Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis

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Summary

Background 2·6 million stillbirths occur annually worldwide. The association between malaria in pregnancy and stillbirth has yet to be comprehensively quantified. We aimed to quantify the association between malaria in pregnancy and stillbirth, and to assess the influence of malaria endemicity on the association.

Methods We did a systematic review of the association between confirmed malaria in pregnancy and stillbirth. We included population-based cross-sectional, cohort, or case-control studies (in which cases were stillbirths or perinatal deaths), and randomised controlled trials of malaria in pregnancy interventions, identified before Feb 28, 2017. We excluded studies in which malaria in pregnancy was not confirmed by PCR, light microscopy, rapid diagnostic test, or histology. The primary outcome was stillbirth. We pooled estimates of the association between malaria in pregnancy and stillbirth using meta-analysis. We used meta-regression to assess the influence of endemicity. The study protocol is registered with PROSPERO, protocol number CRD42016038742.

Findings We included 59 studies of 995 records identified, consisting of 141 415 women and 3387 stillbirths. *Plasmodium falciparum* malaria detected at delivery in peripheral samples increased the odds of stillbirth (odds ratio [OR] 1·81 [95% CI 1·42–2·30]; I^2=26·1%; 34 estimates), as did *P falciparum* detected in placental samples (OR 1·95 [1·48–2·57]; I^2=33·6%; 31 estimates). *P falciparum* malaria detected and treated during pregnancy was also associated with stillbirth, but to a lesser extent (OR 1·47 [95% CI 1·13–1·92]; 19 estimates). *Plasmodium vivax* malaria increased the odds of stillbirth when detected at delivery (2·81 [0·77–10·22]; three estimates), but not when detected and treated during pregnancy (1·09 [0·76–1·57]; four estimates). The association between *P falciparum* malaria in pregnancy and stillbirth was two times greater in areas of low-to-intermediate endemicity than in areas of high endemicity (ratio of ORs 1·96 [95% CI 1·34–2·89]). Assuming all women with malaria are still parasitaemic at delivery, an estimated 20% of the 1 059 700 stillbirths in malaria-endemic sub-Saharan Africa are attributed to *P falciparum* malaria in pregnancy; the population attributable fraction decreases to 12%, assuming all women with malaria are treated during pregnancy.

Interpretation *P falciparum* and *P vivax* malaria in pregnancy both increase stillbirth risk. The risk of malaria-associated stillbirth is likely to increase as endemicity declines. There is a pressing need for context-appropriate, evidence-based interventions for malaria in pregnancy in low-endemicity settings.

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Introduction

An estimated 2·6 million stillbirths occur worldwide each year, resulting in substantial psychosocial and economic costs.[1,2] 98% of stillbirths occur in resource-limited settings and many are preventable.[2] Annually, 125 million women are at risk of *Plasmodium falciparum* or *Plasmodium vivax* malaria in pregnancy.[3] Although *P falciparum* malaria in pregnancy is recognised as a cause of stillbirth,[4] the association between *P falciparum* and *P vivax* malaria in pregnancy and stillbirth has yet to be comprehensively quantified using all available data. Precise estimates of the association between *P falciparum* and *P vivax* malaria in pregnancy and stillbirth requires consideration of malaria endemicity; in low-endemicity areas, the effect of malaria in pregnancy might be greater because maternal antimalarial immunity is low.[5,6] Malaria endemicity is declining worldwide, particularly in Africa,[7] and 76% of women at risk of malaria in pregnancy live in low-endemicity areas outside of Africa where *P falciparum* and *P vivax* malaria coexist.[3] Quantification of the contribution of malaria in pregnancy to stillbirth is essential for resource allocation for stillbirth prevention (for malaria or other factors).

We aimed to systematically review and synthesise population studies of pregnant women living in malaria-endemic areas, in which researchers collected data on malaria in pregnancy and stillbirth, to quantify the association between malaria in pregnancy and stillbirth, for both *P falciparum* and *P vivax* malaria, detected either during pregnancy or at delivery. We also aimed to assess

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Research in context

Evidence before this study

We searched Scopus, PubMed, and Web of Science for articles published up to Feb 28, 2017, in any language, that reviewed, or estimated a population attributable fraction for, the association between malaria in pregnancy and stillbirth using the search terms "malaria", "pregnan*", "still* OR perinatal", and "review OR attributable". Before this review, one systematic review had been done for the association between placental *Plasmodium falciparum* malaria and stillbirth, which pooled associations from nine studies. One study had calculated the population attributable fraction for the contribution of *P falciparum* malaria in pregnancy in Africa to stillbirth using the estimated association between malaria in pregnancy and stillbirth from a single study-site in Africa. We found no systematic reviews of the association between *Plasmodium vivax* malaria in pregnancy and stillbirth through our search. No studies had quantified the influence of endemicity on the association between malaria in pregnancy and stillbirth.

Added value of this study

To our knowledge, this large and comprehensive systematic review and meta-analysis, including data from 59 studies, provides the most accurate estimates of the associations between both *P falciparum* and *P vivax* malaria in pregnancy and stillbirth to date. This review also provides the first quantification of the influence of malaria endemicity on this association, which is particularly pertinent as malaria endemicity is declining globally. Using the estimates from this review, we have quantified the number of stillbirths attributed to malaria in pregnancy in malaria-endemic sub-Saharan Africa, assuming initially that no malaria in pregnancy is resolved before delivery, and then assuming that all malaria in pregnancy is treated before delivery.

Implications of all the available evidence

P falciparum and *P vivax* malaria in pregnancy both increase the risk of stillbirth, but to a lesser extent if malaria is treated before delivery. In areas transitioning from high to moderate endemicity, the proportion of stillbirths attributed to malaria in pregnancy is likely to increase due to an increased risk of malaria-associated stillbirth in infected individuals. In sub-Saharan Africa, where the average endemicity is now moderate, one to two in ten stillbirths are attributed to *P falciparum* malaria in pregnancy, and the risk of malaria-associated stillbirth in infected individuals is likely to increase as endemicity decreases further. There is a pressing need for context-appropriate, evidence-based interventions for malaria in pregnancy in low-endemicity settings.

sources of heterogeneity across studies, particularly endemicity, and to determine population attributable fractions (PAFs) to quantify the contribution of malaria in pregnancy to stillbirth at varying levels of endemicity.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched Scopus, PubMed, and Web of Science for studies published in any language up to and including Feb 28, 2017, which assessed the association between malaria in pregnancy and birth outcomes, and reported on stillbirth or perinatal death (appendix p 3). We also contacted key researchers in the field for unpublished data. We included population-based, cross-sectional, cohort, or case-control studies (in which cases were stillbirths or perinatal deaths) done in malaria-endemic areas if the association between confirmed malaria in pregnancy and stillbirth or perinatal death could be obtained. We also included groups of randomised controlled trials of malaria in pregnancy interventions in which women received the status-quo intervention when the study was done, or no intervention. We excluded studies in which malaria in pregnancy was not confirmed by PCR, light microscopy, rapid diagnostic test, or histology. The primary outcome was stillbirth. We included studies reporting on perinatal death that were unable to provide data specifically for stillbirth in a secondary analysis of perinatal death. We did not exclude studies on the basis of definitions used to define stillbirth and perinatal death, which vary widely between studies, but instead extracted gestational age thresholds for meta-regression analyses. This review is reported according to the MOOSE guidelines[8] and the PRISMA guidelines for systematic reviews (appendix p 2).[9]

