The effect and control of malaria in pregnancy and lactating women in the Asia-Pacific region

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Half of all pregnancies at risk of malaria worldwide occur in the Asia–Pacific region, where *Plasmodium falciparum* and *Plasmodium vivax* co-exist. Despite substantial reductions in transmission, malaria remains an important cause of adverse health outcomes for mothers and offspring, including pre-eclampsia. Malaria transmission is heterogeneous, and infections are commonly subpatent and asymptomatic. High-grade antimalarial resistance poses a formidable challenge to malaria control in pregnancy in the region. Intermittent preventive treatment in pregnancy reduces infection risk in meso-endemic New Guinea, whereas screen-and-treat strategies will require more sensitive point-of-care tests to control malaria in pregnancy. In the first trimester, artemether–lumefantrine is approved, and safety data are accumulating for other artemisinin-based combinations. Safety of novel antimalarials to treat artemisinin-resistant *P falciparum* during pregnancy, and of 8-aminoquinolines during lactation, needs to be established. A more systematic approach to the prevention of malaria in pregnancy in the Asia–Pacific is required.

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Introduction

Malaria in pregnancy can have devastating effects on maternal health,[1–3] including severe maternal anaemia, hypoglycaemia, acute lung injury, and death.[1,3] Adverse pregnancy outcomes associated with *Plasmodium falciparum* and *Plasmodium vivax* include miscarriage, stillbirth, preterm birth, and fetal growth restriction.[1] In utero exposure has been associated with increased risks of malaria, growth faltering, and neurological sequelae in childhood.[2]

Although pregnancies at risk of *P falciparum* and *P vivax* infection decreased 17·2% in southeast Asia and 52·6% in the Western Pacific region since 2000 (compared with 2020), half the pregnancies at risk of malaria in 2020 occurred in the Asia-Pacific region.[4–6] In the 20 countries included in this Review, 56·8 million pregnancies were at risk of *P falciparum* infection and 65·5 million were at risk of *P vivax* infection in 2020.[5] WHO currently only recommends using insecticide-treated bednets (ITNs) to prevent malaria in pregnancy in the Asia-Pacific region.[7]

A hallmark of malaria in the Asia-Pacific region is its heterogeneity. Artemisinin-resistant *P falciparum* has emerged in the Greater Mekong subregion, although artemisinin combination treatment (ACTs) remain highly effective in most other locations.[8] *P vivax* forms hypnozoites that require radical cure with primaquine, which is contraindicated in pregnancy and early breastfeeding.[9] *Plasmodium knowlesi* malaria, a potential cause of pregnancy-related morbidity, is found exclusively in the Asia-Pacific region where macaques, the primary host, have their natural habitat.[10] Multiple mosquito species have ecology and behaviours that could affect control measures,[11,12] and parasite–host interactions are complex.[8,13] Transmission is mostly unstable and hypoendemic, and low-density and asymptomatic infections in pregnancy are common; these hidden reservoirs of infection pose formidable challenges to malaria control and eradication.[3,14–16] Infrequent infection might limit the development of immunity, increasing the risk of severe malaria when infected,[17] and attenuating the parity-dependent decrease in placental malaria that would otherwise occur.[1]

We reviewed 106 original articles published from Jan 1, 2011 to Jan 15, 2023 to provide an update of an earlier comprehensive review.[17] In addition to summarising disease burden and advances in prevention, diagnosis, and treatment of malaria in pregnancy, we, for the first time, discuss pharmacokinetic studies and national guidelines and strategic plans from 20 malaria-endemic countries in the Asia-Pacific region (panel).[17]

Burden of infection in pregnancy

There have been major reductions in annual malaria parasite indices and the number of pregnancies at risk of malaria in most endemic Asia-Pacific countries in the past decade (appendix p 7).[5,6,18] Notably, Malaysia, Timor-Leste, North Korea, South Korea, and Thailand reported no local *P falciparum* cases in 2020, and the percentage change of clinical malaria in pregnancy in Indonesia from 1990 to 2019 was –2500%.[19] Despite these successes, progress is fragile, as highlighted by the COVID-19 pandemic, which undermined many regional malaria control programmes.[13]

Most studies reporting malaria prevalence at antenatal clinics in the Asia-Pacific region originated from India, Papua New Guinea, Indonesia, and the Thailand–Myanmar border (figure; appendix pp 8–9),[3,14,20–40] and most used light-microscopy and rapid diagnostic tests (RDT). Some studies performed repeated testing.[36,37] Prevalence of malaria was higher in studies that selected participants on the basis of fever or a history of recent febrile illness.[29,31] Burden data suggest that malaria endemicity in the region was greatest on the island of Papua. *P falciparum* predominated in most countries, apart from in Afghanistan, Laos, Pakistan, and Thailand, where *P vivax* was the predominant species.[20,24–26,34,35] There was marked regional heterogeneity in burden and species distribution in

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India, where *P vivax* is dominant in some, but not all, areas (figure).[30] Estimates of infection using PCR were generally double those generated from light-microscopy studies,[22,27,33,39] but estimates of infection can be substantially higher when an RDT is a comparator.[14] In Bangladesh, where transmission was localised with little seasonality, most infections were asymptomatic and subpatent.[3,21]

Studies indicated a reduction in the burden of patent infection over time, sometimes accompanied by a concurrent decline in subpatent infection. From Oct 1, 1999 to Sept 30, 2011, the incidence of malaria in pregnancy by light-microscopy test at the Thailand–Myanmar border declined significantly from 1·1 to 0·1 episodes per pregnant person-year.[41] In Sumba, Indonesia, there was a ten-fold decline in women with patent infection, 5·0% to 0·5% over 4 years (2012–16), whereas submicroscopic infection remained static (6·6% to 5·6%).[32,33] In Papua New Guinea, the burden of infection fell from 35·4% to 5·3% by light-microscopy test, and 66·2% to 12·6% by PCR, between 2005 and 2013.[24,38,39]

Most studies reporting the prevalence of malaria at delivery originate from India and Papua New Guinea (appendix pp 5, 10, 11).[20,22,24,25,27,33,35,38–40,42,43] The principal species detected at delivery was *P falciparum*, and on average, light-microscopy or RDT missed half or more of peripheral and placental blood infections detected by PCR. In Papua New Guinea, placental blood PCR missed 58·1% of active infections detected by histology.[39] The burden of active and past placental infection on histology decreased from 63·6% in 2005 to 18·5% in 2013, coinciding with increased ITN coverage and the introduction of intermittent treatment in pregnancy (IPTp) with sulfadoxine–pyrimethamine, and consistent with declining local transmission in Papua New Guinea.[13,38,43] *P falciparum* remained the predominant species in Papua New Guinea, with a *P falciparum* to *P vivax* ratio of 8:2 in 2005 and 7:3 in 2013 (by PCR). In India, malaria was reported in a quarter of women with pyrexia at delivery in Uttar Pradesh,[44] whereas in Laos, only one of 250 febrile women was RDT-positive for *P falciparum*.[45] At the Thailand–Myanmar border from 2007 to 2009, postpartum women had fewer *P falciparum,* but more *P vivax,* episodes compared with non-pregnant women.[46] The increase in postpartum *P vivax* was attributed to relapse.

