

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

Holger W Unger, Sanjaya Acharya, Lachlan Arnold, Connie Wu, Anna Maria van Eijk, Georgia R Gore-Langton, Feiko O ter Kuile, Elvin Lufele, R Matthew Chico, Ric N Price, Brioni R Moore, Kamala Thriemer, Stephen J Rogerson



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.

## Introduction

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

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.<sup>4-6</sup> 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.<sup>5</sup> WHO currently only recommends using insecticide-treated bednets (ITNs) to prevent malaria in pregnancy in the Asia-Pacific region.<sup>7</sup>

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.<sup>8</sup> *P vivax* forms hypnozoites that require radical cure with primaquine, which is contraindicated in pregnancy and early breastfeeding.<sup>9</sup> *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.<sup>10</sup> Multiple mosquito species have ecology and behaviours that could affect control measures,<sup>11,12</sup> and parasite-host interactions are complex.<sup>8,13</sup> 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.<sup>3,14-16</sup> Infrequent infection

might limit the development of immunity, increasing the risk of severe malaria when infected,<sup>17</sup> and attenuating the parity-dependent decrease in placental malaria that would otherwise occur.<sup>1</sup>

We reviewed 106 original articles published from Jan 1, 2011 to Jan 15, 2023 to provide an update of an earlier comprehensive review.<sup>17</sup> 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).<sup>17</sup>

## 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).<sup>5,6,18</sup> 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%.<sup>19</sup> Despite these successes, progress is fragile, as highlighted by the COVID-19 pandemic, which undermined many regional malaria control programmes.<sup>13</sup>

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),<sup>3,14,20-40</sup> and most used light-microscopy and rapid diagnostic tests (RDT). Some studies performed repeated testing.<sup>36,37</sup> Prevalence of malaria was higher in studies that selected participants on the basis of fever or a history of recent febrile illness.<sup>29,31</sup> 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.<sup>20,24-26,34,35</sup> There was marked regional heterogeneity in burden and species distribution in

Lancet Glob Health 2023;  
11: e1805-18

Global and Tropical Health Division, Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia (H W Unger PhD, S Acharya MD, E Lufele MMedSc, K Thriemer PhD, Prof R N Price MD); Department of Obstetrics and Gynaecology, Royal Darwin Hospital, Tiwi, NT, Australia (H W Unger); Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK (A M van Eijk PhD, Prof F O ter Kuile PhD, H W Unger); Royal Melbourne Hospital Clinical School, The University of Melbourne, Parkville, VIC, Australia (L Arnold BBiomedSc, C Wu BBiomedSc); Department of Disease Control, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK (G R Gore-Langton MD, R M Chico PhD); Vector-Borne Diseases Unit, Papua New Guinea Institute of Medical Research, Madang, Papua New Guinea (E Lufele); Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK (Prof R N Price); Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (Prof R N Price); Curtin Medical School (B R Moore PhD) and Curtin Health Innovation Research Institute (B R Moore), Curtin University, Bentley, WA, Australia; Telethon Kids Institute, Perth Children's Hospital, Nedlands, WA, Australia (B R Moore); Department of Infectious Diseases (Prof S J Rogerson PhD) and Department of Medicine (Prof S J Rogerson), University of Melbourne, The Doherty Institute, Melbourne, VIC, Australia

Correspondence to:  
Dr Holger W Unger, Global and  
Tropical Health Division, Menzies  
School of Health Research,  
Charles Darwin University,  
Darwin, NT 0811, Australia  
[hwunger@doctors.org.uk](mailto:hwunger@doctors.org.uk)  
See Online for appendix

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

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.<sup>41</sup> 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%).<sup>32,33</sup> 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.<sup>24,38,39</sup>

Most studies reporting the prevalence of malaria at

delivery originate from India and Papua New Guinea (appendix pp 5, 10, 11).<sup>20,22,24,25,27,33,35,38–40,42,43</sup> 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.<sup>39</sup> 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.<sup>13,38,43</sup> *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,<sup>44</sup> whereas in Laos, only one of 250 febrile women was RDT-positive for *P falciparum*.<sup>45</sup> 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.<sup>46</sup> The increase in postpartum *P vivax* was attributed to relapse.