See Online for appendix

Data analysis

Two independent authors (KAM and MJLS) extracted data using a proforma; discrepancies were resolved by discussion with a third reviewer (FJIF). Authors of studies were contacted and provided a proforma (appendix p 4) to complete if collection of data on malaria in pregnancy and stillbirth or perinatal death was indicated in the methods or results sections, but the association between malaria in pregnancy and stillbirth was not reported. We also contacted authors to clarify information regarding eligibility, and for species-specific estimates. Risk of bias was assessed using the Risk of Bias in Non-randomised Studies—of Interventions (ROBINS-I) tool (appendix p 5).[10] We extracted measures of association and 95% CIs from the most fully adjusted model or calculated odds ratios (ORs) and 95% CIs using cross-tabulated data.

We categorised *P falciparum* endemicity as low, intermediate, or high using information in the published papers. If there was insufficient information and study enrolment started after 2005, we categorised endemicity using the Malaria Atlas Project Data Explorer (endemicity class [proportion of children aged 2–10 years in the

general population infected with *P falciparum* at any one time in 2010, $PfPR_{2-10}$] was approximated using the endemicity colour scale as low [<10%], intermediate [≥10% to <50%], or high [≥50%]).[7]

We estimated pooled ORs for the association between malaria in pregnancy and stillbirth from random-effects meta-analyses, done separately according to species (*P falciparum* or *P vivax*), time of detection (during pregnancy or at delivery), and sample (peripheral or placental). The exposed group for estimates of malaria detected during pregnancy assumes both detection and treatment during pregnancy; however, whether exposed women were malaria-free at delivery is unknown. The exposed group for estimates of malaria detected at delivery includes women who might have been treated during pregnancy (including presumptive treatment), but were parasitaemic at the time of delivery (ie, unresolved malaria). If studies used multiple detection methods, we included the estimate using the most common method within the relevant meta-analysis.

Where appropriate (low between-study variance and more than ten contributing estimates), we assessed bias due to small-study effects with funnel plots and Egger's asymmetry test.[11,12] We explored heterogeneity using meta-regression to estimate the association between the log-transformed study-specific ORs and prespecified variables (definition of stillbirth, *P falciparum* endemicity class, first year of enrolment, when women were enrolled during pregnancy, and ultrasound gestational age estimation). We used the pooled ORs for the association between peripheral *P falciparum* malaria detected at delivery (assuming all malaria in pregnancy goes unresolved) or during pregnancy (assuming all malaria in pregnancy is treated during pregnancy) and stillbirth in areas of low-to-intermediate and high *P falciparum* endemicity to calculate PAFs for population prevalences between 1% and 50% and between 50% and 100%, respectively. All analyses were done in Stata (version 14). The study protocol is registered with PROSPERO, protocol number CRD42016038742.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 995 records, and 455 records were potentially relevant after screening titles and abstracts (figure 1). After full-text reviews, 332 articles were excluded (appendix p 7), 29 articles met the inclusion criteria for stillbirth, and 85 potentially met the inclusion criteria for stillbirth. Contact with 85 authors yielded a further 34 studies that met the inclusion criteria for stillbirth. Four more studies were identified that met the inclusion criteria following contact with 71 key researchers. 59 studies were included in our primary review of the association between malaria in pregnancy and stillbirth; eight studies were included in a secondary review of the association between malaria in pregnancy and perinatal death (appendix p 8).[14–80]

46 of the 59 included studies were done in Africa, ten were done in Asia, and two were done in the Americas