Panel: Research priorities to enhance the prevention and control of malaria in pregnancy in the Asia-Pacific region

- Effect of subpatent infections on health outcomes and malaria transmission
- Longitudinal cohort studies to determine effects of *Plasmodium falciparum* and *Plasmodium vivax* infection in pregnancy on adverse health outcomes in infancy and childhood
- Evaluation of the effect of *Plasmodium knowlesi* infection in pregnancy on maternal health and pregnancy outcomes
- Clinical trials and observational studies to determine and monitor the first trimester safety of artemisinin-based combination treatments beyond artemether–lumefantrine
- Clinical trials of integrated interventions to control and reduce malaria and non-malaria attributable adverse pregnancy outcomes in high burden settings
- Regular and timely molecular surveillance of drug resistance and burden
- Strategies to prevent, detect, and treat malaria infections before and during early pregnancy, including affordable ultra-sensitive rapid diagnostic tests for *P falciparum* and *P vivax*
- Prioritisation of pharmacokinetic and treatment studies of novel antimalarials or combinations for artemisinin-resistant malaria in pregnancy
- Diagnosis of glucose-6-phosphate dehydrogenase deficiency in women, fetuses, and infants
- Studies to determine effective strategies to block the harmful effects of vivax malaria relapses during pregnancy—eg, suppressive treatment or safe and effective radical cure agents
- Evaluation of the optimal timing, safety, and pharmacokinetics of anti-relapse therapy with 8-aminoquinolines during lactation
- Development of vaccines or monoclonal antibody therapies for the safe, effective prevention of *P falciparum* and *P vivax* in pregnancy or in women of childbearing potential
- Systematic approach to targeted deployment of preventive measures against malaria in pregnancy in the Asia-Pacific region

Adverse outcomes

Maternal anaemia

Malaria infection was frequently associated with maternal anaemia. Hospital-based studies from India and Pakistan report a high burden of anaemia (≥40%) among women admitted with *P falciparum* and *P vivax* malaria (appendix pp 12, 13).[26,47–50] Multiple observational studies examined the association of malaria infection with anaemia.[22–24,36,37,39,42,43,51–53] At the Thailand–Myanmar border, anaemia (haematocrit <30%, haemoglobin <10 g/L) was present in approximately 10% of women with *P falciparum* and *P vivax* infections,[36] and in Papua New Guinea anaemia (haemoglobin <11 g/dL) prevalence was approximately 70% of women with *P falciparum* and *P vivax* infections.[39]

Symptomatic malaria was associated with severe anaemia (<7 g/dL) at birth in Papua, Indonesia (relative risk [RR] 1·7, 95% CI 1·3–2·4).[53] In Papua New Guinea, patent, but not subpatent, *P falciparum* at first antenatal clinic doubled the risk of anaemia at delivery compared with mothers without infection.[39] In a multi-centre observational study of 3600 women from India and Papua New Guinea, anaemia at birth was at least 3 times more common in women with concurrent *P falciparum* infection by light-microscopy or PCR, and symptomatic, but not asymptomatic, *P vivax* parasitaemia was associated with anaemia.[24] Women with active or past infections on histology had increased odds of anaemia (adjusted odds ratio 1·66, 95% CI 1·09–2·51) compared with women with no history of infection.[24] In a subsequent study from Papua New Guinea, chronic, but not acute or past, histological infection doubled the risk of anaemia.[43] By contrast, in Madhya Pradesh, India, women with acute

placental infection had lower mean haemoglobin concentrations than women with chronic or past infections.[42] In case reports, *P knowlesi* infection in pregnancy was associated with anaemia and preterm birth.[10]

Maternal death and morbidity

Both *P falciparum* and *P vivax* were associated with maternal mortality.[54] In Sumba, Indonesia, 21 of 141 pregnant women admitted to hospital with clinical malaria developed severe malaria, and two died (one infected with *P falciparum*, one with *P vivax*).[54] In institutional reviews, cohort studies, and national surveys (appendix p 14),[52,55–70] malaria in pregnancy was the cause of 2·7–23·4% of intensive care unit admissions in India.[58,69,70] Malaria was the cause of 3·9% of maternal hospital deaths reported from case reviews in India and 2·2% in Papua New Guinea and the Solomon Islands.[66,67] The contribution of malaria to severe maternal morbidity and maternal deaths in the community remains poorly

