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

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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 [Crl] 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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**Introduction** *Plasmodium falciparum* malaria infection during pregnancy leads to infected erythrocytes sequestering within the placenta. This placental infection can have severe consequences for both mother and child, causing maternal anaemia, intrauterine growth restriction, preterm delivery, and fetal death. 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. 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 used estimates of the global distribution of *P falciparum* transmission 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, an important risk factor for infant morbidity and mortality, 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. These early infections are best captured with placental histology, 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 \textit{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.\textsuperscript{11,12} 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 \textit{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).\textsuperscript{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, using a relation between measured prevalence and entomological inoculation rate (EIR) obtained from fitting to data from an extensive range of transmission settings.\textsuperscript{15,16} 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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.

![Table 1: Estimated burden of infection and malaria-attributable low birthweight (LBW) by prevalence (transmission intensity) strata in Africa](https://www.thelancet.com/lancetgh)
(CrIs), providing an indication of the uncertainty inherent in our estimates of parity-dependent immunity. Further analysis of the level of uncertainty attributable to Malaria Atlas Project-based estimates of parasite prevalence and of the relation between prevalence and intensity of infection was not computationally feasible.

**Incorporation of LBW into model**

To estimate the incremental risk of LBW posed by the different placental infection categories, we extended the model to obtain a relation between parity-specific and histology-specific placental infection categories and the risk of LBW in the absence of competing LBW hazards.

| Country                  | Total pregnancies exposed | Total placental infections | Total attributable LBW | % of total exposure in first pregnancy | % total infection in first pregnancy | % total attributable LBW in first pregnancy |
|--------------------------|---------------------------|----------------------------|------------------------|---------------------------------------|------------------------------------|-----------------------------------------------|
| Angola                   | 298,374                   | 270,503                    | 19,968                 | 19%                                   | 21%                                | 38%                                           |
| Benin                    | 227,247                   | 206,793                    | 15,641                 | 21%                                   | 23%                                | 43%                                           |
| Botswana                 | 512,26                    | 496,596                    | 494                    | 27%                                   | 27%                                | 33%                                           |
| Burkina Faso             | 407,404                   | 369,541                    | 27,864                 | 23%                                   | 25%                                | 48%                                           |
| Burundi                  | 113,245                   | 106,704                    | 9,274                  | 21%                                   | 22%                                | 31%                                           |
| Cameroon                 | 436,292                   | 398,117                    | 31,180                 | 24%                                   | 26%                                | 47%                                           |
| CAR                      | 128,241                   | 115,710                    | 8,449                  | 21%                                   | 23%                                | 43%                                           |
| Chad                     | 218,576                   | 200,476                    | 15,452                 | 20%                                   | 22%                                | 37%                                           |
| Côte d’Ivoire            | 361,912                   | 333,946                    | 27,981                 | 28%                                   | 30%                                | 50%                                           |
| Djibouti                 | 797                       | 786                        | 84                     | 38%                                   | 39%                                | 41%                                           |
| DRC                      | 1,501,677                 | 1,358,364                  | 99,373                 | 20%                                   | 22%                                | 40%                                           |
| Equatorial Guinea        | 14,111                    | 12,851                     | 1,002                  | 24%                                   | 27%                                | 48%                                           |
| Eritrea                  | 14,284                    | 13,863                     | 1,388                  | 26%                                   | 26%                                | 31%                                           |
| Ethiopia                 | 235,988                   | 228,972                    | 22,881                 | 25%                                   | 26%                                | 30%                                           |
| Gabon                    | 45,554                    | 40,706                     | 2,941                  | 20%                                   | 23%                                | 44%                                           |