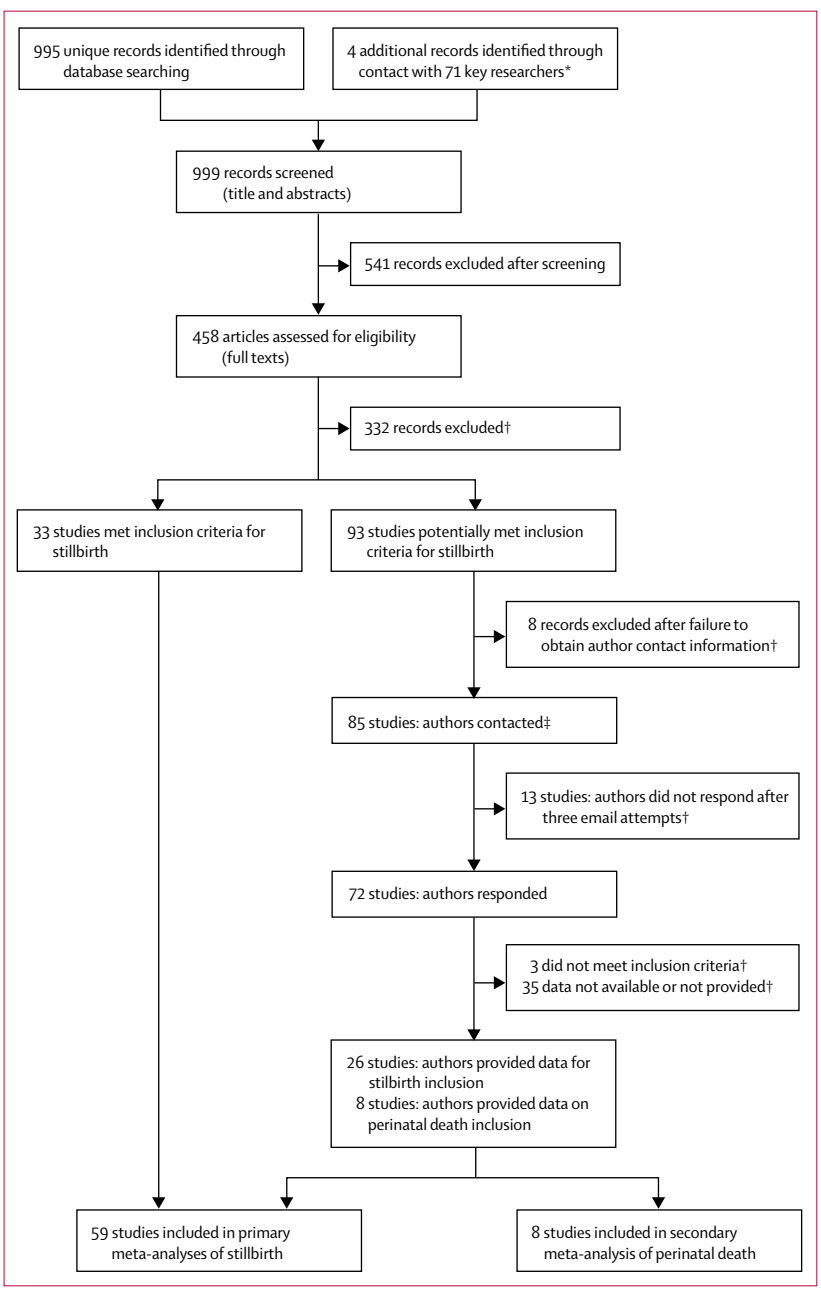


***Figure 1*: Study selection**

*Key researchers were identified systematically using the references of a review of malaria in pregnancy,[13] and through our search; the four studies identified through contact with key researchers rather than our systematic search were Natureeba, 2014; Mbonye, 2015; Gutman, 2015; and Moore, 2017. †Citations and reasons for exclusion are given in the appendix (p 7). ‡Including seven studies that met the inclusion criteria for perinatal death before author contact.

	Country	Study type	Stillbirth definition (weeks)*	*Plasmodium falciparum* endemicity†	*P falciparum* malaria in pregnancy (%)‡	N§	Stillbirths¶
Africa							
Ako-Nai, 2013‖	Nigeria	Cohort	DNS	Intermediate	78% (during pregnancy)	74	2
Anagnos, 1986‖	Zaire (Democratic Republic of Congo)	Cross-sectional	DNS	High	64% (at delivery; placental sample)	100	7
Arinaitwe, 2013**	Uganda	Cross-sectional	DNS	High	19% (at delivery; peripheral sample)	565	13
Asundep, 2014††	Ghana	Cross-sectional	DNS	Intermediate	9% (at delivery; peripheral sample)	630	DNS
Axemo, 1995‖	Mozambique	Case-control	20	High	Case-control	370	163
Ayisi, 2003‖	Kenya	Cohort	32	Unknown	22% (at delivery; peripheral or placental)	5168	34
Braun, 2015††	Uganda	Cross-sectional	DNS	Intermediate	4% (at delivery; placental sample)	915	39
Briand, 2009**	Benin	RCT	28	Low	3% (during pregnancy)	799	15
De Beaudrap, 2013††	Uganda	Cohort	28	Intermediate	Includes PCR detection	1218	22
Desai, 2015**	Kenya	RCT	20	High	7% (at delivery; peripheral sample)	514	16
Diallo, 2007**	Mali	RCT	DNS	Unknown	5% (at delivery; peripheral sample)	301	2
Fouelifack, 2015**	Cameroon	Retrospective cohort	22	Intermediate	Only symptomatic tested	462	12
Geidam, 2011‡‡	Nigeria	Retrospective cohort	DNS	Intermediate	Only symptomatic tested	518	19
Gutman, 2015**	Malawi	Cross-sectional	28	Intermediate	5% (at delivery; peripheral sample)	1851	6
Gutman, 2013**	Malawi	Cross-sectional	DNS	High	5% (at delivery; peripheral sample)	703	12
Hamer, 2007**	Zambia	RCT	28	Intermediate	3% (at delivery; peripheral sample)	456	7
Huynh, 2011**	Benin	Cohort	28	High	30% (during pregnancy)	982	32
Kakuru, 2016**	Uganda	RCT	28	High	4% (at delivery; peripheral sample)	106	1
Kalanda, 2006§§	Malawi	Cohort	24	High	20% (during pregnancy)	1571	54
Kalilani-Phiri, 2013**	Malawi	Cohort	DNS	Intermediate	17% (during pregnancy)	450	9
Kasumba, 2000‖	Uganda	Cross-sectional	DNS	Low	6% (at delivery; placental sample)	544	23
Kayentao, 2007**	Mali	Cross-sectional	DNS	High	26% (at delivery; peripheral sample)	453	21
Kayentao, 2005**	Mali	RCT	DNS	High	22% (at delivery; peripheral sample)	389	18
Klement, 2014**	Togo	RCT	DNS	High	49% (during pregnancy or at delivery)	264	5
Lamikanra, 1993‖	Nigeria	Cross-sectional	DNS	Unknown	3% (at delivery; peripheral sample)	101	6
Luntamo, 2010**	Malawi	RCT	22	High	8% (during pregnancy)	436	17
Mace, 2015**	Zambia	Cross-sectional	28	High	5% (at delivery; peripheral sample)	435	9
Maiga, 2011**	Mali	RCT	DNS	High	15% (at delivery; peripheral sample)	814	10
Mbonye, 2015**	Uganda	Cohort	DNS	High	Includes PCR detection	1387	16
Mbonye, 2008**	Uganda	RCT	28	High	Only asymptomatic tested	2785	14
McGregor, 1983‖	The Gambia	Cross-sectional	DNS	High	12% (at delivery; placental sample)	6605	414
Natureeba, 2014§§	Uganda	RCT	20	High	3% (at delivery; placental sample)	389	11
Newman, 2003‖	Ethiopia	Cross-sectional	DNS	Low	6% (at delivery; placental sample)	1018	28
Obieche, 2015**	Nigeria	Cross-sectional	20	Intermediate	10% (at delivery; peripheral or placental)	236	3
Okoko, 2002††	The Gambia	Cross-sectional	24	High	51% (at delivery; placental sample)	320	35
Olliaro, 2008‖	Senegal	Cohort	20	Intermediate	Only symptomatic tested	1781	20
Osman, 2001††	Mozambique	Cohort	22	Intermediate	4% (during pregnancy)	908	35
Rulisa, 2012‖	Rwanda	Cohort	DNS	Low	Only symptomatic women tested	77	1
Sule-Odu, 2002‖	Nigeria	Cross-sectional	28	High	24% (at delivery; peripheral sample)	564	16
Tagbor, 2015**	Multicountry	RCT	DNS	High	41% (during pregnancy)	2678	76
Taha, 1993††	Sudan	Case-control	DNS	Unknown	Case-control	1009	197
Ticconi, 2003‖	Zimbabwe	Cross-sectional	20	Unknown	Only symptomatic tested	1046	15
Valente, 2011**	Angola	Cross-sectional	DNS	Low	Includes PCR detection	567	22
van Spronsen, 2012**	Ghana	Cross-sectional	DNS	High	53% (at delivery; placental sample)	107	5
Watson-Jones, 2007††	Tanzania	Cohort	22	Unknown	10% (at delivery; peripheral sample)	1688	40
Wort, 2007**	Tanzania	Cross-sectional	DNS	Unknown	9% (at delivery; placental sample)	836	10
Wort, 2006**	Tanzania	Cross-sectional	DNS	High	28% (at delivery; peripheral sample)	1902	113

(Table continues on next page)