	Country	Study site	Time period	Detection method	Sample size	Percentage (95% CI)	*Plasmodium falciparum* among positives (%)	*Plasmodium vivax* among positives (%)	Mixed infections (%)	Other infections (%)
South-East Asia										
Howard et al (2015)[20]	Afghanistan	Nangarhar province	2004–05	LM	286	10·8 (7·7–15·0)	35·5	64·5	..	..
Khan et al (2014)[3]	Bangladesh	Chittagong Hills	2009–13	LM/RDT	909	2·3 (1·5–3·5)	100·0	0·0	0·0	..
Khan et al (2014)[3]	Bangladesh	Chittagong Hills	2009–13	PCR*	454	7·3 (5·2–10·0)	100·0	0·0	0·0	..
Singh et al (2015)[22] and Singh et al (2012)[23]	India	Chhattisgarh	2007–08	LM	2477	1·2 (0·8–1·7)	86·7	13·3	0·0	0·0
Singh et al (2015)[22] and Singh et al (2012)[23]	India	Chhattisgarh	2007–08	PCR	2477	3·4 (2·7–4·2)	51·1	45·3	2·4	1·2
Bardaji et al (2017)[24]	India	Rajasthan	2008–11	LM	2021	1·3 (0·9–1·9)	3·8	96·2	0·0	0·0
Bardaji et al (2017)[24]	India	Rajasthan	2008–11	PCR	298	1·0 (0·3–2·9)	0·0	100·0	0·0	0·0
Sohail et al (2015)[25]	India	Jharkhand	2012–13	LM	1271	5·4 (4·2–6·7)	4·4	86·7	8·8	0·0
Hirani et al (2015)[26]	India	Jharkhand	2014–15	LM/RDT/PCR	263	19·0 (14·7–24·2)	0·0	100·0	0·0	0·0
Kuepfer et al (2019)[27]	India	Jharkhand	2012–15	RDT	3163	3·2 (2·6–3·9)	83·2	8·9	7·9	0·0
Correa et al (2017)[28]	India	Three states	2015	RDT	563	29·3 (25·7–33·2)	64·2	0·0	35·2†	0·6
Qureshi et al (2014)[29]	India	Two states	2012	RDT (fever)	635	20·6 (17·7–23·9)	..	..	..	..
Garg et al (2020)[30]	India	Chhattisgarh	2019	RDT	21572	0·8 (0·7–0·9)	..	..	..	..
Bal et al (2023)[14]	India	Odisha	2019	RDT	308	3·9 (2·2–6·7)	..	..	..	..
Bal et al (2023)[14]	India	Odisha	2019	PCR	308	54·2 (48·6–59·7)	..	..	..	..
Poespoprodjo et al (2014)[31]	Indonesia	Papua	2004–09	LM‡	6475	26·0 (24·9–27·1)	62·4	27·1	6·7	3·7
Ahmed et al (2015)[32]	Indonesia	Sumba	2012	LM	934	5·0 (3·8–6·6)	51·1	27·7	10·6	10·6
Ahmed et al (2015)[32]	Indonesia	Sumba	2012	PCR	934	6·6 (5·2–8·4)	51·6	37·0	11·3	..
Ahmed et al (2019)[33]	Indonesia	Sumba	2013–16	LM	989	0·5 (0·2–1·2)	..	..	..	..
Ahmed et al (2019)[33]	Indonesia	Sumba	2013–16	PCR	988	5·6 (4·3–7·2)	54·5	36·4	0·5	0·0
Ahmed et al (2019)[33]	Indonesia	Papua	2013–16	LM	1289	6·1 (4·9–7·5)	..	..	..	..
Ahmed et al (2019)[33]	Indonesia	Papua	2013–16	PCR	1290	12·2 (10·5–14·1)	52·9	25·5	19·1	2·6
Qureshi et al (2021)[34]	Pakistan	Baanu	2018	LM/RDT	3911	1·4 (1·1–1·9)	1·8	98·2	0·0	0·0
Briand et al (2016)[35]	Laos	Salavan	2014	PCR	204	5·9 (3·4–10·0)	0·0	91·7	8·3	0·0
Harrington et al (2021)[36]	Thailand	TMB	1986–2016	LM§	23262	16·5 (16·0–17·0)	27·3	45·1	0·0	27·5
Moore et al (2017)[37]	Thailand	TMB	1986–2015	LM¶	61836	15·1 (14·8–15·4)	37·2	45·7	16·9	..
Western Pacific										
Stanisic et al (2015)[38]	Papua New Guinea	Madang	2005–07	LM	328	34·5 (29·5–39·7)	90·3	9·0	1·7	0·0
Stanisic et al (2015)[38]	Papua New Guinea	Madang	2005–07	PCR	328	66·2 (60·9–71·1)	73·7‖	29·5‖	..	..
Bardaji et al (2017)[24]	Papua New Guinea	Madang	2008–11	LM	1665	8·4 (7·2–9·8)	79·3	18·6	..	2·1
Bardaji et al (2017)[24]	Papua New Guinea	Madang	2008–11	PCR	266	23·7 (19·0–29·1)	42·9	52·4	4·8	..
Unger et al (2019)[39]	Papua New Guinea	Madang	2009–13	LM	2190	5·3 (4·4–6·3)	88·8**	11·2	..	..
Unger et al (2019)[39]	Papua New Guinea	Madang	2009–13	PCR	2190	12·6 (11·2–14·0)	77·8**	22·2	..	..
Wini et al (2013)[40]	Solomon Islands	Honiara	2009–10	LM	657	1·5 (0·8–2·8)	70·0	20·0	10·0	0·0
Wini et al (2013)[40]	Solomon Islands	Honiara	2009–10	RDT	658	0·6 (0·2–1·6)	25·0	50·0	25·0	..

Figure: **Prevalence of malaria infection during pregnancy by country in the Asia-Pacific region, studies published between 2011 and 2023**
ANC=antenatal clinic. LM=light-microscopy. RDT=rapid diagnostic test. TMB=Thailand–Myanmar border. *14 (42·4%) of the 33 PCR infections were negative by LM/RDT (ie, were subpatent infections). †Might include *Plasmodium malariae* and *Plasmodium ovale*. ‡Women admitted to hospital during pregnancy, including women admitted antenatally with fever. §Women were screened at each ANC visit starting in the first trimester of pregnancy (<14 gestational weeks). Other infections included multiple species, mixed infections, *P ovale*, *P malariae*, or unknown species. ¶Women were screened at each ANC visit; mixed infections include *Plasmodium falciparum–Plasmodium vivax* mixed infections and *P falciparum* and *P vivax* infections at different timepoints. ||Of 217 women with an infection, 160 had *P falciparum*, 64 had *P vivax*, and 38 had *P ovale*. The proportion of mixed infections was unavailable. **Includes *P falciparum–P vivax* mixed infection.

	Years of study	Study type	Detection method	n/N (%)		Odds ratio (95% CI)	
				Malaria positive	Malaria negative	Positive grouping	Negative grouping
Miscarriage*							
Thailand[71]							
Thailand–Myanmar border	1986–2010	Cohort†	Maternal LM	329/945 (34·8%)	3198/16 668 (19·2%)	2·25 (1·96–2·59)	ref
Thailand[72]							
Thailand–Myanmar border	1994–2013	Cohort†	Maternal LM	294/2558 (11·5%)	1963/22 927 (8·6%)	1·39 (1·22–1·58)	ref
Stillbirth							
India[42]							
Madhya Pradesh	2006–07	Cross-sectional	Placental histology (active infection)	4/38 (10·5%)	18/468 (3·8%)	2·94 (0·94–9·18)	ref
India[52]							
Jabalpur	2008–09	Cross-sectional‡	Maternal/placental LM	1/21 (4·8%)	2/479 (0·4%)	11·92 (1·04–137·07)	ref
Thailand[37]							
Thailand–Myanmar border	1986–2015	Cohort§	Maternal LM (*P.f.*)	28/3457 (0·8%)	202/51 795 (0·4%)	2·09 (1·40–3·10)	ref
Thailand–Myanmar border	1986–2015	Cohort§	Maternal LM (*P.v.*)	15/3571 (0·4%)	202/51 795 (0·4%)	1·08 (0·64–1·82)	ref
Neonatal death							
Thailand[37]							
Thailand–Myanmar border	1986–2015	Cohort	Maternal LM	50/2467 (2·0%)	94/6623 (1·4%)	1·44 (1·01–2·03)	ref
Perinatal death							
Indonesia[53]							
Timika	2004–10	Cohort	Maternal LM	38/1018 (3·7%)	206/5251 (3·9%)	0·95 (0·67–1·35)	ref

Data from studies published between Jan 1, 2011 and Jan 15, 2023. LM=light-microscopy. *P.f.=Plasmodium falciparum*. *P.v.=Plasmodium vivax*. *Defined as fetal loss <28 gestational weeks. †Restricted to women who attended antenatal clinics in the first trimester. ‡Considered women with fever or history of fever only. §Associations between malaria infection and antepartum stillbirths are presented.