## 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 ( $\geq 40\%$ ) among women admitted with *P falciparum* and *P vivax* malaria (appendix pp 12, 13).<sup>26,47–50</sup> Multiple observational studies examined the association of malaria infection with anaemia.<sup>22–24,36,37,39,42,43,51–53</sup> 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,<sup>36</sup> and in Papua New Guinea anaemia (haemoglobin  $< 11$  g/dL) prevalence was approximately 70% of women with *P falciparum* and *P vivax* infections.<sup>39</sup>

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).<sup>53</sup> 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.<sup>39</sup> 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.<sup>24</sup> 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.<sup>24</sup> In a subsequent study from Papua New Guinea, chronic, but not acute or past, histological infection doubled the risk of anaemia.<sup>43</sup> By contrast, in Madhya Pradesh, India, women with acute

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

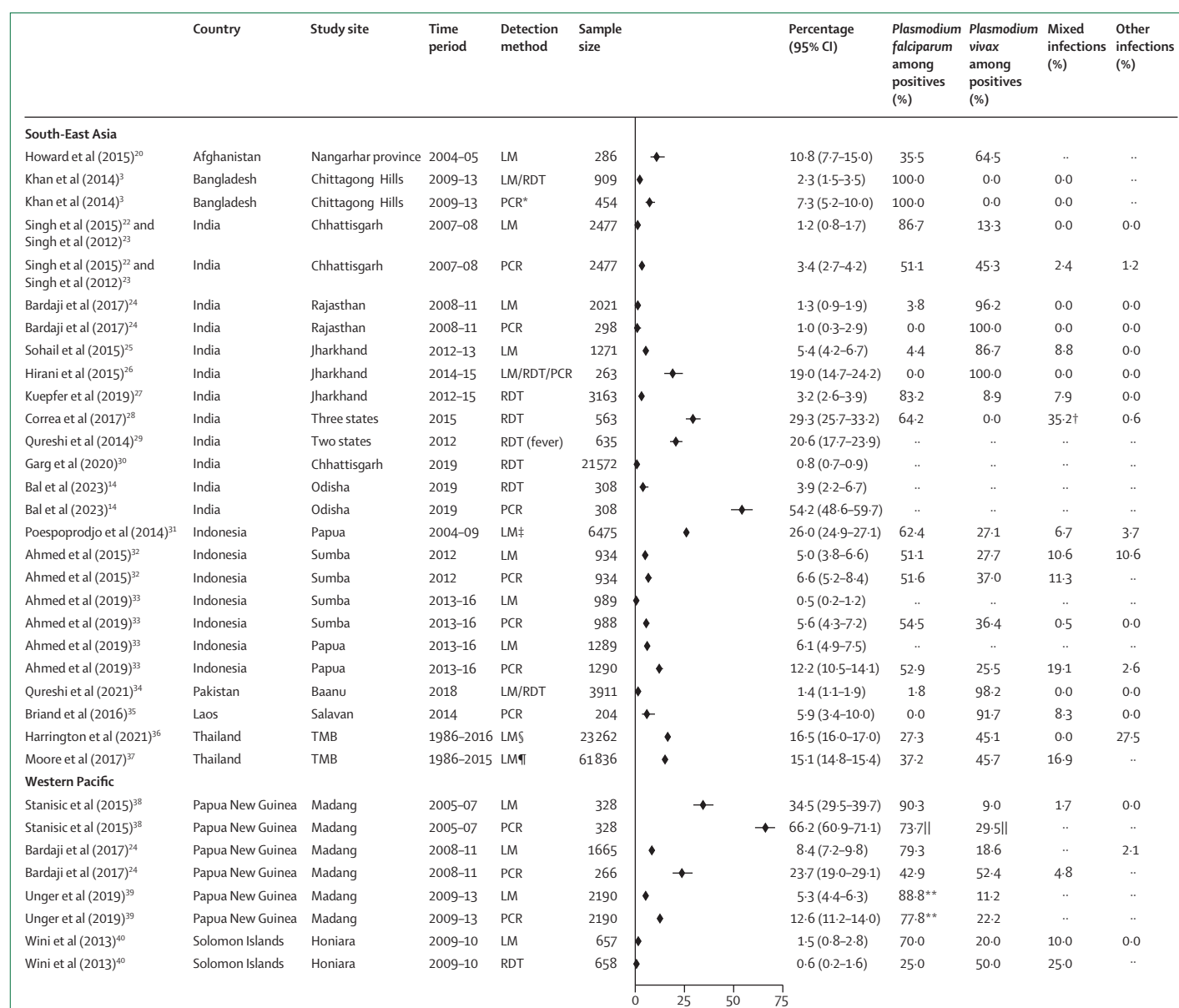
- Effect of subpatent infections on health outcomes and malaria transmission
- Longitudinal cohort studies to determine effects of *Plasmodium falciparum* and *Plasmodium vivax* infection in pregnancy on adverse health outcomes in infancy and childhood
- Evaluation of the effect of *Plasmodium knowlesi* 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