	Country	Study type	Stillbirth definition (weeks)*	*Plasmodium falciparum* endemicity†	*P falciparum* malaria in pregnancy (%)‡	N§	Stillbirths¶
(Continued from previous page)							
Asia							
Ahmed, 2014††	India	Cross-sectional	22	Low	7% (at delivery; placental sample)	506	22
Amoa, 1998††	Papua New Guinea	Case-control	20	Unknown	Case-control	630	315
Das, 2000‖	India	Cohort	DNS	High	Includes *Plasmodium vivax* cases	209	6
Hamer, 2009‖	India	Cross-sectional	DNS	Low	Includes *P vivax* cases	718	30
Moore, 2017††	Thailand	Cohort	28	Intermediate	9% (during pregnancy)	61836	526
Poespoprodjo, 2015**	Indonesia	Retrospective cohort	28	Intermediate	10% (at delivery; peripheral sample)	7744	188
Singh, 2014‖	India	Cohort	DNS	Low	Includes *P vivax* cases	203	7
Singh, 2001‖	India	Cohort	DNS	Intermediate	48% (during pregnancy)	274	5
Singh, 2015‖	India	Cross-sectional	28	Intermediate	Includes *P vivax* cases	1030	23
Singh, 1998**	India	Cohort	28	Intermediate	20% (during pregnancy or at delivery)	456	4
The Americas							
Carles, 1998‖	French Guyana	Retrospective cohort	28	Intermediate	3% (during pregnancy)	3931	51
Carmona-Fonseca, 2009**	Colombia	Cohort	20	Low	2% (at delivery; peripheral sample)	2117	9

DNS=did not state. RCT=randomised controlled trial. *Weeks' gestation used to differentiate a stillbirth from a miscarriage. †*P falciparum* endemicity categorised as low, intermediate, or high using information in the published papers or using the Malaria Atlas Project Data Explorer if insufficient information was given in papers and enrolment started after 2005. ‡Proportion of women with *P falciparum* malaria in pregnancy detected by light microscopy, rapid diagnostic test, or placental histology; proportion is not given if malaria cases included those detected by PCR or loop-mediated isothermal amplification, or the study design was case-control, or if only symptomatic women were tested. §Total number of pregnant women enrolled, including women with missing exposure or outcome data. ¶Total number of stillbirths recorded. ‖Cross-tabulation of malaria and stillbirth reported in publication. **Cross-tabulation of malaria and stillbirth or perinatal death provided by author. ††Measure of association reported in publication (all odds ratios except Ahmed, 2014 [risk ratio] and Moore, 2017 [hazard ratio]). ‡‡Measure of association provided by author (all odds ratios). §§Cross-tabulation of malaria and stillbirth or odds ratio provided by key researcher.

***Table*: Study characteristics by world region**

(table). Of 51 studies in which *P falciparum* endemicity could be confidently classified (using information provided in the published papers in 42 of the studies, and using Malaria Atlas Project data in nine of the studies), most were done in settings of high *P falciparum* endemicity (24 [47%] of 51 studies) or intermediate *P falciparum* endemicity (18 [35%] of 51 studies), and only nine (18%) were done in settings of low *P falciparum* endemicity (table). Studies done in settings of low or intermediate *P falciparum* endemicity were pooled into one low-to-intermediate group in subsequent meta-regression analyses because of the limited number of studies in the low-endemicity group. Six (10%) of 59 studies contributed *P vivax*-specific estimates. Half of the studies (30 [51%] of 59 studies) provided a gestational age to define stillbirth: eight studies used 20 weeks, five studies used 22 weeks, two studies used 24 weeks, 14 studies used 28 weeks, and one study used 32 weeks. The stillbirth proportion in women with no malaria in pregnancy (determined from the most sensitive diagnostic method from each study; case-control studies excluded) varied considerably between studies, ranging from 0% to 8% (median 2·17% [25–75th percentile 1·09–3·88, minimum to maximum 0–8·33], I^2=90%; appendix p 13).

There were 19 estimates from 14 studies of the association between *P falciparum* malaria detected through screening of all women (ie, regardless of symptoms) and treated during pregnancy and stillbirth. *P falciparum* malaria detected and treated during pregnancy (19 estimates) was associated with a 1·47 times increase in the odds of stillbirth (95% CI 1·13–1·92; I^2=23·5%; figure 2). There was no evidence of small-study effects (p=0·763; appendix p 14). The pooled OR from a meta-analysis including only estimates for malaria diagnosed by light microscopy was similar (OR 1·48 [95% CI 1·11–1·97], I^2=27·7%; appendix p 10). *P falciparum* malaria detected and treated during pregnancy was not associated with stillbirth in a meta-analysis of three studies that contributed estimates for HIV-positive women specifically (0·97 [0·23–4·06], I^2=0%); all women in these populations were given either antiretroviral drugs, intermittent preventive treatment for malaria in pregnancy, or daily co-trimoxazole throughout pregnancy. The association between *P falciparum* malaria detected and treated during pregnancy was lower in a subgroup of nine estimates for malaria detected and treated before 30 weeks' gestation (OR 1·25 [0·95–1·79], I^2=18·7%) than in a subgroup of 12 estimates for malaria detected at any time, or an unspecified time, during pregnancy (1·57 [1·06–2·34], I^2=34·7%; appendix p 15).

There were 68 estimates from 48 studies of the association between *P falciparum* malaria at delivery and stillbirth. Peripheral *P falciparum* malaria at delivery (34 estimates) was associated with a 1·81 times increase in the odds of stillbirth (95% CI 1·42–2·30, I^2=26·1%; figure 3). Similarly, placental *P falciparum* malaria at