Table 1: **Association between maternal malaria infection and perinatal loss, by country, in the Asia-Pacific region**

studied. At the Thailand–Myanmar border, one in every six maternal deaths was attributable to *P falciparum* malaria before the introduction of weekly antenatal screening for malaria.[68] At the same site, maternal *P falciparum* (but not *P vivax*) infection was associated with pre-eclampsia or eclampsia in primigravid women and gestational hypertension in multigravid women.[36]

Miscarriage, stillbirth, and neonatal death

Malaria infection is associated with miscarriage, stillbirth, and neonatal death (table 1). In longitudinal studies at the Thailand–Myanmar border, first and recurrent *P falciparum* infections were associated with increased hazards of miscarriage (first episode: hazard ratio [HR] 1·61 [95% CI 1·32–1·97]; recurrence: HR 3·24 [2·24–4·68]), and recurrent symptomatic vivax malaria with an increase in miscarriage (HR 2·44 [1·01–5·88]).[71,72] The association of *Plasmodium* infection with stillbirth was evaluated in three studies (table 1).[37,42,52] In Madhya Pradesh, acute but not chronic or past placental *P falciparum* infection on histology doubled the risk of stillbirth.[42] At the Thailand–Myanmar border, symptomatic peripheral *P falciparum* or *P vivax* infection in later pregnancy doubled the risk of antepartum (pre-labour) stillbirth.[37] Much of this risk appeared to be mediated via fetal growth restriction and maternal anaemia.[37] In the same setting, *P falciparum* and *P vivax* infections were associated with 2·0–2·5-fold (*P falciparum*: HR 2·55 [95% CI 1·54–4·22]; *P vivax*: HR 1·98 [1·10–3·57]) increases in the hazards of neonatal death, largely attributable to preterm birth or fetal growth restriction.[37]

Low birthweight, preterm birth, and fetal growth restriction

Several studies examined the association between malaria infection and birthweight, low birthweight (<2500 g), preterm birth, and measuring small-for-gestational-age at birth (SGA; table 2).[39,42,43,52,53,71,73] Acute placental infection was associated with reductions in mean birthweight of 200–400 g in India and Papua New Guinea, and low birthweight was most common among women with acute and chronic placental infection (table 2).[42,43] Acute

	Study type	Detection method	Grouping	n	Mean difference in birthweight, g (95% CI)	Low birthweight* n (%)	Odds ratio (95% CI)
India							
Madhya Pradesh[42]							
2006–07	Cross-sectional	Placental histology	Acute	16	−400 (−687 to −113)	..	..
2006–07	Cross-sectional	Placental histology	Chronic	17	−38 (−316 to 240)	..	..
2006–07	Cross-sectional	Placental histology	Past	12	188 (−141 to 517)	..	..
2006–07	Cross-sectional	Placental histology	No	419	ref	..	..
Chhattisgarh[23]							
2007–08	Cross-sectional	Placental LM/RDT	Positive	12	−310 (−97 to −523)	9 (75·0%)	5·87 (1·56 to 21·74)
2007–08	Cross-sectional	Placental LM/RDT	Negative	674	ref	229 (34·0%)	ref
2007–08	Cross-sectional	Placental PCR†	Positive	24	80 (−74 to 235)	5 (20·8%)	0·50 (0·18 to 1·36)
2007–08	Cross-sectional	Placental PCR†	Negative	650	ref	224 (34·5%)	ref
Madhya Pradesh[52]							
2008–09	Cross-sectional	Placental LM	Positive	21	−290 (..)	..	..
2008–09	Cross-sectional	Placental LM	Negative	479	ref	..	..
Indonesia							
Timika[53]							
2004–10	Cohort	Peripheral LM	Positive	1008	..	173 (17·2%)	1·26 (1·05 to 1·51)
2004–10	Cohort	Peripheral LM	Negative	5223	..	736 (14·1%)	ref
Papua New Guinea							
Madang[43]							
2009–13	Cross-sectional	Placental histology	Acute	54	−189 (−55 to −323)	12 (22·2%)	1·91 (0·98 to 3·70)
2009–13	Cross-sectional	Placental histology	Chronic	55	−64 (−199 to 72)	11 (20·0%)	1·67 (0·84, 3·30)
2009–13	Cross-sectional	Placental histology	Past	160	−76 (−159 to −7)	26 (16·3%)	1·30 (0·82 to 2·03)
2009–13	Cross-sectional	Placental histology	No	1182	ref	154 (13·0%)	ref
Madang[39]							
2009–13	Cohort	Peripheral LM/PCR	Microscopic	92	−12 (−108 to 83)	17 (18·5%)	1·27 (0·74 to 2·19)
2009–13	Cohort	ANC	Submicroscopic	98	−2 (−94 to 90)	14 (14·3%)	0·94 (0·52 to 1·67)
2009–13	Cohort	ANC	Negative	1786	ref	270 (15·1%)	ref
2009–13	Cross-sectional	Peripheral LM/PCR	Microscopic	37	−126 (−273 to 21)	11 (29·7%)	2·49 (1·22 to 5·10)
2009–13	Cross-sectional	Delivery	Submicroscopic	29	−48 (−214 to 118)	5 (17·2%)	1·22 (0·46 to 3·24)
2009–13	Cross-sectional	Delivery	Negative	1872	ref	272 (15·0%)	ref
Thailand							
Thailand–Myanmar border[71]							
1986–2010	Cohort	Maternal LM‡	Positive	392	30 (..)§	..	..
1986–2010	Cohort	Maternal LM‡	Negative	11 204	ref	..	..
Thailand–Myanmar border[73]							
2001–10	Cohort	Maternal LM	Positive	1292	50 (−72 to −29)	225 (17·4%)	1·55 (1·32 to 1·81)
2001–10	Cohort	Maternal LM	Negative	8972	ref	1072 (11·9%)	ref

Data from studies published between Jan 1, 2011 and Jan 15, 2023. ANC=antenatal clinic. LM=light-microscopy. *Low birthweight defined as <2500 g. †Submicroscopic infection only (PCR positive, LM negative). ‡Cohort considered women with first trimester infections only (200 *Plasmodium falciparum*, 192 *Plasmodium vivax*). §Mean birthweight 2970 g in non-malaria group and 2940 g in malaria group (p=0·22).

