria-endemic areas is generally reported as rare[75] and more frequent in offspring of non-immune mothers with malaria.[76] However, more recent reports from both malaria-endemic and non-endemic areas show higher prevalences of congenital malaria ranging from 8% to 33%.[7,77–88] The apparent increasing trend in the incidence of congenital malaria may be the result of increasing drug resistance, increasing virulence of the parasite, HIV, or increased reporting or detection of cases by use of PCR. To date, researchers have not identified the clinical (or immunological) significance of cord-blood parasitaemia, an area in need of further study.

Long-term consequences for the child

There is a dearth of literature on the long-term consequences of malaria in pregnancy for the child. A large number of mainly nutritional studies indicate that exposure to an abnormal intrauterine environment affects mental, metabolic, and anthropometric development, resulting in increased risk of disease later in life. In high-income countries, low birthweight has been associated with higher arterial pressure, chronic kidney disease, ischaemic cardiomyopathy, stroke, diabetes, respiratory disease, and syndrome X (a combination of metabolic abnormalities) in adult age.[89,90] Some reviews also suggest high rates of cognitive impairment, learning disability, and behavioural problems among children who were born with lower birthweight,[91–93] which is likely to be caused by suboptimum development of the brain.[94]

	Study area	Gravidity	Mortality*	
			Neonatal	Infant
Steketee et al[11]	Sub-Saharan Africa	All	..	3–8%
Greenwood et al[30]	Gambia	Primi/multi	42%/6%	18%/4%
Luxemburger et al[50]	Thailand	All	..	Hazard ratio 4·0 (95% CI 1·2–13·7) at 1–3 months
Guyatt et al[52]	Sub-Saharan Africa	Primi/all	18%/11%	10%/6%
Murphy et al[61]	Sub-Saharan Africa	All	..	3–17 per 1000 livebirths
Goodman et al[69]	Sub-Saharan Africa	Primi	24%	..

*Estimate given as the attributable fraction (percentage of adverse outcome among those exposed to malaria in pregnancy that is attributable to malaria in pregnancy), unless otherwise indicated; neonatal mortality measured up to 28 days, and infant mortality up to 12 months, unless otherwise indicated. ..=not reported.

Table 6: Effect of malaria in pregnancy on infant and neonatal mortality, by study

However, there are few data specifically for malaria, and it is unclear whether and how malaria in pregnancy affects developmental outcomes in infancy independent of low birthweight. Only one study from Malawi has implicated placental malaria as a risk factor for poor anthropometric status in infancy independent of low birthweight.[61] Low birthweight may also affect the second generation; low birthweight is associated with incomplete catch-up growth and subsequent short stature in adolescence and adulthood,[95,96] which in turn may increase the risk of delivering low-birthweight babies when these women become pregnant.[97–99]

Interaction with HIV

The burden of malaria in pregnancy is exacerbated by co-infection with HIV. Sub-Saharan Africa bears the brunt of this comorbidity, where approximately 25 million pregnant women are at risk of *P falciparum* infection every year,[11,100] and 77% (13·5 million) of the world's HIV-infected women reside.[101] A review of 11 studies from Africa highlights the deleterious effect of HIV on malaria, reporting higher risks of placental malaria (summary relative risk 1·66, 95% CI 1·48–1·87), high-density parasitaemia, and febrile illness in HIV-infected women.[72] HIV increases the degree to which malaria is associated with maternal severe anaemia and low birthweight beyond the effect of HIV itself on anaemia and birthweight (interaction).[72]

HIV infection seems to compromise malarial immunity such that HIV-infected multigravidae have at least as high a risk of placental infection as non-HIV-infected primigravidae. Thus, HIV essentially eliminates the typical gravidity-specific pattern of malaria risk in stable malaria transmission areas by shifting the burden from paucigravidae to all pregnant women. The proportional increase of overall malaria prevalence during pregnancy, regardless of gravidity, that could be attributed to HIV is estimated to be 5·5% and 18·8% for areas with HIV prevalences of 10% and 40%, respectively.[72] No data are currently available on the effect of HIV on severe malaria in pregnancy and on death from maternal malaria. Three studies investigating whether placental malaria increased mother-to-child HIV-1 transmission showed conflicting results, possibly reflecting a complex balance between placental malarial immune responses and stimulation of HIV-1 viral replication.[72]

Effect of other *Plasmodium* species

Although all four *Plasmodium* species can infect pregnant women, only susceptibility to *P vivax* and *P falciparum* has been studied.[102,103] Most of the data on *P vivax* infections are from regions outside Africa. Women are at increased risk of *P vivax* infection during pregnancy, although the increased risk is less pronounced than with *P falciparum*; data from Brazil show that the ratio of *P falciparum* to *P vivax* was 1:5·6 in a group of non-pregnant infected women, whereas it was only half that