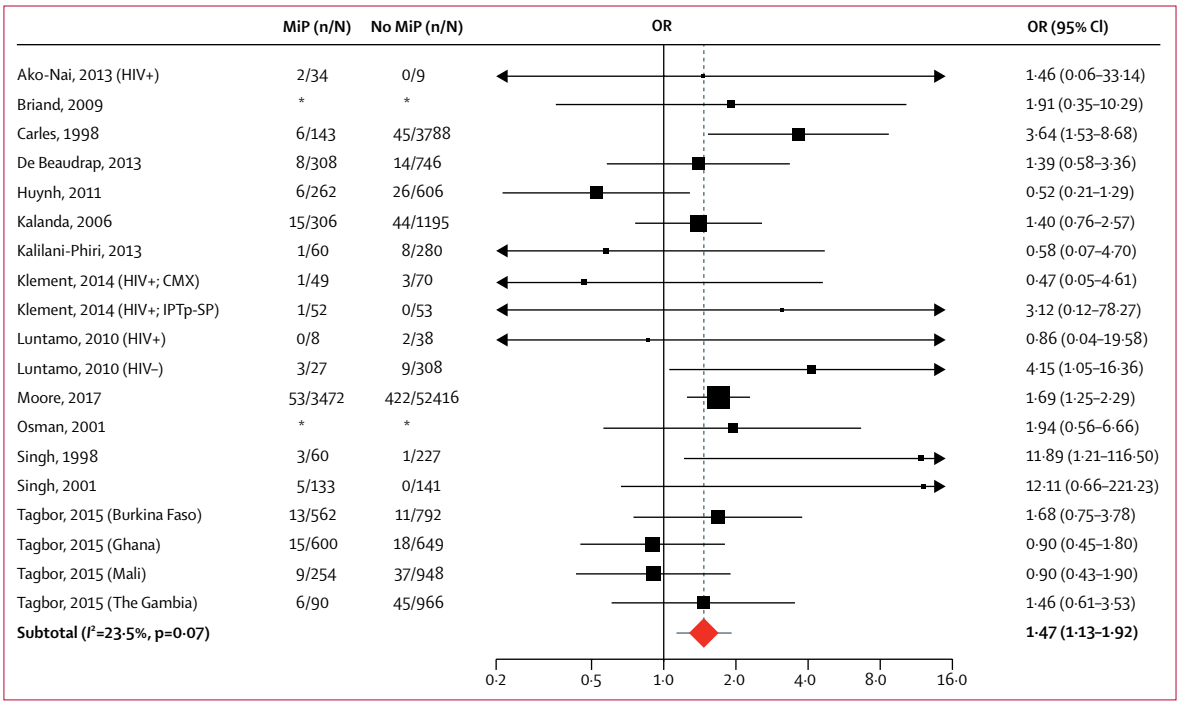


***Figure 2*: Association between peripheral *P falciparum* malaria detected during pregnancy and stillbirth**

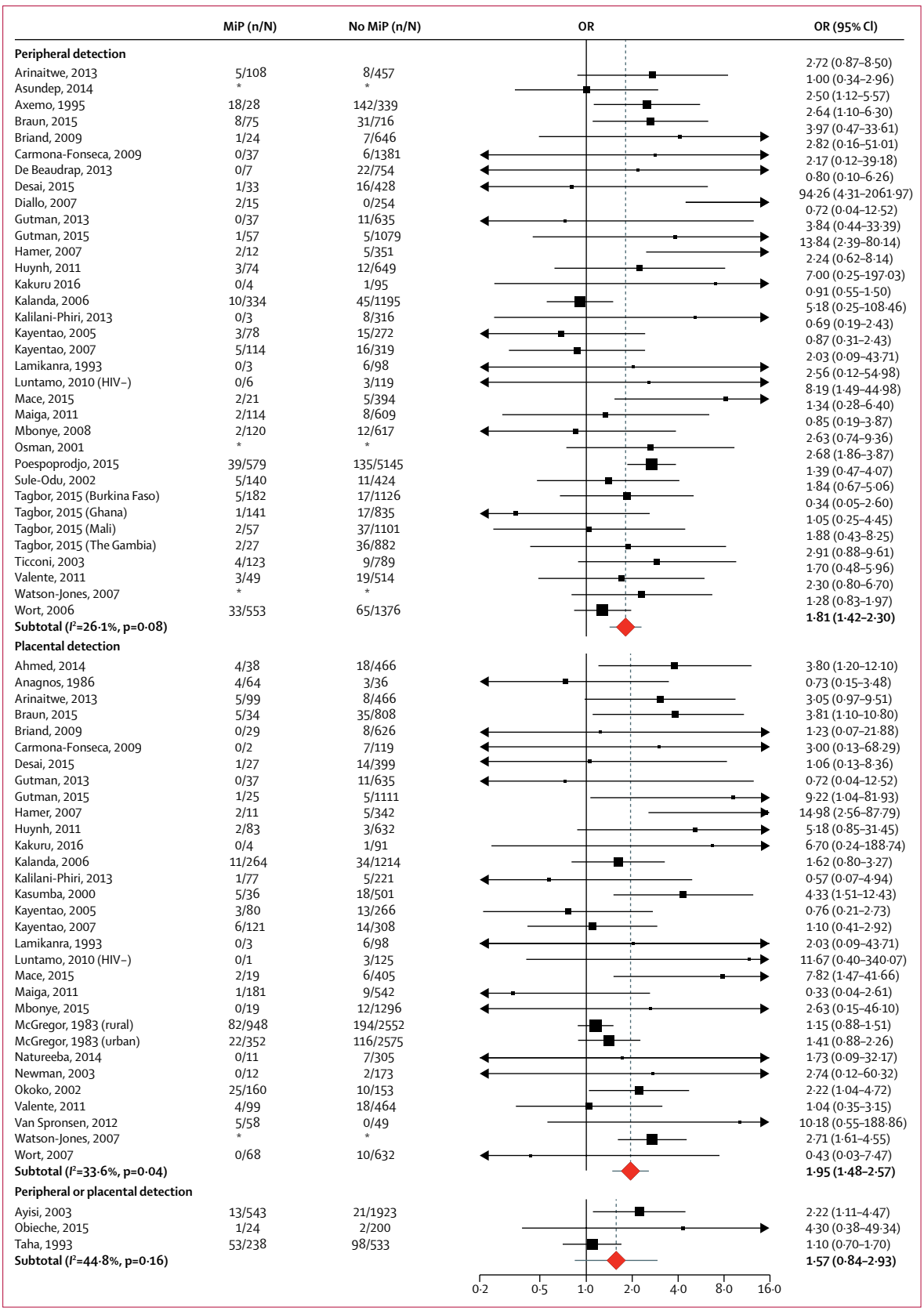
CMX=co-trimoxazole. IPTp-SP=intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine. LM=light microscopy. MiP=malaria in pregnancy. n=number of stillbirths. N=total number of births. OR=odds ratio. Detection method was LM for all estimates, except for Klement, 2014 (either LM or placental histology) and De Beaudrap, 2013 (PCR, LM, or rapid diagnostic test). Klement, 2014, contributed two cohorts: HIV-positive women receiving IPTp-SP and HIV-positive women receiving CMX. Luntamo, 2010, contributed two cohorts: HIV-positive women receiving IPTp-SP and HIV-negative women receiving IPTp-SP. In Huynh, 2011, *Plasmodium* species was not specified, but assumed to be *P falciparum* because the study was done in an area of unstable *P vivax* transmission and high Duffy negativity. In De Beaudrap, 2013, estimates were not species-specific; however, only 4·5% of all *Plasmodium* spp infections in the cohort were not *P falciparum*. In Klement, 2014, and Singh, 1998, malaria exposure might have also been at delivery (included in this meta-analysis because separate estimates were not provided for malaria during pregnancy and malaria at delivery, and the studies were designed to detect malaria during pregnancy). Klement, 2014, used rapid diagnostic tests if LM was not available. Briand, 2009, provided estimates for malaria detected at enrolment (about 22 weeks; OR 0·82 [95% CI 0·048–13·99]), and malaria detected at the second IPTp administration visit (about 31 weeks; 3·03 [0·37–24·48]), which we pooled to obtain a single OR. A meta-analysis of the association between symptomatic *P falciparum* malaria detected during pregnancy and stillbirth is in the appendix (p 20; pooled OR 1·80 [95% CI 1·31–2·47]). *Cross-tabulation unknown.

delivery (31 estimates) was associated with a 1·95 times increase in the odds of stillbirth (1·48–2·57, I^2=33·6%; figure 3). There was some evidence of small-study effects for placental detection (p=0·0490), but not for peripheral detection (p=0·3190; appendix p 14). The method of malaria diagnosis had a small, but negligible, effect on the association between peripheral *P falciparum* malaria and stillbirth (appendix p 10). The association between placental *P falciparum* malaria and stillbirth was greater when malaria was detected by microscopy (OR 2·40 [95% CI 1·60–3·59]), but still present if it was detected by more sensitive methods such as histology (1·53 [1·15–2·04]) and PCR (1·59 [0·88–2·85]; appendix p 10).