| The Gambia               | 16,406                    | 15,611                     | 1,426                  | 24%                                   | 25%                                | 33%                                           |
| Ghana                    | 370,514                   | 346,966                    | 30,616                 | 29%                                   | 31%                                | 47%                                           |
| Guinea                   | 213,778                   | 195,950                    | 15,257                 | 22%                                   | 24%                                | 40%                                           |
| Guinea-Bissau            | 17,628                    | 16,628                     | 1,467                  | 22%                                   | 24%                                | 43%                                           |
| Kenya                    | 147,559                   | 140,392                    | 1,298                  | 29%                                   | 31%                                | 42%                                           |
| Liberia                  | 76,222                    | 70,171                     | 6,128                  | 24%                                   | 26%                                | 44%                                           |
| Madagascar               | 256,619                   | 245,169                    | 20,831                 | 26%                                   | 28%                                | 44%                                           |
| Malawi                   | 295,588                   | 271,555                    | 21,764                 | 23%                                   | 25%                                | 42%                                           |
| Mali                     | 354,503                   | 317,071                    | 22,108                 | 19%                                   | 21%                                | 42%                                           |
| Mauritania               | 31,458                    | 29,329                     | 2,646                  | 19%                                   | 20%                                | 30%                                           |
| Mozambique               | 590,301                   | 539,791                    | 39,504                 | 20%                                   | 22%                                | 42%                                           |
| Namibia                  | 15,760                    | 15,047                     | 1,422                  | 29%                                   | 30%                                | 40%                                           |
| Niger                    | 301,726                   | 274,391                    | 20,241                 | 19%                                   | 21%                                | 37%                                           |
| Nigeria                  | 3,311,949                 | 3,024,553                  | 232,403                | 21%                                   | 23%                                | 42%                                           |
| Republic of Congo        | 72,776                    | 67,601                     | 5,736                  | 27%                                   | 29%                                | 46%                                           |
| Rwanda                   | 28,722                    | 27,899                     | 2,809                  | 26%                                   | 27%                                | 32%                                           |
| Senegal                  | 104,623                   | 99,320                     | 5,306                  | 22%                                   | 23%                                | 31%                                           |
| Sierra Leone             | 135,298                   | 124,775                    | 10,222                 | 25%                                   | 27%                                | 45%                                           |
| Somalia                  | 29,208                    | 28,331                     | 2,823                  | 25%                                   | 26%                                | 30%                                           |
| South Africa             | 48,987                    | 46,980                     | 4,462                  | 25%                                   | 26%                                | 33%                                           |
| Sudan (including South Sudan) | 424,707                | 398,681                    | 34,194                 | 22%                                   | 23%                                | 33%                                           |
| Swaziland                | 367                       | 352                        | 34                     | 29%                                   | 30%                                | 37%                                           |
| Tanzania                 | 496,605                   | 460,849                    | 38,104                 | 22%                                   | 24%                                | 37%                                           |
| Togo                     | 152,643                   | 139,215                    | 10,755                 | 22%                                   | 25%                                | 44%                                           |
| Uganda                   | 630,085                   | 577,616                    | 45,731                 | 23%                                   | 25%                                | 43%                                           |
| Zambia                   | 192,154                   | 176,690                    | 13,761                 | 19%                                   | 20%                                | 31%                                           |
| Zimbabwe                 | 72,625                    | 70,102                     | 2,675                  | 26%                                   | 26%                                | 32%                                           |