(1:2·3) in pregnant women enrolled in the same study,[104] which may be explained by the lack of cytoadherence of *P vivax* in the placenta.[18] However, there is now evidence that single infections with *P vivax* in the peripheral blood are associated with a reduction in birthweight and maternal haemoglobin, although its effect on these outcomes seems smaller than that of *P falciparum*.[28,105] Interestingly, compared with *P falciparum*, the effect of *P vivax* on birthweight may be more pronounced in multigravidae despite a higher incidence of *P vivax* infection in primigravidae.[28] Pregnant women with *P vivax* are also more likely to present *P vivax* relapses than non-pregnant women.[28]

Luxemburger and colleagues[17] report that pregnant women on the Thai-Burmese border experienced a four times reduced risk of severe malaria if infected with both *P falciparum* and *P vivax* compared with *P falciparum* alone. If mixed infections indeed reduce *P falciparum* morbidity, this finding may have negative repercussions for the outcome of programmes that are more effective in controlling *Plasmodium* species other than *P falciparum*.

Robust data on the prevalence and effect of *Plasmodium ovale* and *Plasmodium malariae* in any population, let alone in pregnancy, are currently unavailable.[102] Their prevalence has typically been reported to be low, but this was based on microscopy, and more recent studies using PCR suggest this is likely to be a gross underestimate since many *P ovale* and *P malariae* infections are not evident by microscopy.[106,107] Furthermore, in sub-Saharan Africa, they often present as co-infections with *P falciparum*. A study from Cameroon reported a much higher prevalence of mixed infections among pregnant women than previously recognised;[34] the prevalence of mixed infections decreased with increasing age and gravidity and was not associated with an increased risk of anaemia.

Revisiting methods to measure morbidity and mortality

Estimating burden

Any attempt to quantify the global burden of malaria in pregnancy is made more difficult by a lack of an accurate and good quality estimation of both the numerator (ie, women affected by adverse outcomes of malaria in pregnancy) and the denominator (ie, the population at risk). The numbers of women at risk of malaria in pregnancy are underestimated because of the practice of using routine national reporting systems, especially outside Africa, and because the number of unidentified pregnancies is ignored. Even within demographic surveillance sites where pregnancies are followed, not all pregnancies are reported. In the demographic surveillance sites based in Ifakara, Tanzania, only 85% of pregnancies are reported before birth (Rose Nathan, Ifakara Health Research and Development Centre, Ifkara, Tanzania, personal communication). If only those pregnancies that

reach delivery are counted, then this will also underestimate the clinical effect of malaria in pregnancy; high proportions of miscarriages occur early in pregnancy and in specific groups such as adolescents, and are therefore difficult to identify in low-income countries. Estimating the malaria burden during early gestation continues to pose a challenge. Furthermore, discounting out-of-hospital deliveries and pregnancy losses compounds the problem of under-reporting the effect of malaria in pregnancy. Thus, better estimation will require accurate identification of women of reproductive age, their pregnancies, and birth outcomes.

Recent advances in modelling the disease by use of multilayered maps could help to provide better global and regional estimates of the magnitude of the problem. Risk maps that link data on transmission intensity and *Plasmodium* species distribution with demographic data, such as fertility rates, are needed to estimate the number of pregnancies exposed. This information can then be combined with efficacy and effectiveness estimates obtained from randomised controlled trials to estimate the potential effect in terms of health and costs of successful control of malaria in pregnancy.[108,109]

Low birthweight as an indicator of malaria control and predictor of infant mortality

Continuing monitoring and evaluation efforts in the context of the President's Malaria Initiative, World Bank's Malaria Booster Program, The Global Fund, and WHO's Roll Back Malaria Partnership make it imperative for the scientific community to agree on cost-effective methods and robust indicators for routine collection of data that can track the changing burden of malaria in pregnancy as control interventions (ie, IPT and insecticide-treated bednets) are scaled-up programmatically. Because infants born to primigravidae are at greatest risk of low birthweight, it has been proposed that this excess risk relative to that in multigravidae can be used as a simple indicator of malaria transmission and exposure in pregnant women in Africa.[54] Since birthweight and parity are routinely recorded in many delivery centres across Africa, these data could be incorporated in a simple,

available, and inexpensive tool for monitoring the effectiveness of malaria-control activities for this high-risk group. However, this method has not been widely applied and its usefulness remains to be established with the high prevalence of HIV in many malaria-endemic areas, which is known to put both primigravidae and multigravidae at similar risk of acquiring malaria.