Table 2: **Association of maternal malaria infection with birthweight and low birthweight, by country, in the Asia-Pacific region**

placental infection was associated with shorter gestational length in India, whereas chronic placental infection was associated with an increase in the odds of preterm birth in Papua New Guinea.[42,43] Neither submicroscopic nor microscopic peripheral infection at the first antenatal visit was associated with SGA in Papua New Guinea, but prevalence was low.[39] In India, microscopic infection at birth was associated with lower birthweight (125–300 g), and higher odds of low birthweight and preterm birth, whereas submicroscopic infection was not.[22,39] At the Thailand–Myanmar border, babies of women with microscopic parasitaemia during pregnancy were 30–50 g lighter and more likely to have a low birthweight than babies of women without microscopic parasitaemia.[71,73] At the same site, microscopic *P falciparum* and *P vivax* infections in the first trimester conveyed no increased

risk of SGA or preterm birth.[74]

Later in pregnancy, both symptomatic and asymptomatic *P falciparum* and *P vivax* infection episodes resulted in a 1·5-fold increase in SGA and preterm birth even when promptly treated with antimalarials.[74] In Papua New Guinea, symptomatic *P falciparum* infection during pregnancy was associated with fetal growth restriction detected by ultrasound.[75] Microscopic and submicroscopic infections during pregnancy were associated with increased umbilical artery resistance and reduced middle cerebral artery pulsatility indices, and submicroscopic *P falciparum* infection with a low cerebroplacental ratio indicative of fetal brain-sparing.[76] At the Thailand–Myanmar border, *P falciparum* malaria was associated with lower placental volume Z scores,[77] and *P falciparum* or *P vivax* infections between 14 and 24 weeks were associated with reduced biparietal diameter Z scores,[78] although no gross effects on fetal brain development were detected.[79]

Diagnosis

RDTs and light-microscopy are used in managing women with suspected malaria, and in some settings for screening all pregnant women. In Papua New Guinea, RDT (HRP-2/pLDH) and light-microscopy had comparable performance to PCR for detecting peripheral *P falciparum* infection in symptomatic women, suggesting that RDTs could have a role in managing clinical malaria in pregnancy.[80] The performances of RDT (HRP-2/pLDH) and light-microscopy were similar for screening for *P falciparum* in pregnancy in Sumba and Maluku, Indonesia,[32,81] but the sensitivity of each was only approximately 30% compared with PCR, and in both settings, they were worse for detection of PCR-confirmed *P vivax*.[32,80] Light-microscopy and RDT of peripheral blood also missed more than 50% of women with active placental infection on histology in Papua New Guinea.[80] The first generation of ultrasensitive HRP-2 RDTs had similar, low sensitivity to a standard combination RDT for detecting PCR-confirmed *P falciparum* infection in asymptomatic pregnant women in Papua, Indonesia.[82] RDT-based screen-and-treat approaches would require RDTs with better sensitivity, especially for *P vivax*, to detect asymptomatic low-density infection.[27]

Treatment

Artemether–lumefantrine, artesunate–mefloquine, artesunate–amodiaquine, artesunate–sulfadoxine–pyrimethamine and dihydroartemisinin–piperaquine are used for the treatment of malaria in pregnancy in the Asia-Pacific region. ACT is considered safe after the first trimester of pregnancy, and artemether–lumefantrine is now endorsed by WHO as first-line malaria treatment in the first trimester,[7] as studies in the Asia-Pacific region have shown the safety and superior antimalarial efficacy of artemether–lumefantrine compared with quinine.[71,72,83] Given the limited experience with other ACTs in the first trimester, WHO recommends that artesunate–amodiaquine, artesunate–mefloquine, and dihydroartemisinin–piperaquine should only be used when artemether–lumefantrine is not recommended or unavailable. There are no data to support the use of artesunate–pyronaridine in pregnancy.

Compared with non-pregnant populations, extended time to recrudescence could occur in pregnancy,[84] and extended follow-up in efficacy studies might be required.[85] Dihydroartemisinin–piperaquine, artesunate–mefloquine, and an extended 4-day artemether–lumefantrine regimen (AL$^+$) were compared in pregnant women with uncomplicated *P falciparum* or *P vivax* malaria at the Thailand–Myanmar border (appendix p 15).[83,86] For *P falciparum,* PCR-corrected cure rates were highest for dihydroartemisinin–piperaquine (93·7%), followed by AL$^+$ (87·5%). PCR-corrected cure rates were lowest for artesunate–mefloquine (79·6%), which also had inferior tolerability.[83] For uncomplicated *P vivax* malaria, the median time to recurrence was similar between dihydroartemisinin–piperaquine (70 days) and artesunate-mefloquine (76 days), and shortest with AL$^+$ (45·5 days), highlighting the differences in the duration of post-treatment prophylaxis provided by these regimens. In India, artesunate–mefloquine (96·8%) and artesunate–sulfadoxine–pyrimethamine (95·1%) had similarly high cure rates for uncomplicated *P falciparum* malaria in pregnancy, but women randomly assigned to artesunate–mefloquine reported more gastrointestinal side-effects.[87] 7 days of oral artesunate monotherapy was reported to clear *P falciparum* parasitaemia in 82·5% of pregnant women in India.[88] In Papua, Indonesia, the replacement of sulfadoxine–pyrimethamine plus chloroquine, or sulfadoxine–pyrimethamine plus quinine, with dihydroartemisinin–piperaquine for the treatment of malaria in 2006 resulted in a 54% reduction in peripheral parasitaemia at delivery,[31,53] and a greater chance of being discharged with an ongoing pregnancy.[31] Weekly mefloquine reduced spleen size and improved haematocrit in pregnant women with hyper-reactive malarial splenomegaly at the Thailand–Myanmar border.[89] Barriers to timely initiation of antimalarial treatment now need to be overcome to reduce morbidity and mortality further.[90]

Prevention of malaria in pregnancy

WHO recommends the universal use of ITNs in all malaria-endemic settings.[91] In Papua, Indonesia, only 23·2% of pregnant women used an ITN, citing limited access to government-issued nets.[92] Despite the free distribution of bednets, there was low household coverage of ITNs in Myanmar (25% had one ITN per two people), but when available, nets were preferentially used by pregnant women.[93–95] Similarly, ITN use by pregnant women at the Thailand–Myanmar border was high (90·0%), yet adequate household ownership remained low (30·8%).[96] In Pakistan, a third of women

reported using an ITN at the first antenatal visit. ITN use was associated with receipt of intensive health education, mobile phone use, and a personal history of malaria.[97,98] In Bangladesh, free distribution of ITNs plus counselling by community health workers improved uptake,[99] as was the case in Papua New Guinea,[100] and mass distribution enhanced women's awareness of malaria in pregnancy in Timor-Leste.[101]