DRC=Democratic Republic of Congo. CAR=Central African Republic.

Table 2: Estimated burden of infection and malaria-attributable low birthweight (LBW) by country
which might vary in differing settings (see appendix for full details of how the relation between infection and LBW was fitted to data from Ifakara, Tanzania,12 and Kilifi, Kenya13). Notably, this approach means that our estimate of malaria-attributable LBW will include deliveries that would already have been LBW in the absence of infection. However, because the consequences of LBW are more severe the lower the weight, with very low birthweight babies (<2000 g) at greatest risk of neonatal mortality,21 it seems reasonable to assume that deliveries already destined to be LBW, which then receive sufficient exposure to placental infection to cause malaria-attributable LBW, are likely to be at great risk of negative birth outcomes due to malaria, especially if malaria contributes to further reduction of birthweight. As a result, we believe that to count these deliveries within our estimates of LBW attributable to malaria is likely to be a good indication of the underlying morbidity caused by malaria. We did our analyses using C++ and the R statistical package.

Role of the funding source
The funders had no role in study design, collection, analysis, and interpretation of the data, writing of the Article, or the decision to submit the Article for publication.

Results
We estimate that, in 2010, from a total of 27.6 million pregnancies leading to livebirths occurring in malaria-endemic areas in Africa, 12.4 million (44.9%) would have been exposed to infection if not specifically protected. Taking into account the effects of parity-dependent immunity, we estimate that 41.2% (95% CrI 38.8–43.8) or 11.4 million (10.7–12.1 million) women would have had placental infection at some stage during pregnancy. Our estimates show substantial geographical variation in these statistics, mainly due to heterogeneity in transmission intensity, with prevalence of placental infection in pregnant women ranging from 73% along the Nigeria–Cameroon border to 2% in the Kenyan highlands. Tables 1 and 2 show the distribution of these pregnancies by transmission intensity strata and country. Primigravidae were at the highest risk of placental infection, with an estimated 2.7 million (48.2%) of 5.6 million first pregnancies infected, although risk of infection during pregnancy was high in multigravidae, with 8.7 million (39.5%) of 22.0 million pregnancies infected. The proportion of women potentially exposed to and having placental infection during pregnancy increases with transmission intensity (figures 1D and 2D, tables 1 and 2). Placental infection prevalence decreases with parity (figure 2A–C), because women acquire parity-dependent immunity, and a higher degree of age-dependent immunity, and are therefore better able to clear infection than are women of lower parity.

Figure 3 shows our estimates of the timing of infection during gestation. In the absence of malaria in pregnancy-specific interventions, 65.2% (95% CrI 60.9–70.0) of
Placental infections are estimated to occur early in gestation, when the placenta reaches the stage of development at which it can be parasitised by an ongoing infection (in our model this point is assumed to be at 12 weeks’ gestation, but could occur as early as at 7 weeks). Subsequently throughout pregnancy, the incidence of placental infection is directly related to the incidence of peripheral infection, which is much lower and, as a consequence of our model assumptions, is constant until delivery. We also did a sensitivity analysis of the potential effect of seasonality on these estimates (appendix). The risk of placental infection early in pregnancy varies with transmission season, with women who deliver about 30 weeks after the seasonal peak being most likely to have had an ongoing infection when their placenta first becomes susceptible. However, when we controlled for prevalence in children aged 2–10 years and assumed constant overall fertility, this seasonal variation did not substantially change our estimates of the averaged risk across the year (appendix).

Because of the absence of parity-dependent immunity, primigravidae are estimated to have more prolonged placental infection. Untreated, infected primigravidae spent, on average, 120·4 days (95% CrI 113·5–125·8) with placental infection, compared with 83·3 days (74·7–95·4) in multigravidae. This longer period is likely to cause, or at least indicate, an inflammatory immune response liable to lead to LBW.

The appendix shows the data and fitted model for the association between placental infection and LBW risk in Kilifi, Kenya, and Ifakara, Tanzania. In both settings the risk of a LBW delivery was associated with the different placental infection categories, and the risk of being infected at delivery (evidence of either acute or chronic infection) is highest for primigravidae. In Kilifi, where transmission was less intense, a degree of placental infection-attributable risk of LBW in paucigravidae (gravidae 2–4; appendix) seems to exist, whereas in Ifakara, where transmission intensity was higher, the association between risk of LBW and the different placental infection categories in paucigravidae was weaker, and absent in grand-multigravidae, suggesting that malaria might have little effect on birthweight in most multigravid women in this setting (appendix). By contrast, the risk of LBW by infection stage, particularly among previously unexposed primigravidae, seems to follow a consistent pattern across both transmission settings, with women with chronic infection at delivery at highest risk than those whose placentas were not infected (drawing attention to the requirement to capture the role of early infection within our model). By contrast, across both settings, acute infection by histology at delivery and the risk of LBW seem to have very little association.

Of all the combinations of variables tested (appendix), we noted that a model in which LBW risk depends solely on the duration of chronic infection during pregnancy, and which is estimated to be most affected by the acquisition of parity-dependent immunity, provided the closest fit to these observed patterns of LBW (figure 4).
Figure 4: Spatial distribution of estimated risk of placental-malaria-attributable low birthweight (LBW)
Maps show the LBW risk per delivery for first (A), second (B), and third (C) pregnancies, and the same measure averaged over all gravidities (D). Map (D) is presented on a different colour scheme from A–C to show spatial difference in the overall per-pregnancy risk at a higher resolution.