The circumstances under which birthweight is properly used as an indicator of perinatal health continue to be debated. Although the strong association between birthweight and infant mortality is generally accepted in the research community, the causality of this relation remains questionable. Despite large differences in mortality curves by birthweight within a population, mortality differences between populations are generally independent of birthweight. Wilcox[110] argues that a change in the weight distribution of full-term births is unlikely to be a consistent predictor of mortality and, therefore, low birthweight may not be a reliable indicator of perinatal risk. Instead, he argues that populations of births should be compared using the percentage of high-risk small and preterm births represented in the lower tail of the birthweight distribution.[110] Of note, most of this argument is based on data from populations unexposed to malaria in high-income countries, and does not adequately address IUGR, which is also an important correlate of poor infant health. Although the lower tail of the birthweight distribution may be informative as an indicator for perinatal health, it is not as good as acquiring accurate gestational data to clearly distinguish the preterm and IUGR groups. A recent report suggests that African populations may not even have a prominent lower tail, or so-called residual distribution, but instead the entire birthweight curve may be shifted to the left, resulting in high proportions with low birthweight.[111] Research and intervention studies should seek to collect data on gestational age in addition to birthweight to examine the arguments presented above, and to assess the effects of specific interventions (eg, IPT) on the change in birthweight distribution resulting from reductions in preterm birth or IUGR. The definition of low birthweight may also need to be revised to account for maternal stature.

Gaps in public-health knowledge

On the basis of the above review, it is clear that the clinical consequences of malaria in pregnancy to mother and child and the magnitude of the problem are enormous. However, we have very little information from Asia and Latin America, and even for Africa we are currently unable to make an evidence-based statement on whether the overall burden of malaria in pregnancy has increased, decreased, or remained at a steady state in the past few decades. At present, there are substantial knowledge gaps regarding the burden of malaria in pregnancy that impede our understanding of and ability to control this important public-health problem (panel).

Panel: Key gaps in knowledge of the burden of malaria in pregnancy

- Prevalence of malaria in pregnancy in Asia and Latin America
- Longitudinal data
    Effect of single plasmodium infection or asymptomatic infections on the burden of malaria in pregnancy
    Effect of malaria in pregnancy on newborn baby and infant health, as well as true cumulative effect of malaria in pregnancy
    Prevalence of malaria in pregnancy in the first trimester and its correlation with adverse outcomes
- Direct and indirect effect of malaria on
    Severe maternal morbidity and mortality
    Hypertensive disorders of pregnancy and post-partum complications

Lack of estimates on the burden of malaria in pregnancy in Asia and the Americas

Although there are some data from Asia and the Americas on the clinical implications of malaria on the outcome of individual pregnancies, there are few data on the effect of *P vivax* malaria, and on the absolute numbers of pregnant women at risk and what proportion of them have malaria in pregnancy and its adverse outcomes (population estimates). Methods of assessment need to be standardised so that morbidity and mortality estimates can be compared across regions. Although little work has been done on genetic polymorphisms and placental malaria, ideally, estimates of burden should take account of altered genetic susceptibility to malaria in some groups of women. Rapid assessments of the burden of malaria in pregnancy have recently been developed and done in Asia (Bangladesh, India, Burma, Indonesia), in low-transmission areas of French-speaking Africa (Madagascar, Senegal, Niger, Mali, and Mauritania), and will soon be done in Central and South America. However, these assessments have not always been done over a sufficient length of time (a full year), or in sufficiently varied transmission strata to generate good estimates of the burden of malaria in pregnancy, which are essential to design evidence-based interventions for these regions. Year-long, rolling, cross-sectional studies or prospective cohort studies in the respective regions should allow us to fill this gap.

Insufficient longitudinal data

The first gap in knowledge is on the effect of a single plasmodium infection or asymptomatic infections on the burden of malaria in pregnancy. Detailed cohort studies with weekly follow-up from the Thai-Burmese border indicate that even a single pauci-symptomatic infection with either *P falciparum* or *P vivax* that is promptly and adequately treated is associated with a decrease in birthweight that is similar in magnitude to what is found in malaria-endemic settings of Africa.[28] Additionally, it is now clear from two systematic reviews of randomised controlled trials in semi-immune pregnant women in Africa that successful prevention of mostly symptomless infections is associated with clear health benefits to mothers and children.[48,49] This finding suggests that all infections (regardless of symptoms) must be prevented or promptly treated. Similar longitudinal studies are needed elsewhere, especially in Latin America.