In the past decade, clinical trials of IPTp were conducted in Papua New Guinea and Indonesia (appendix pp 16–17).[33,102] An IPTp trial in the Solomon Islands was terminated early because of low malaria prevalence, poor adherence, and a high prevalence of self-reported allergy to sulfa drugs.[40] In Papua New Guinea, compared with a single treatment course of sulphadoxine–pyrimethamine plus chloroquine at antenatal enrolment, IPTp with sulphadoxine–pyrimethamine plus azithromycin reduced the risks of low birthweight by 26%, peripheral parasitaemia at delivery by 43%, and active placental infection on histology by 32%.[102] Papua New Guinea is the only country in the region to adopt IPTp with sulphadoxine–pyrimethamine as national policy.[103] Another potentially promising option is the combination of azithromycin and piperaquine.[104] This option was safe, had similar antimalarial efficacy to sulfadoxine–pyrimethamine, and resulted in a 250 g higher live mean birthweight (appendix p 17), but mild gastrointestinal side-effects (eg, nausea and vomiting) were more common.[104]

A cluster-randomised trial in Sumba and Papua in Indonesia compared dihydroartemisinin–piperaquine for IPTp, intermittent screening and treatment in pregnancy (ISTp), with a single screen-and-treat (SST) at first antenatal visit (standard of care).[33] SST was introduced in 2012, with variable success in implementation.[105,106] There was a reduced risk of peripheral or placental malaria infection at delivery in IPTp (risk ratio [RR] 0·59; 95% CI 0·42–0·83) and ISTp clusters (0·56; 0·40–0·77), and of *P vivax* infection at delivery in IPTp (0·35; 0·1–0·73) and ISTp clusters (0·31, 0·19–0·53), suggesting that dihydroartemisinin–piperaquine might control both new *P vivax* infections and relapses.[107] However, results for ISTp require validation, as fewer women had malaria infections at antenatal enrolment in ISTp (5·7%) compared with SST clusters (12·6%). In Papua, Indonesia, IPTp with dihydroartemisinin–piperaquine was highly cost-effective compared with SST, at a cost of US$54 per disability-adjusted life-year due to malaria in pregnancy.[107] In Papua and Sumba, women were generally receptive to IPTp, but health-care workers expressed concerns over drug resistance and in utero drug exposure.[108] ISTp was more acceptable to health-care workers (in the context of SST already being used), but concerns were raised over the validity of RDTs, and light-microscopy was the preferred screening tool preferred by health-care providers.[108] In Jharkhand, India, ISTp with artesunate–sulfadoxine–pyrimethamine was compared with passive case detection, the current standard of care.[27] Although ISTp detected more cases of malaria infection during pregnancy than passive case detection (4·9% *vs* 0·6%), the prevalence of placental malaria, low birthweight, preterm birth, pregnancy loss, and maternal anaemia were similar between trial groups (appendix pp 16–17). Pregnant women were receptive to ISTp, which might be the better option when community acceptance of chemoprevention, such as IPTp or prophylaxis, is low,[109] yet better RDTs are needed for enhanced health-care worker acceptability and protection from malaria.[110] Qualitative studies highlight the importance of health-care worker training to facilitate the provision of preventive measures,[111,112] and to enhance their uptake by women through education about malaria in pregnancy, including the effects of asymptomatic infection.[113]

Pharmacokinetics of antimalarials

Pregnancy is associated with physiological changes that can alter the pharmacokinetics of drugs. Although available evidence from the region has increased (appendix pp 18–19), a scarcity of pregnancy-specific pharmacokinetic studies and disparity in findings, probably due to varying control populations (non-pregnant *vs* postpartum women) and small sample size, remain substantial limitations for informed dose regimens during pregnancy.[114] The recent use of population pharmacokinetic modelling and dose simulations has shown potential for evaluation of the effect of pregnancy on antimalarial pharmacokinetics.[115]

In the past decade, most antimalarial pharmacokinetic evaluations from the Asia-Pacific region have originated from Thailand and Papua New Guinea.[115–126] Neither pregnancy status nor gestational age substantially affected the disposition of amodiaquine, which is not prescribed extensively.[116,117] By contrast, lumefantrine exposure was substantially altered during pregnancy. A shorter elimination half-life resulted in lower day-7 drug concentrations, probably translating to reduced treatment efficacy.[118] Simulations predicted that 4–10 day regimens would result in day-7 plasma concentrations exceeding the target, 280 ng/mL,[118] yet a recent evaluation showed suboptimal antimalarial efficacy of AL+ (4 days; appendix p 15).[83]

Pharmacokinetics of artemisinin derivatives during pregnancy are also variable, ranging from no difference compared with non-pregnant women,[121] to higher rates of drug clearance and 23–38% reduction in total drug exposure after the second trimester.[119,122] Regardless, treatment efficacy remains high, suggesting current dose recommendations are appropriate. However, with increasing artemisinin resistance in the region, evaluation of the efficacy, safety, and pharmacokinetics of higher doses or extended treatments might be required.[119,122]

Although pregnancy is associated with the increased clearance and shortened elimination half-life of piperaquine (16–22 days *vs* 20–26 days in non-pregnant

	Year	ITN	Screen and treat for malaria		Chemoprevention
			SST	IST	
WHO	2022	Yes	..	..	Chloroquine*
Afghanistan	2017	Yes	..	..	..
Bangladesh	2019	Yes†	Yes‡	Yes‡	Consider chemoprophylaxis
Bhutan	2019	..	..	..	Chloroquine*
Cambodia	2014	Yes	Yes§	Yes§	..
North Korea	2017	Yes¶	..	..	..
India	2014	Yes‖	..	..	..
Indonesia	2020	Yes	Yes**	Yes**	..
Laos	2022	Yes	..	..	..
Malaysia	2013	Yes	Yes††	..	Chloroquine*
Myanmar	2018	..	..	..	..
Nepal	2019	Yes‡‡	..	..	Chloroquine*
Pakistan	2018	Yes§§	..	Yes§§	..
Papua New Guinea	2009	Yes	..	..	IPTp-SP (3 doses)
Philippines	2018	..	..	..	..
South Korea	2022	..	..	..	..
Solomon Islands	2018	Yes	..	..	Chloroquine¶¶
Thailand	2019	..	..	..	..
Timor-Leste	2017	Yes‖‖	Yes‖‖	..	..
Vanuatu	2021	Yes	..	..	Chloroquine¶¶
Viet Nam	2016	..	..	..	..