There were seven estimates from six studies of the association between *P vivax* malaria in pregnancy and stillbirth (four estimates of *P vivax* malaria detected in peripheral blood during pregnancy, and three estimates of *P vivax* malaria detected in peripheral blood at delivery; figure 4). Peripheral *P vivax* malaria was not associated with stillbirth when detected and treated during pregnancy (OR 1·09 [95% CI 0·76–1·57]; I^2=0%;

***Figure 3*: Association between *P falciparum* malaria detected at delivery and stillbirth**

LM=light microscopy. MiP=malaria in pregnancy. n=number of stillbirths. N=total number of births. OR=odds ratio. Pooled ORs calculated for malaria detected in peripheral blood and placental blood, or either. Detection method was LM for all estimates, except for Braun, 2015 (peripheral) and Valente, 2011—PCR; Ahmed, 2014, Kalilani-Phiri, 2013 (placental), Watson-Jones, 2007 (placental), Okoko, 2002, and Anagnos, 1986—placental histology; Mbonye, 2015—PCR or LM; McGregor, 1983—LM or placental histology; De Beaudrap, 2013—PCR, LM, rapid diagnostic test, or placental histology; Obieche, 2015—LM or rapid diagnostic test; and Taha, 1993—LM or placental histology. McGregor, 1983, contributed two cohorts: women living in rural areas and women living in urban areas. Several cohorts detected malaria in both peripheral and placental samples, so a pooled OR combining placental and peripheral malaria was not estimated. In Arinaitwe, 2013; De Beaudrap, 2013; Huynh, 2011; Ostrowski, 2007; Watson-Jones, 2007; Ayisi, 2003; Sule-Odu, 2002; Axemo, 1995; and Lamikanra, 1993, *Plasmodium* species was not specified, but assumed to be *P falciparum* because the studies were done in areas of unstable *P vivax* transmission and high Duffy negativity. In Taha, 1993, *Plasmodium* species was not specified, but assumed to be *P falciparum* because the study was done in an area of unstable *P vivax* transmission. In Ahmed, 2014, and McGregor, 1983, estimates were not species-specific; however, only 5% (Ahmed) and <1% (McGregor) of all *Plasmodium* spp infections in the cohort were not *P falciparum*. Watson-Jones, 2007, reported ORs for active (OR 7·74 [95% CI 1·80–32·70]), active chronic (1·92 [0·50–6·90]), and past chronic placental infection (1·84 [0·60–5·20]), which we pooled to obtain a single OR. All studies included all women, regardless of the presence of symptoms, except for Mbonye, 2015 (asymptomatic women only) and Mbonye 2008 (asymptomatic women only). *Cross-tabulation unknown.


MiP (n/N)
No MiP (n/N)
OR
OR (95% CI)
Peripheral detection
Arinaitwe, 2013 5/108 8/457 2·72 (0·87–8·50)
Asundep, 2014 * * 1·00 (0·34–2·96)
Axemo, 1995 18/28 142/339 2·50 (1·12–5·57)
Braun, 2015 8/75 31/716 2·64 (1·10–6·30)
Briand, 2009 1/24 7/646 3·97 (0·47–33·61)
Carmona-Fonseca, 2009 0/37 6/1381 2·82 (0·16–51·01)
De Beaudrap, 2013 0/7 22/754 2·17 (0·12–39·18)
Desai, 2015 1/33 16/428 0·80 (0·10–6·26)
Diallo, 2007 2/15 0/254 94·26 (4·31–2061·97)
Gutman, 2013 0/37 11/635 0·72 (0·04–12·52)
Gutman, 2015 1/57 5/1079 3·84 (0·44–33·39)
Hamer, 2007 2/12 5/351 13·84 (2·39–80·14)
Huynh, 2011 3/74 12/649 2·24 (0·62–8·14)
Kakuru 2016 0/4 1/95 7·00 (0·25–197·03)
Kalanda, 2006 10/334 45/1195 0·91 (0·55–1·50)
Kalilani-Phiri, 2013 0/3 8/316 5·18 (0·25–108·46)
Kayentao, 2005 3/78 15/272 0·69 (0·19–2·43)
Kayentao, 2007 5/114 16/319 0·87 (0·31–2·43)
Lamikanra, 1993 0/3 6/98 2·03 (0·09–43·71)
Luntamo, 2010 (HIV−) 0/6 3/119 2·56 (0·12–54·98)
Mace, 2015 2/21 5/394 8·19 (1·49–44·98)
Maiga, 2011 2/114 8/609 1·34 (0·28–6·40)
Mbonye, 2008 2/120 12/617 0·85 (0·19–3·87)
Osman, 2001 * * 2·63 (0·74–9·36)
Poespoprodjo, 2015 39/579 135/5145 2·68 (1·86–3·87)
Sule-Odu, 2002 5/140 11/424 1·39 (0·47–4·07)
Tagbor, 2015 (Burkina Faso) 5/182 17/1126 1·84 (0·67–5·06)
Tagbor, 2015 (Ghana) 1/141 17/835 0·34 (0·05–2·60)
Tagbor, 2015 (Mali) 2/57 37/1101 1·05 (0·25–4·45)
Tagbor, 2015 (The Gambia) 2/27 36/882 1·88 (0·43–8·25)
Ticconi, 2003 4/123 9/789 2·91 (0·88–9·61)
Valente, 2011 3/49 19/514 1·70 (0·48–5·96)
Watson-Jones, 2007 * * 2·30 (0·80–6·70)
Wort, 2006 33/553 65/1376 1·28 (0·83–1·97)
Subtotal (I^2=26·1%, p=0·08) 1·81 (1·42–2·30)
Placental detection
Ahmed, 2014 4/38 18/466 3·80 (1·20–12·10)
Anagnos, 1986 4/64 3/36 0·73 (0·15–3·48)
Arinaitwe, 2013 5/99 8/466 3·05 (0·97–9·51)
Braun, 2015 5/34 35/808 3·81 (1·10–10·80)
Briand, 2009 0/29 8/626 1·23 (0·07–21·88)
Carmona-Fonseca, 2009 0/2 7/119 3·00 (0·13–68·29)
Desai, 2015 1/27 14/399 1·06 (0·13–8·36)
Gutman, 2013 0/37 11/635 0·72 (0·04–12·52)
Gutman, 2015 1/25 5/1111 9·22 (1·04–81·93)
Hamer, 2007 2/11 5/342 14·98 (2·56–87·79)
Huynh, 2011 2/83 3/632 5·18 (0·85–31·45)
Kakuru, 2016 0/4 1/91 6·70 (0·24–188·74)
Kalanda, 2006 11/264 34/1214 1·62 (0·80–3·27)
Kalilani-Phiri, 2013 1/77 5/221 0·57 (0·07–4·94)
Kasumba, 2000 5/36 18/501 4·33 (1·51–12·43)
Kayentao, 2005 3/80 13/266 0·76 (0·21–2·73)
Kayentao, 2007 6/121 14/308 1·10 (0·41–2·92)
Lamikanra, 1993 0/3 6/98 2·03 (0·09–43·71)
Luntamo, 2010 (HIV−) 0/1 3/125 11·67 (0·40–340·07)
Mace, 2015 2/19 6/405 7·82 (1·47–41·66)
Maiga, 2011 1/181 9/542 0·33 (0·04–2·61)
Mbonye, 2015 0/19 12/1296 2·63 (0·15–46·10)
McGregor, 1983 (rural) 82/948 194/2552 1·15 (0·88–1·51)
McGregor, 1983 (urban) 22/352 116/2575 1·41 (0·88–2·26)
Natureeba, 2014 0/11 7/305 1·73 (0·09–32·17)
Newman, 2003 0/12 2/173 2·74 (0·12–60·32)
Okoko, 2002 25/160 10/153 2·22 (1·04–4·72)
Valente, 2011 4/99 18/464 1·04 (0·35–3·15)
Van Spronsen, 2012 5/58 0/49 10·18 (0·55–188·86)
Watson-Jones, 2007 * * 2·71 (1·61–4·55)
Wort, 2007 0/68 10/632 0·43 (0·03–7·47)
Subtotal (I^2=33·6%, p=0·04) 1·95 (1·48–2·57)
Peripheral or placental detection
Ayisi, 2003 13/543 21/1923 2·22 (1·11–4·47)
Obieche, 2015 1/24 2/200 4·30 (0·38–49·34)
Taha, 1993 53/238 98/533 1·10 (0·70–1·70)
Subtotal (I^2=44·8%, p=0·16) 1·57 (0·84–2·93)
0·2
0·5
1·0
2·0
4·0
8·0
16·0