The second gap is on the effect of malaria in pregnancy (by gravidity) on infant and child health, as well as the long-term cumulative effect of malaria in pregnancy. The two studies (one *P falciparum* and the other *P vivax*), which showed that infants of malaria-infected multigravidae are at a higher risk of malaria infection and morbidity in infancy than previously appreciated, suggest that the burden of malaria in pregnancy may have been underestimated by focusing on paucigravidae.[28,68] To better quantify the burden of malaria

in pregnancy, future prospective cohort studies in different transmission strata should follow pregnant women throughout pregnancy and the infant through at least 1 year of age and preferably for 5 years to assess the effect on congenital malaria, malaria parasitaemia, clinical malaria, other infectious morbidity (eg, measles), anaemia, and growth. A generic study design, which also accounts for the effect of HIV on malaria-associated outcomes, should be developed for research groups to adopt in their respective settings. Furthermore, statistical modelling strategies may need to be used to assess the chronological effect of malaria in pregnancy on maternal health, newborn and infant health, the child, the adult, and on the next generation.

The third gap is on the burden of malaria in pregnancy in the first trimester and its correlation with adverse outcomes. There are few data on this subject, which hinders our ability to determine how aggressively researchers should pursue the development of safe preventive strategies that would reach women either early in their pregnancy or before they become pregnant. The challenge in many settings will be to encourage women, particularly adolescents, to declare their pregnancy during the first trimester. Prospective cohort studies should be done in settings that can assure longitudinal follow-up of plasmodium-infected and un-infected women identified early in pregnancy.

Paucity of data on the direct and indirect burden of malaria on severe maternal morbidity and mortality

Accurate measurement of malaria-associated maternal morbidity and mortality (both in and out of a health facility setting) is an essential component to quantify the

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Search strategy and selection criteria

Papers for this Review were identified by searches of PubMed with the search terms "malaria" AND ["pregnancy" OR "pregnant"] AND ["burden" OR "prevalence"] to January, 2006. Additional references were obtained from references of the articles in the search, and from malaria in pregnancy databases of published and unpublished literature at CDC and Liverpool School of Tropical Medicine. Special consideration was given to articles identified as reviews in PubMed. Only papers published in English were included. For data on malaria in pregnancy in areas of low malaria transmission, the search was not limited by location or year of study. However, only studies published in English were selected. Papers were considered of interest if they had defined the transmission pattern and malaria in pregnancy was the focus of the paper. The first search used the keywords "malaria", "pregnancy", and "low transmission". Through this search, nine publications were identified based on their titles and their abstracts were read. Six of the publications treated the topic of interest and qualified by our study criteria, whereas the remaining topics were not relevant to our study. A second search was done using the keywords "malaria", "pregnancy", and "unstable transmission". Of the 17 publications identified, two had already been identified during the first search. Three new publications of interest to the study were retrieved. On each of the nine selected papers, the references were reviewed and two additional studies found to be related to our search were selected. A further search done on the CDC malaria branch database revealed two more articles of interest, one each from Latin America and central India.

full burden of malaria in pregnancy. This includes measurement of direct causes (eg, severe and uncomplicated malaria even in endemic settings) and indirect mortality through anaemia, which may reflect a more insidious process. Severe malaria should also be considered as an element in the differential diagnoses of other maternal illnesses such as severe respiratory syndromes, coma, or convulsions (eg, women with cerebral malaria may be misdiagnosed as having eclampsia). Further exploration of whether malaria may increase the risk for pre-eclampsia is also required;[112] a detailed epidemiological analysis of eight datasets from Africa provides evidence for an association between malaria and hypertensive disorders of pregnancy (Uddenfeldt-Wort U, Karolinska Institute, Stockholm, personal communication). Additionally, current mortality datasets need to be analysed by season and the association between mortality and malaria transmission patterns identified. Prospective demographic assessments, or case-control studies of pregnant women at sentinel hospital sites may be needed to derive better estimates of mortality from different geographic regions and for different species. These include estimates in epidemic-prone areas, which are important to monitor in the context of scaling up transmission-reducing interventions such as use of insecticide-treated bednets.

Conclusion

Although much is known about the epidemiology and burden of malaria in pregnancy, there remain substantial gaps in our understanding that impede our ability to control this important public-health problem. The effect of infection in the first trimester, and the longer term effects of malaria in pregnancy beyond infancy are largely unknown and may be substantial. Better estimates are also needed of the effects of malaria in pregnancy outside Africa, and on maternal morbidity and mortality globally. Global risk maps would allow better estimation of potential impact of successful control of malaria in pregnancy.

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