API=annual parasite index. IPTp=intermittent treatment in pregnancy. IST=intermittent screening and treatment. ITN=insecticide-treated bed net. RDT=rapid diagnostic test. SP=sulphadoxine–pyrimethamine. SST=single screen and treat. *Relapse control (5 mg/kg once a week) after confirmed Plasmodium vivax malaria during pregnancy. †Use of ITNs in all endemic areas, with enhanced provision at first antenatal visit in higher endemicity areas.[131] ‡Screen-and-treat approach by RDT (number and frequency unclear) in higher endemicity areas (stratum 2 and 3). §In high prevalence areas, consideration should be given to screening pregnant women during antenatal visits. The frequency of antenatal clinic screenings should be determined by local malaria epidemiology and logistical factors. ¶Behavioural change communication activities linked with ITN mass-distribution will emphasise coverage among pregnant and lactating women. ‖ITN use should be encouraged for pregnant women intending to stay for a long period in high-endemic areas. **By light-microscopy or RDT, frequency and interval not defined. ††By light-microscopy at first antenatal clinic. ‡‡ITN at first antenatal clinic in moderate-risk and high-risk areas. §§Mass and continuous ITN distribution for pregnant women in high-risk rural districts of the stratum I (annual parasite index [API] >5) and stratum 2 (API 1–5); regular RDT-based malaria screening in high-transmission areas. ¶¶Primary chemoprophylaxis (5 mg/kg once a week), starting at first antenatal clinic. ‖‖ITN-based and RDT-based SST at first antenatal clinic in high-risk areas.

Table 3: **Country approaches to prevention of malaria pregnancy in the Asia-Pacific region, based on current national treatment guidelines and malaria programme directives**

women), reported pregnancy effects on total drug exposure vary between study populations.[119,121,125] Shortened post-treatment prophylaxis could threaten the use of the current dihydroartemisinin–piperaquine regimen for IPTp. Reassuringly, there were no cases of placental malaria in women in Indonesia who received monthly IPTp with dihydroartemisinin–piperaquine. Piperaquine troughs greater than 10·3 ng/mL (a drug concentration associated with 95·0% protection) were reported in 90·6% of participants, suggesting adequate drug exposure for prophylactic efficacy.[126]

Pharmacokinetic evaluation of chloroquine in Papua New Guinea reported increased clearance of both chloroquine (16%) and its primary metabolite (49%), and a 24% reduction in chloroquine's relative bioavailability in pregnancy.[123] These data imply that higher doses of chloroquine could be required to ensure appropriate therapeutic or chemoprophylactic efficacy.[123] Using population non-linear mixed-effect modelling, sulphadoxine–pyrimethamine dosing regimens for IPTp have been evaluated using Papua New Guinea data.[127] Simulations suggested that for pregnant women to receive equivalent drug exposure compared with non-pregnant women, two conventional daily doses of sulphadoxine–pyrimethamine given 24 h apart, or a double dose given once, would be required.[127] If combined with azithromycin, three daily sulfadoxine–pyrimethamine doses might be required for comparable day-28 concentrations. These data suggest that current dosing for IPTp might be insufficient to maintain adequate prophylactic efficacy, particularly in late pregnancy. The first pharmacokinetic evaluation of a 3-day azithromycin–piperaquine regimen for IPTp, conducted in Papua New Guinea, suggested azithromycin dose-dependent effects on absorption of piperaquine and higher tissue distribution of azithromycin at higher doses.[125] Furthermore, there was a 52% increase in relative bioavailability of piperaquine with each subsequent dose, postulated to result from parasite clearance during dosing. Although azithromycin–piperaquine is promising, related tolerability and corrected QT interval changes might limit the use of this regimen.[104,125] Lastly, although primaquine is contraindicated during pregnancy, treatment of breastfeeding mothers resulted in minimal exposure of infants to the 8-aminoquinoline.[9] This finding indicates that, rather than deferring by 6 months or until breastfeeding is completed, earlier postpartum radical cure to reduce the risk of relapse after birth might be safe.[46]

Country-specific malaria in pregnancy treatment and prevention guidelines in the Asia-Pacific region

Treatment of malaria in pregnancy

An overview of national malaria guidelines and strategic plans from 20 countries is provided in the appendix (p 20).[103,128–161] At time of review, quinine was the recommended first-line treatment for uncomplicated *P falciparum* malaria in the first trimester, combined with clindamycin in eight countries,[128,132,144,145,148,152,155,156,160] or with sulphadoxine–pyrimethamine in Papua New Guinea,[103] and as monotherapy in five countries (appendix p 21).[134,137,143,154,159] Four countries used ACTs as first-line treatment for *P falciparum* malaria throughout pregnancy (artemether–lumefantrine in Bangladesh [2019], Laos [2022], and Nepal [2019]; dihydroartemisinin–piperaquine in Indonesia [2020]).[130,139,141,146] The most frequently recommended ACT for uncomplicated *P falciparum* malaria in the second and third trimesters was artemether–lumefantrine.[103,128,130,132,141,143–146,148,152,154,156,159] Artesunate was the first-line treatment for severe *P falciparum* malaria in all trimesters of pregnancy in 13 countries.[103,128,130,132,139,141,143–146,148,152,155,159]

Chloroquine was the most frequently recommended

first-line treatment for uncomplicated *P vivax* malaria throughout pregnancy (appendix pp 22–23).[128,130,132,136,138,143,144,146,148,155,160] Dihydroartemisinin–piperaquine was used for *P vivax* during all trimesters in Indonesia, and more recently artemether–lumefantrine was used in Vanuatu and Laos.[139,141] For *P vivax* after the first trimester, ACTs were recommended in Cambodia, Papua New Guinea, the Philippines, Solomon Islands, Timor-Leste, and Vanuatu (appendix p 24 for treatment of other species).[103,134,152,154,156] Radical cure during pregnancy was contraindicated in all countries. Recommendations varied regarding radical cure in breastfeeding women. North Korea, India, Papua New Guinea, and Timor-Leste did not specifically caution against primaquine use during lactation.[103,136,138,156] Of 16 countries cautioning against using primaquine during lactation, 11 recommended delaying until the breastfed infant was 6 months or older. Pakistan, Thailand, and Viet Nam advised that the breastfed infant should be confirmed glucose-6-phosphate dehydrogenase normal before maternal treatment.[148,155,160]