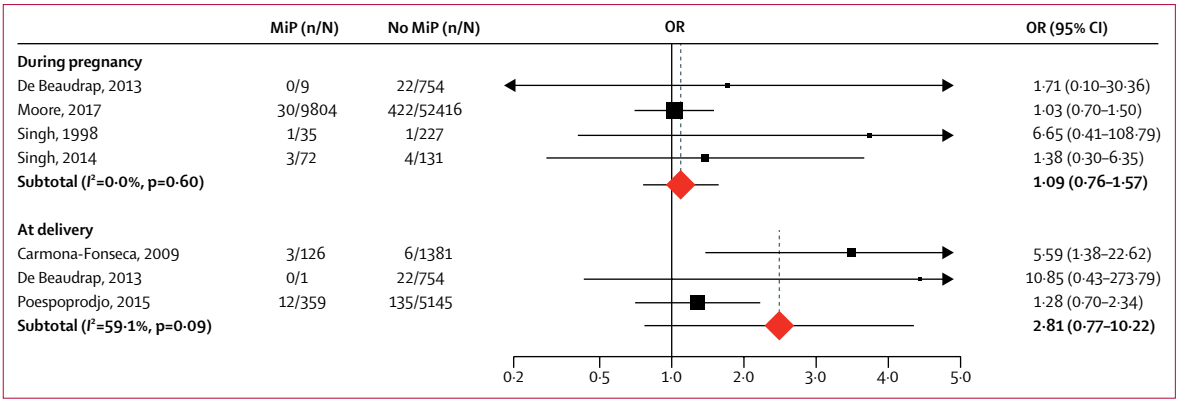


***Figure 4*: Association between peripheral *P vivax* malaria and stillbirth**

LM=light microscopy. MiP=malaria in pregnancy. n=number of stillbirths. N=total number of births. OR=odds ratio. Pooled ORs calculated for malaria detected during pregnancy or at delivery. Detection method was LM in all studies, except for De Beaudrap, 2013 (PCR, LM, rapid diagnostic test or histology at delivery). De Beaudrap, 2013, contributed two estimates: *P vivax* malaria detected during pregnancy and *P vivax* malaria detected at delivery. Estimates from Singh, 2014, were not species-specific, but 83% of *Plasmodium* spp infections in the cohort were *P vivax*. All studies included all women, regardless of the presence of symptoms. In Singh, 1998, malaria exposure might have also been at delivery, but the study was designed to detect malaria during pregnancy. The magnitude of association was also large in studies with a high proportion of *P vivax* malaria that did not provide species-specific estimates (appendix p 21).

four estimates), but increased the odds of stillbirth by 2·81 times (95% CI 0·77–10·22; I^2=62·5%; three estimates) when detected at delivery (figure 4).

Low-to-intermediate *P falciparum* endemicity was associated with greater ORs for the association between *P falciparum* malaria in pregnancy and stillbirth, especially for malaria detected at delivery, compared with high *P falciparum* endemicity (ratio of ORs during pregnancy 1·62 [95% CI 1·02–2·60]; at delivery (peripheral) 1·96 [1·34–2·89]; at delivery (placental) 2·09 [1·14–3·82]), and endemicity reduced between-study variance (appendix p 16). Studies that provided a gestational age threshold for the definition of stillbirth were associated with greater ORs for the association between *P falciparum* malaria in pregnancy and stillbirth compared with those that did not provide a threshold (appendix p 16). No other factors were consistently found to influence the associations between *P falciparum* malaria in pregnancy and stillbirth (appendix p 16).

Despite lower infection rates, PAFs in low-to-intermediate *P falciparum* endemicity areas were similar to or higher than those in high *P falciparum* endemicity areas (appendix p 18). In 2015, the $PfPR_{2-10}$ in malaria-endemic Africa was 16·2% (95% CI 14·24–19·02), and 9% of the total population were living in high-endemicity areas.[7] An estimated 1059700 stillbirths occurred in sub-Saharan Africa in 2015.[81] Therefore, assuming that all malaria in pregnancy goes unresolved before delivery, an estimated 20·5% (217026 of 1059700) of stillbirths in sub-Saharan Africa would be attributed to *P falciparum* malaria in pregnancy (range from lower and upper CI limits for OR and prevalence estimates: 11·6% [n=122713] to 32·2% [n=341541]; appendix p 18). Assuming that all malaria in pregnancy is treated during pregnancy, regardless of symptoms, the PAF in sub-Saharan Africa would be 12·5% (range 4·7–23·6%; n=132 221 [range 50308–249608]; appendix p 18). The population prevalence of *P falciparum* is not yet available for regions outside of Africa; we have provided formulas to calculate PAFs at any population prevalence (appendix p 18).