Panel: Research in context

Systematic review

We searched PubMed (date last search done Sept 2, 2013) with no date limits or language restrictions using the search terms “malaria”, “burden”, AND “pregnancy” to identify previous estimates of the number of pregnancies affected by malaria and the associated burden of low birthweight in Africa. This identified three key studies. The most recent study used estimates of the distribution of Plasmodium falciparum parasite prevalence to estimate pregnancies and livebirths at risk, but did not estimate the risk of placental infection or the burden of low birthweight attributable to P falciparum malaria. The two older studies did estimate these quantities, but are now more than 10 years old and hence do not capture the heterogeneity in transmission that occurs across Africa, nor the extent to which this has changed in recent years. We therefore sought to capture these important aspects to obtain contemporary estimates of burden.

Interpretation

We estimate that the exposure to, and risk of, placental infection increases with transmission intensity. At the same time, pregnant women develop increasing immunity with exposure to malaria through successive pregnancies, such that the overall attributable burden of LBW women have throughout child-bearing age is similar in all areas of moderate-to-high transmission, decreasing as the prevalence of infection in the population reduces to less than 10%. A large proportion of this burden is estimated to be due to infections acquired early in or before pregnancy. Protection of women from malaria in pregnancy should therefore be a public-health priority, and increased focus should be placed on adequate protection of women early in, or immediately before, their first pregnancy.

We estimated that 900 000 (95% CrI 530 000–1 240 000) malaria-attributable LBW deliveries in the absence of pregnancy-specific interventions occurred in Africa in 2010. Figure 4 shows how this risk varies spatially and by parity. LBW risk is estimated to be strongly concentrated in women having their first pregnancies, comprising 39% (95% CrI 32–46) of the total placental-infection-attributable LBW burden. This risk is also subject to the greatest degree of spatial heterogeneity, with estimates of malaria-attributable risk of LBW ranging from more than 12% in areas of very high prevalence (above 70% slide prevalence in ages 2–10 years) such as inland west Africa and northern Mozambique to less than 1.5% in areas where the same population prevalence is less than 10% (figure 4A; table 1). Assuming our model of LBW risk also holds for seasonal settings, our sensitivity analysis of seasonality (appendix) suggests that these results are generally insensitive to variation in transmission throughout the year.

In second and subsequent pregnancies, parity-dependent immunity reduces the burden of infection and reduces spatial heterogeneity in LBW risk, with women in high transmission areas acquiring a greater degree of immunity than those in less-intensive settings. As a result, by their third pregnancy, pregnant women are estimated to be at very similar low levels of malaria-attributable LBW risk (2–4%) in all areas of moderate-to-high transmission (more than 10% 2–10-year-old prevalence; table 1). This parity-dependent pattern also means that patterns of fertility might cause substantial spatial variation in overall per-pregnancy risk of LBW, with areas where women have a low mean number of lifetime pregnancies having a higher burden of LBW per pregnancy than areas where women have a high mean number of pregnancies, due to the higher relative proportion of primigravidae and secundigravidae (appendix).

The overall numbers of infected pregnancies and malaria-attributable LBW deliveries have a similar geographical pattern (appendix), with the largest burden occurring in areas where high levels of transmission coincide with high population density.

Discussion

Our estimates are the first of the distribution of the parity-specific risk of placental sequestration in Africa, and the only contemporary estimates of the corresponding malaria-associated risk of LBW (panel). We estimated that, in the absence of pregnancy-specific interventions, 12.4 million women delivering live babies (44–9% of all liveborn deliveries) would be exposed to infection capable of sequestering within the placenta. When we applied our estimates of parity-dependent immunity, which can prevent placental infection, and the risk of LBW, this translated into 11.4 million (41·2%) placental infections and 900 000 (3·3%) LBW deliveries. This burden estimate does not include the effect of symptomatic malaria and its effect on the risk of preterm delivery in women without immunity in areas of low transmission intensity; which might modify the relation between malaria-attributable LBW and the risk of neonatal mortality. However, because we estimate that only 6% of pregnancies exposed to malaria occur in areas with prevalence lower than 10%, this number might not contribute substantially
to LBW burden relative to the effect of chronic asymptomatic infection in higher transmission settings. Our estimates suggest that primigravidae, who have yet to acquire parity-dependent immunity, have a slightly higher risk of placental infection than do multigravidae, but that the progression of infection is the main contributor to the disproportionate level of malaria-attributable LBW they experience. In particular we noted that the high risk of prolonged chronic infection in women without pregnancy-specific immunity as estimated by our model, and evidenced by a much higher proportion of chronic infection in primigravidae at delivery, provides the best fit to patterns of LBW risk by parity and histology. A risk of LBW dependent on the chronicity of infection could also be partly due to the fact that these infections are likely to have occurred earlier in pregnancy (a factor captured in our model).