Prevention of malaria in pregnancy

14 of 20 endemic countries explicitly emphasise ITN use during pregnancy (table 3). The specific approaches included recommendations for universal use and provision of ITNs to women at their first antenatal visit (eg, Vanuatu); restricting distribution of ITNs to ANCs in higher endemicity areas (eg, Bangladesh, India, Nepal, Pakistan, and Timor-Leste); and prioritising ITNs to pregnant women during mass distribution efforts (North Korea).[131,136,149,158] Papua New Guinea, Solomon Islands, and Vanuatu recommended chemopreventive strategies during pregnancy. Papua New Guinea implemented SP-IPTp in 2009 (three doses).[103] In the Solomon Islands and Vanuatu, pregnant women were recommended weekly chloroquine from the first antenatal visit until birth. In Bangladesh, pregnant women were encouraged to consider chemoprophylaxis when travelling to higher endemicity areas.[131] Use of weekly chloroquine as secondary prophylaxis for relapse control following an episode of vivax malaria in pregnancy was recommended in Bhutan, Malaysia, and Nepal.[132,143,146]

Six countries recommended screen-and-treat interventions. In Bangladesh, screening in pregnancy by RDT was recommended in higher endemicity areas, although frequency of screening was not reported.[130,131] Similarly, Cambodia recommended screening during ANC visits, with the caveat that "screenings should be determined by local malaria epidemiology and logistical factors".[134] In Indonesia, screening using light-microscopy or RDT was recommended, but the frequency and geographical areas were not stated.[139] Regular RDT-based screening during ANC was recommended in higher risk areas in Pakistan.[148] Routine screening at the first ANC visit only was recommended in Malaysia and high-risk areas of Timor-Leste.[142,143,156,157]

Discussion

In the past decade, our knowledge of the burden and deleterious effects of malaria on maternal and birth outcomes in the Asia-Pacific region has increased substantially. *P vivax* infection during pregnancy reduces birthweight and causes pregnancy loss and anaemia; *P falciparum* or *P vivax* in the first trimester double the risk of miscarriage, and in the second trimester have lasting consequences for the fetus even when treated promptly and effectively. Novel and innovative approaches are urgently required to prevent these early infections. Furthermore, at least half of peripheral infections are subpatent, and most infected women are asymptomatic. Asymptomatic low-density infections in pregnant women are common in hypoendemic areas, and this group could form a hidden reservoir of infection, impeding elimination efforts.[13,14] Recurrent or symptomatic infections substantially increase the risk of adverse health outcomes, highlighting the need for effective prevention, detection, and treatment of malaria infection during pregnancy, and for safe and timely anti-relapse treatment after pregnancy.

Four clinical trials of malaria prevention in pregnancy were reported from the Asia-Pacific region in the past decade, compared with none in the preceding decade.[17] All trials critically enhance our understanding of the challenges regarding preventing malaria in pregnancy in the region. In Papua New Guinea, IPTp with sulfadoxine–pyrimethamine plus azithromycin reduced the risks of low birthweight and placental malaria, thereby indirectly supporting an extension of IPTp with sulfadoxine–pyrimethamine to meso-endemic settings outside sub-Saharan Africa. IPTp with dihydroartemisinin–piperaquine reduced the risks of both falciparum and vivax malaria in Indonesia. Current clinical trials (NCT04336189, NCT05426434) are testing the hypothesis that combining dihydroartemisinin–piperaquine with sulfadoxine–pyrimethamine (which has malaria-independent benefits on maternal weight gain and fetal growth)[162–164] might maximise the benefit for birth outcomes in areas where the malaria parasite has become highly resistant to sulfadoxine–pyrimethamine. By contrast, ISTp with current RDTs did not translate into substantial reductions in placental malaria and adverse birth outcomes, highlighting the need for better diagnostic tools. Innovative approaches to measuring outcomes in prevention trials in hypo-endemic settings are needed.

Our Review of national malaria treatment guidelines highlights approaches taken by some national malaria control programmes to overcome the current absence of global guidance for the Asia-Pacific region. For example, Bangladesh, Cambodia, India, Nepal, Pakistan, and Timor-Leste already deploy targeted use of preventive measures, with interventions rolled out and scaled up depending on transmission intensity (eg, in Pakistan; table 3). Likewise, screen-and-treat strategies are used in

Search strategy and selection criteria

We searched the Malaria in Pregnancy Library (MIPL) using country and region names for relevant studies of malaria in pregnancy in the Asia-Pacific region (appendix pp 3–4). MIPL draws on numerous sources (eg, PubMed, Google Scholar, The Global Health Library, Web of Knowledge, and clinical trial registries), and is updated regularly (https://www.wwarn.org/tools-resources/literature-reviews/malaria-pregnancy-library). We considered all countries in the WHO South-East Asian regional office and Western Pacific regional office that were not declared malaria-free before 2022, and other members of the Asia Pacific Leaders Malaria Alliance (ie, Pakistan and Afghanistan). Therefore, material from Brunei, the Maldives, China, Taiwan, Singapore, and Sri Lanka was not considered. Searches were limited to English language articles published between Jan 1, 2011 and Jan 15, 2023 to serve as an update of an earlier comprehensive review. We considered observational studies, clinical trials, pharmacokinetic studies, social science, health economics, implementation science, surveys, and ultrasound studies relating to malaria in pregnancy. Review articles, animal and laboratory studies, reports, conference abstracts, case studies (apart from one case series on *Plasmodium knowlesi*), and research exclusively reporting on congenital malaria were excluded. National malaria treatment guidelines and strategic plans for malaria control and elimination were obtained through MIPL and Google searches and through contacting national malaria control programmes. This search was not restricted by language.

several countries, yet might not be supported by currently available evidence. There is a need to develop a framework for prevention in the Asia-Pacific region using a more systematic approach (appendix p 6). Factors such as disease burden, drug resistance, and species distribution could guide national and subnational policy, which could involve a scaled approach to prevention, as currently done in Bangladesh. Furthermore, cultural preferences regarding presumptive treatment versus screen-and-treat approaches are important to consider as they critically shape the success of implementation. More flexible approaches are needed to keep guidelines up to date and relevant, allowing programme managers and health-care workers to deliver the best possible, locally appropriate preventive strategy. Any framework must ensure sustained malaria control within resilient health systems to maintain gains and advance towards elimination.

Contributors

HWU, SJR, SA, LA, CW, AMvE, BRM, RNP, FOtK, KT, and EL conducted the literature search, and collected and summarised the data. HWU, SJR, and BRM wrote the first draft of the manuscript. AMvE assisted with drafting figures. GRG-L and RMC co-drafted supplemental table 1 (appendix p 7). All authors interpreted the final data and contributed to the writing of the report.

Declaration of interests

We declare no competing interests.

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