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

### Maternal death and morbidity

Both *P falciparum* and *P vivax* were associated with maternal mortality.<sup>54</sup> 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*).<sup>54</sup> In institutional reviews, cohort studies, and national surveys (appendix p 14),<sup>52,55–70</sup> malaria in pregnancy was the cause of 2.7–23.4% of intensive care unit admissions in India.<sup>58,69,70</sup> 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.<sup>66,67</sup> The contribution of malaria to severe maternal morbidity and maternal deaths in the community remains poorly



**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 <sup>71</sup>							
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 <sup>72</sup>							
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 <sup>42</sup>							
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 <sup>52</sup>							
Jabalpur	2008–09	Cross-sectional‡	Maternal/placental LM	1/21 (4.8%)	2/479 (0.4%)	11.92 (1.04–137.07)	ref
Thailand <sup>37</sup>							
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 <sup>37</sup>							
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 <sup>53</sup>							
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.<sup>68</sup> 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.<sup>36</sup>

#### 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]).<sup>71,72</sup> The association of *Plasmodium* infection with stillbirth was evaluated in three studies (table 1).<sup>37,42,52</sup> In Madhya Pradesh, acute but not chronic or past placental *P falciparum* infection on histology doubled the risk of stillbirth.<sup>42</sup> At the Thailand–

Myanmar border, symptomatic peripheral *P falciparum* or *P vivax* infection in later pregnancy doubled the risk of antepartum (pre-labour) stillbirth.<sup>37</sup> Much of this risk appeared to be mediated via fetal growth restriction and maternal anaemia.<sup>37</sup> 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.<sup>37</sup>

#### 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).<sup>39,42,43,52,53,71,73</sup> 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).<sup>42,43</sup> Acute

	Study type	Detection method	Grouping	n	Mean difference in birthweight, g (95% CI)	Low birthweight* n (%)	Odds ratio (95% CI)
India							
Madhya Pradesh <sup>42</sup>							
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 <sup>23</sup>							
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 <sup>52</sup>							
2008–09	Cross-sectional	Placental LM	Positive	21	−290 (..)	..	..
2008–09	Cross-sectional	Placental LM	Negative	479	ref	..	..
Indonesia							
Timika <sup>53</sup>							
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 <sup>43</sup>							
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 <sup>39</sup>							
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 <sup>71</sup>							
1986–2010	Cohort	Maternal LM‡	Positive	392	30 (..)§	..	..
1986–2010	Cohort	Maternal LM‡	Negative	11 204	ref	..	..
Thailand–Myanmar border <sup>73</sup>							
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 <i>Plasmodium falciparum</i> , 192 <i>Plasmodium vivax</i> ). §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							

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.<sup>42,43</sup> Neither submicroscopic nor microscopic peripheral infection at the first antenatal visit was associated with SGA in Papua New Guinea, but prevalence was low.<sup>39</sup> 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.<sup>22,39</sup> 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.<sup>71,73</sup> At the same site, microscopic *P. falciparum* and *P. vivax* infections in the first trimester conveyed no increased



risk of SGA or preterm birth.<sup>74</sup>

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.<sup>74</sup> In Papua New Guinea, symptomatic *P falciparum* infection during pregnancy was associated with fetal growth restriction detected by ultrasound.<sup>75</sup> 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.<sup>76</sup> At the Thailand–Myanmar border, *P falciparum* malaria was associated with lower placental volume Z scores,<sup>77</sup> and *P falciparum* or *P vivax* infections between 14 and 24 weeks were associated with reduced biparietal diameter Z scores,<sup>78</sup> although no gross effects on fetal brain development were detected.<sup>79</sup>

### 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.<sup>80</sup> The performances of RDT (HRP-2/pLDH) and light-microscopy were similar for screening for *P falciparum* in pregnancy in Sumba and Maluku, Indonesia,<sup>32,81</sup> 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*.<sup>32,80</sup> Light-microscopy and RDT of peripheral blood also missed more than 50% of women with active placental infection on histology in Papua New Guinea.<sup>80</sup> 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.<sup>82</sup> RDT-based screen-and-treat approaches would require RDTs with better sensitivity, especially for *P vivax*, to detect asymptomatic low-density infection.<sup>27</sup>

