Estimated risk of placental infection and low birthweight attributable to *Plasmodium falciparum* malaria in Africa in 2010: a modelling study

Patrick G T Walker, Feiko O ter Kuile, Tini Garske, Clara Menendez, Azra C Ghani

Summary

Background ***Plasmodium falciparum*** **infection during pregnancy leads to adverse outcomes including low birthweight; however, contemporary estimates of the potential burden of malaria in pregnancy in Africa (in the absence of interventions) are poor. We aimed to estimate the need to protect pregnant women from malaria across Africa.**

Methods **Using a mathematical model applied to estimates of the geographical distribution of *P falciparum* across Africa in 2010, we estimated the number of pregnant women who would have been exposed to infection that year in the absence of pregnancy-specific intervention. We then used estimates of the parity-dependent acquisition of immunity to placental infection and associated risk of low birthweight to estimate the number of women who would have been affected.**

Findings **We estimate that, without pregnancy-specific protection, 12·4 million pregnant women (44·9% of all 27·6 million livebirths in malaria endemic areas in Africa in 2010) would have been exposed to infection, with 11·4 million having placental infection (41·2% of all livebirths). This infection leads to an estimated 900 000 (95% credible interval [CrI] 530 000–1 240 000) low birthweight deliveries per year. Around the end of the first trimester, when the placenta becomes susceptible to infection, is a key period during which we estimate that 65·2% (95% CrI 60·9–70·0) of placental infections first occur.**

Interpretation **Our calculations are the only contemporary estimates of the geographical distribution of placental infection and associated low birthweight. The risk of placental infection across Africa in unprotected women is high. Prevention of malaria before conception or very early in pregnancy is predicted to greatly reduce incidence of low birthweight, especially in primigravidae. The underlying lifetime risk of low birthweight changes slowly with decreasing transmission, drawing attention to the need to maintain protection as transmission falls.**

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MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London, UK (P G T Walker PhD, T Garske PhD, Prof A C Ghani PhD)**; Malaria Epidemiology Unit, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK** (Prof F O ter Kuile PhD)**; Kenya Medical Research Institute, University of Oxford-Wellcome Trust Collaborative Programme, Kenyatta National Hospital Grounds, Nairobi, Kenya** (Prof F O ter Kuile)**; Barcelona Centre for International Health Research, Hospital Clínic-Universitat de Barcelona, Barcelona, Spain** (C Menendez PhD)**; and Centro de Investigação em Saúde da Manhiça (CISM), Manhiça, Mozambique** (C Menendez)

Correspondence to:
Dr Patrick Walker, Department of Infectious Disease Epidemiology, Norfolk Place, London W2 1PG, UK
patrick.walker@imperial.ac.uk

Introduction

Plasmodium falciparum malaria infection during pregnancy leads to infected erythrocytes sequestering within the placenta.[1] This placental infection can have severe consequences for both mother and child, causing maternal anaemia, intrauterine growth restriction, preterm delivery, and fetal death.[2] The prevalence and consequences of malaria in pregnancy are uniquely parity-dependent because women acquire adaptive immunity that restricts the extent of placental infection with successive infected pregnancies.[3] Understanding of the risk of infection during pregnancy, and the associated burden of low birthweight (LBW; <2500 g) this infection can cause, and how this burden varies across the wide range of transmission intensities of *P falciparum* in Africa, is of high priority in assessment of the importance of protection of pregnant women from malaria.

A 2010 analysis[4] used estimates of the global distribution of *P falciparum* transmission[5] to calculate that 31·3 million pregnancies and 22·8 million livebirths occur in areas of stable transmission in Africa. Although this analysis provided a useful indication of the potential scope of the population at risk, it did not include estimates of the actual risk of malaria infection in pregnancy and the various heterogeneities in the likelihood and consequences of infection in pregnant women across Africa. Nor did this calculation of risk indicate the fact that, especially in areas of high transmission, women with high parity have much lower risk of the adverse consequence of malaria infection than do those with low parity, because of immunity acquired from infection during previous pregnancies. Previous estimates of the burden of malaria-attributable LBW,[6,7] an important risk factor for infant morbidity and mortality,[8] similarly did not take into account heterogeneity in transmission or parity-dependent effects on birthweight. These estimates also relied on infection measured by parasites in the placenta at delivery; therefore they do not adequately take into account the effect of infections early in pregnancy, which are a strong risk factor for LBW.[9,10] These early infections are best captured with placental histology,[11] which enables identification of both active

infections and cleared infections (through the persistence of malaria pigment in the placenta).