These estimates accord with findings from a 2011 study that women infected early in pregnancy have a disproportionately high risk of LBW, and suggests that clearing of infection as early in pregnancy as possible should be a priority. On the basis of our previous model fitting, the available evidence, and the peak in the incidence of placental infection begins around the end of the first trimester, or soon before a woman becomes pregnant, is likely to have the largest effect both on the number of women with placental infection and the LBW burden this creates.

Our estimates suggest that, because of the effects of parity-dependent immunity, the overall per-pregnancy risk of LBW changes very gradually with increasing transmission intensity, with the risk becoming more concentrated in women who have had fewer pregnancies. If transmission has recently reduced, however, our estimates might temporarily overestimate LBW burden, because primigravidae are less likely to become infected than are multigravidae, whereas multigravidae maintain a level of immunity acquired at a time when transmission was more intense. Instead, in areas where this is true, our estimates should be interpreted as the risk a woman starting her first pregnancy is likely to have throughout her lifetime if transmission rates are constant.

This estimate of the relation between placental infection and the burden of LBW is based on data from only two sites because these were the only available large-scale datasets to our knowledge that provide the risk of LBW by parity and the histological stage of infection before the introduction of insecticide-treated nets or intermittent preventive therapy. This relation would be likely to replicate similar patterns of LBW risk by placental histology to those observed in smaller datasets from other settings. However, the assumption that our estimates can be extended to all of Africa is impossible to validate. Our estimates also ignore various heterogeneities that could affect the probability of infection and associated LBW risk, such as the distribution of sickle-cell trait, glucose-6-phosphate dehydrogenase deficiency, and maternal undernutrition, which vary by region. Similarly, any seasonality in fertility could also affect the overall risk of infection and burden of LBW in seasonal transmission settings. However, the most important factor not included in the model is HIV infection, which disrupts the development of parity-dependent immunity, leaving women of high parity with HIV at similar susceptibility to placental malaria as during their first pregnancies. Our model was fitted to data from areas of similar HIV prevalence (8·5% among pregnant women in Kilifi, and 6·5% in Ifakara). This consistency could affect the generalisability of our model to areas of lower prevalence such as west Africa, and of higher prevalence such as southern Africa. However, despite these limitations, we do seem to have captured many of the most fundamental aspects of the epidemiology of placental infection in areas of sustained transmission that have not been previously incorporated into estimates of the burden of malaria in pregnancy in Africa. These include parity-dependent reductions in susceptibility to placental infection depending on infection during previous pregnancies, the importance of early infection, which might clear by delivery, and the inflammatory reaction within the placenta associated with chronic infection.

In conclusion, despite documented reductions in malaria transmission in various parts of Africa, the burden of placental infection in unprotected pregnant women remains. This draws attention to the need to maintain high levels of intervention coverage in pregnant women during the transition to universal coverage. Our results also suggest that measures that reduce exposure to infection in the early stages of, or immediately before, pregnancy, such as insecticide-treated nets, are likely to be very effective in prevention of placental infection and corresponding LBW, especially in women during their first pregnancy.

**Contributors**
PGTW and ACG conceived and designed the study. PGTW did the literature search and the analysis. CM, TG, and PGTW prepared the data. All authors contributed to data interpretation and writing of the Review, and approved the final version.

**Declaration of interests**
ACG received grants from Liverpool School of Tropical Medicine, Bill & Melinda Gates Foundation, and Medical Research Council during the study; personal fees from Oxford Policy Management/UK Department for International Development (DFID) for work done as part of a mid-term review of the UK Malaria Framework for Results, and grants from WHO/DFID, Malaria Vaccine Initiative, Medicines for Malaria Venture, Bill & Melinda Gates Foundation, The Wellcome Trust, and non-financial support from GlaxoSmithKline Biologicals outside this work. PGTW, FoE, TG, and CM declare no competing interests.
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