### 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,<sup>7</sup> as studies in the Asia-Pacific region have shown the safety and superior antimalarial efficacy of artemether–lumefantrine compared with quinine.<sup>71,72,83</sup> 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,<sup>84</sup> and extended follow-up in efficacy studies might be required.<sup>85</sup> Dihydroartemisinin–piperaquine, artesunate–mefloquine, and an extended 4-day artemether–lumefantrine regimen (AL<sup>+</sup>) were compared in pregnant women with uncomplicated *P falciparum* or *P vivax* malaria at the Thailand–Myanmar border (appendix p 15).<sup>83,86</sup> For *P falciparum*, PCR-corrected cure rates were highest for dihydroartemisinin–piperaquine (93.7%), followed by AL<sup>+</sup> (87.5%). PCR-corrected cure rates were lowest for artesunate–mefloquine (79.6%), which also had inferior tolerability.<sup>83</sup> 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<sup>+</sup> (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.<sup>87</sup> 7 days of oral artesunate monotherapy was reported to clear *P falciparum* parasitaemia in 82.5% of pregnant women in India.<sup>88</sup> 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,<sup>31,53</sup> and a greater chance of being discharged with an ongoing pregnancy.<sup>31</sup> Weekly mefloquine reduced spleen size and improved haematocrit in pregnant women with hyper-reactive malarial splenomegaly at the Thailand–Myanmar border.<sup>89</sup> Barriers to timely initiation of antimalarial treatment now need to be overcome to reduce morbidity and mortality further.<sup>90</sup>

### Prevention of malaria in pregnancy

WHO recommends the universal use of ITNs in all malaria-endemic settings.<sup>91</sup> In Papua, Indonesia, only 23.2% of pregnant women used an ITN, citing limited access to government-issued nets.<sup>92</sup> 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.<sup>93–95</sup> Similarly, ITN use by pregnant women at the Thailand–Myanmar border was high (90.0%), yet adequate household ownership remained low (30.8%).<sup>96</sup> 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.<sup>97,98</sup> In Bangladesh, free distribution of ITNs plus counselling by community health workers improved uptake,<sup>99</sup> as was the case in Papua New Guinea,<sup>100</sup> and mass distribution enhanced women's awareness of malaria in pregnancy in Timor-Leste.<sup>101</sup>

In the past decade, clinical trials of IPTp were conducted in Papua New Guinea and Indonesia (appendix pp 16–17).<sup>33,102</sup> 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.<sup>40</sup> 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%.<sup>102</sup> Papua New Guinea is the only country in the region to adopt IPTp with sulphadoxine–pyrimethamine as national policy.<sup>103</sup> Another potentially promising option is the combination of azithromycin and piperazine.<sup>104</sup> 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.<sup>104</sup>

A cluster-randomised trial in Sumba and Papua in Indonesia compared dihydroartemisinin–piperazine for IPTp, intermittent screening and treatment in pregnancy (ISTp), with a single screen-and-treat (SST) at first antenatal visit (standard of care).<sup>33</sup> SST was introduced in 2012, with variable success in implementation.<sup>105,106</sup> 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–piperazine might control both new *P. vivax* infections and relapses.<sup>107</sup> 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–piperazine was highly cost-effective compared with SST, at a cost of US\$54 per disability-adjusted life-year due to malaria in pregnancy.<sup>107</sup> In Papua and Sumba, women were generally receptive to IPTp, but health-care workers expressed concerns over drug resistance and in utero drug exposure.<sup>108</sup> 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.<sup>108</sup> In Jharkhand, India, ISTp with artesunate–sulfadoxine–pyrimethamine was compared with passive case detection, the current

standard of care.<sup>27</sup> 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,<sup>109</sup> yet better RDTs are needed for enhanced health-care worker acceptability and protection from malaria.<sup>110</sup> Qualitative studies highlight the importance of health-care worker training to facilitate the provision of preventive measures,<sup>111,112</sup> and to enhance their uptake by women through education about malaria in pregnancy, including the effects of asymptomatic infection.<sup>113</sup>

### 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.<sup>114</sup> The recent use of population pharmacokinetic modelling and dose simulations has shown potential for evaluation of the effect of pregnancy on antimalarial pharmacokinetics.<sup>115</sup>