To accurately estimate the need to protect pregnant women from malaria, we fitted an existing mathematical model of the dynamics of *P falciparum* to high-resolution prevalence estimates across Africa and, using country-specific fertility data, estimated the number of pregnant women who would have been exposed to malaria during pregnancy in 2010, in the absence of protection from infection during pregnancy. We then combined these estimates with a model of placental infection, incorporating the associated risk of LBW, to capture the parity dependence of the risk of infection. This second step is limited by the fact that only two large-scale datasets of placental histology and LBW before large-scale interventions have been published.[12,13] However, we believe that incorporation of the best available quantitative estimate of this fundamental aspect of the epidemiology of malaria in pregnancy, and how this relates to the level of transmission within a population, enable us to provide a nuanced and up-to-date estimate of the burden of malaria in pregnancy and the potential effect of successful prevention of malaria in this high-risk group.

Methods

Modelling of exposure and infection during pregnancy

We mapped the risk of placental infection with *P falciparum* by parity across a 0·1 by 0·1 grid across Africa using a mathematical model that takes into account estimates of the intensity of transmission and fertility patterns within each grid square (appendix).[14] We back-calculated the intensity of transmission in each pixel from the posterior median estimates of parasite prevalence in 2–10-year-old children in 2010,[15] using a relation between measured prevalence and entomological inoculation rate (EIR) obtained from fitting to data from an extensive range of transmission settings.[14,16] We calculated age-specific and parity-specific fertility rates for each pixel, stratified by urban and rural residence, from the most recent national population-based (Demographic and Health Survey, Malaria Indicator Survey, or AIDS Indicator Survey) surveys.[17] We calculated population estimates for 2010, and the proportion of the population living in urban or rural areas, using the method detailed by Cairns and colleagues.[17] We then weighted overall fertility patterns in each pixel using urban-specific or rural-specific national fertility rates and population proportions. For countries with no post-2002 survey data (Botswana, Central African Republic, Djibouti, Equatorial Guinea, Eritrea, Gabon, The Gambia, Guinea-Bissau, Mauritania, Togo, Somalia, South Africa, South Sudan, and Sudan) we calculated fertility patterns using the rates of the country nearest to each pixel. We then ran the mathematical model for placental infection,[14] which also enables estimation of the risk of exposure to infection during pregnancy, using the estimated EIR and fertility pattern in each pixel, calculated assuming a mortality rate of 0·9% per year,[19] to obtain the risk of placental infection at any stage of pregnancy.

We calculated the number of women of child-bearing age in each pixel by multiplying the estimated population by the national estimate of the proportion of the population who are female and aged 15–49 years from country-specific UN demographic information.[20] We then multiplied this figure by the average number of lifetime pregnancies and divided the result by the assumed reproductive lifespan (35 years) to obtain the yearly number of pregnancies resulting in livebirths exposed to infection (defined as having a prevalent infection at the time the placenta develops, or having a peripheral infection at a later stage of gestation) and the total having placental infection in each pixel. This number was summed over all pixels to estimate the number of deliveries leading to livebirths to women infected during pregnancy in Africa projected for 2010, overall and by parity group. We repeated this analysis for 200 draws from the joint posterior distribution of our model, which enabled construction of credible intervals

See Online for appendix

	First pregnancy			Second pregnancy			Third pregnancy			All pregnancies		
	n (×10³)	Placental infection (%)	Placental infection LBW risk (%)*	n (×10³)	Placental infection (%)	Placental infection LBW risk (%)*	n (×10³)	Placental infection (%)	Placental infection LBW risk (%)*	N (millions)	Placental infection (%)	Placental infection LBW risk (%)*
<10%	1374	11·7%	1·4%	1163	11·5%	1·2%	947	11·4%	1·1%	5·6	11·4%	1·1%
10–20%	555	36·8%	4·5%	502	34·4%	3·5%	439	32·0%	2·7%	2·7	31·4%	2·7%
20–30%	529	51·0%	6·5%	491	46·5%	4·7%	441	42·1%	3·2%	2·8	40·9%	3·3%
30–40%	854	59·8%	7·9%	790	53·7%	5·3%	709	48·2%	3·4%	4·5	47·0%	3·7%
40–50%	1083	66·2%	9·0%	1010	59·5%	5·7%	916	53·3%	3·5%	5·8	51·7%	3·9%
50–60%	799	71·3%	10·0%	742	64·2%	6·1%	660	58·0%	3·6%	4·1	56·8%	4·3%
60–70%	347	76·6%	11·1%	323	69·7%	6·5%	290	63·6%	3·7%	1·8	62·0%	4·5%
>70%	39	81·5%	12·4%	32	75·2%	6·8%	32	69·5%	3·8%	0·2	67·8%	4·9%

Prevalence strata calculated by Malaria Atlas Project-estimated slide prevalence in children aged 2–10 years. *LBW risk attributable to placental infection.

***Table 1*: Estimated burden of infection and malaria-attributable low birthweight (LBW) by prevalence (transmission intensity) strata in Africa**