Discussion

To our knowledge, this large and comprehensive systematic review and meta-analysis provides the most accurate estimates of the association between malaria in pregnancy and stillbirth to date. *P falciparum* and *P vivax* malaria in pregnancy detected at delivery increased the odds of stillbirth. For malaria detected during pregnancy, the magnitude of the association was reduced for *P falciparum* and eliminated for *P vivax*, compared with malaria detected at delivery; we assume this difference in magnitude was due to treatment before delivery and irrespective of symptoms. Associations between *P falciparum* malaria in pregnancy and stillbirth were two times greater in low-to-intermediate *P falciparum* endemicity areas than in high-endemicity areas, suggesting that the risk of malaria-associated stillbirth in infected women will increase as malaria endemicity declines. In areas transitioning from high to moderate endemicity, the proportion of stillbirths attributed to malaria in pregnancy in the population is likely to increase due to the individual-level increase in the association between malaria in pregnancy and stillbirth. These findings have major implications for policies and resource allocation for stillbirth prevention.

We estimated that 217026 stillbirths are attributed to *P falciparum* malaria in pregnancy in malaria-endemic sub-Saharan Africa (20% of all stillbirths in sub-Saharan Africa). This estimate is similar to the estimate obtained by Lawn and colleagues,[81] which used the association between peripheral *P falciparum* malaria detected at delivery and stillbirth derived from one study site in

Africa, and did not consider the effect of endemicity or the contribution of malaria in pregnancy occurring outside of Africa. These PAFs use associations between *P falciparum* malaria in pregnancy detected at delivery and stillbirth, thereby assuming that no malaria in pregnancy is resolved with antimalarial treatment before delivery. If all cases of malaria in pregnancy were treated during pregnancy, irrespective of the presence of symptoms, the PAF would be substantially reduced (from 20% to 12% of all stillbirths in sub-Saharan Africa, corresponding to a difference of 88 767 stillbirths). High coverage of intermittent presumptive treatment with an effective antimalarial could achieve this reduction. Population prevalences of *P falciparum* and *P vivax* infection in other regions are not yet available; instead we have provided equations to calculate PAFs at any population prevalence. PAFs will probably be underestimated at lower population prevalences because we could not estimate the association in areas of low *P falciparum* endemicity specifically because there were few studies in these settings. Our classification of *P falciparum* endemicity was crude because endemicity reporting is not standardised, and is often imprecise. Over a million stillbirths occurred in southern and southeast Asia and Oceania in 2015, which is dominated by low-endemicity areas. Therefore, tens of thousands of stillbirths outside of Africa could also be attributed to malaria in pregnancy; this cannot be ignored.

The major strengths of this review were the inclusion of 59 studies (50 more than a previous review[82] of placental *P falciparum* malaria and stillbirth), and the assessment of both *P vivax* and *P falciparum* malaria, and malaria detected both during pregnancy and at delivery. Stillbirth is rarely a primary outcome of malaria in pregnancy studies because of its rarity. We were able to include many studies that did not report the association between malaria in pregnancy and stillbirth, despite collecting the necessary data, through correspondence with the authors of 85 studies. This approach increased the number of included studies from 29 to 59, and reduced the risk of publication bias. Many studies were excluded because stillbirth was not mentioned in the methods or results sections, although it seems unlikely that moderately sized studies on malaria in pregnancy would report zero stillbirths. Therefore, we also contacted key researchers in the field to request data from malaria in pregnancy studies that had collected, but not reported, stillbirth data. Despite these measures, we found some evidence of small-study effects. Stillbirth is a sensitive indicator of maternal health and quality of care; future population studies of malaria in pregnancy should ensure that stillbirths are reported (including their definition), even if there are none.[81,83]

There are some limitations in this analysis. Malaria in pregnancy was detected using different methods that vary in terms of sensitivity and specificity, and it was not possible to correct for this variability because we did not have individual patient data for the studies that provided adjusted estimates. There was a paucity of data on *P vivax* malaria in pregnancy, resulting in wide confidence intervals. Most estimates were not adjusted for confounding (appendix p 5), because of the rarity of stillbirth and because we gave the option for authors to provide cross-tabulated data. We were able to assess the association between malaria in pregnancy and stillbirth in a subgroup of HIV-positive cohorts. However, there are many other infections, particularly sexually transmitted infections such as syphilis,[84] that are highly prevalent in malaria-endemic settings and strongly associated with stillbirth, which might have modified or confounded estimates of the association between malaria in pregnancy and stillbirth. Rapid and inexpensive point-of-care tests that increase capacity for malaria in pregnancy studies to actively detect both malaria and other infections are needed to elucidate interactions. The threshold used to differentiate fetal deaths as miscarriages or stillbirths varied, and was only provided for 44% of studies; studies that provided a gestational age threshold, which can be indicative of study quality, reported greater magnitudes of association. Studies should ensure that the definition of stillbirth, as well as the method of gestational age estimation, is reported to facilitate data synthesis.[85] Some of the largest studies included in this review provided ORs derived from regression modelling with adjustment for confounding variables. For this reason, and because the OR approximates the risk ratio when the outcome is rare, PAFs were calculated using pooled ORs rather than pooled risk ratios.

This review provides the most accurate quantification of the association between malaria in pregnancy and stillbirth to date, and for the first time, quantifies the influence of malaria endemicity on this association. Our findings suggest that detection and treatment of malaria in pregnancy before delivery, irrespective of symptoms, results in a lower risk of malaria-associated stillbirth and should be encouraged. In areas of stable transmission in Africa, insecticide-treated nets and intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine are recommended to reduce the burden of malaria in pregnancy; efforts to increase coverage should be continued. However, only prevention of malaria in pregnancy will avert the association between treated malaria in pregnancy and stillbirth. In areas of low endemicity outside of Africa where the association between malaria in pregnancy and stillbirth is greater, there are no recommended interventions for malaria in pregnancy, and little context-appropriate evidence. These findings are particularly relevant as malaria endemicity is declining in Africa, and justify more studies of the burden of both *P falciparum* and *P vivax* malaria in pregnancy in low-endemicity settings, and the need for context-appropriate interventions irrespective of endemicity.

Contributors

All authors developed the protocol and the analytical plan. KAM and MJLS did the systematic searches and extracted the data. KAM analysed the data. All authors interpreted the data. KAM drafted the report. All authors read and critically revised the draft report, and approved the final report. All authors agreed to be accountable for all aspects of the work.

Declaration of interests

We declare no competing interests.

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