In the past decade, most antimalarial pharmacokinetic evaluations from the Asia-Pacific region have originated from Thailand and Papua New Guinea.<sup>115–126</sup> Neither pregnancy status nor gestational age substantially affected the disposition of amodiaquine, which is not prescribed extensively.<sup>116,117</sup> 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.<sup>118</sup> Simulations predicted that 4–10 day regimens would result in day-7 plasma concentrations exceeding the target, 280 ng/mL,<sup>118</sup> yet a recent evaluation showed suboptimal antimalarial efficacy of AL+ (4 days; appendix p 15).<sup>83</sup>

Pharmacokinetics of artemisinin derivatives during pregnancy are also variable, ranging from no difference compared with non-pregnant women,<sup>121</sup> to higher rates of drug clearance and 23–38% reduction in total drug exposure after the second trimester.<sup>119,122</sup> 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.<sup>119,122</sup>

Although pregnancy is associated with the increased clearance and shortened elimination half-life of piperazine (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.<sup>131</sup> ‡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.<sup>119,121,125</sup> 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.<sup>126</sup>

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.<sup>123</sup> These data imply that higher doses of

chloroquine could be required to ensure appropriate therapeutic or chemoprophylactic efficacy.<sup>123</sup> Using population non-linear mixed-effect modelling, sulphadoxine-pyrimethamine dosing regimens for IPTp have been evaluated using Papua New Guinea data.<sup>127</sup> 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.<sup>127</sup> 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.<sup>125</sup> 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.<sup>104,125</sup> Lastly, although primaquine is contraindicated during pregnancy, treatment of breastfeeding mothers resulted in minimal exposure of infants to the 8-aminoquinoline.<sup>9</sup> 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.<sup>46</sup>

## 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).<sup>103,128–161</sup> 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,<sup>128,132,144,145,148,152,155,156,160</sup> or with sulphadoxine-pyrimethamine in Papua New Guinea,<sup>103</sup> and as monotherapy in five countries (appendix p 21).<sup>134,137,143,154,159</sup> 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]).<sup>130,139,141,146</sup> The most frequently recommended ACT for uncomplicated *P. falciparum* malaria in the second and third trimesters was artemether-lumefantrine.<sup>103,128,130,132,141,143–146,148,152,154,156,159</sup> Artesunate was the first-line treatment for severe *P. falciparum* malaria in all trimesters of pregnancy in 13 countries.<sup>103,128,130,132,139,141,143–146,148,152,155,159</sup>

Chloroquine was the most frequently recommended



first-line treatment for uncomplicated *P vivax* malaria throughout pregnancy (appendix pp 22–23).<sup>128,130,132,136,138,143,144,146,148,155,160</sup> Dihydroartemisinin–piperaquine was used for *P vivax* during all trimesters in Indonesia, and more recently artemether–lumefantrine was used in Vanuatu and Laos.<sup>139,141</sup> 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).<sup>103,134,152,154,156</sup> 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.<sup>103,136,138,156</sup> 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.<sup>148,155,160</sup>

### 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).<sup>131,136,149,158</sup> Papua New Guinea, Solomon Islands, and Vanuatu recommended chemopreventive strategies during pregnancy. Papua New Guinea implemented SP-IPTp in 2009 (three doses).<sup>103</sup> 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.<sup>131</sup> 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.<sup>132,143,146</sup>

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.<sup>130,131</sup> Similarly, Cambodia recommended screening during ANC visits, with the caveat that “screenings should be determined by local malaria epidemiology and logistical factors”.<sup>134</sup> In Indonesia, screening using light-microscopy or RDT was recommended, but the frequency and geographical areas were not stated.<sup>139</sup> Regular RDT-based screening during ANC was recommended in higher risk areas in Pakistan.<sup>148</sup> Routine screening at the first ANC visit only was recommended in Malaysia and high-risk areas of Timor-Leste.<sup>142,143,156,157</sup>

### 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.<sup>13,14</sup> 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.<sup>17</sup> 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)<sup>162–164</sup> 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 hypoendemic 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.

#### Acknowledgments

We thank Jaehun Jung (Korea Disease Control Agency, Republic of Korea) for assistance with sourcing and translating country guidelines. HWU is supported by a Menzies School of Health Research (Darwin) Future Researcher Fellowship. KT is a CSL Centenary Fellow. Funding sources were not involved in the collection, analysis, and interpretation of the data, the writing of the article, or in submission of the Review for publication. The views expressed in the Review are those of the authors and do not represent the funding agencies.

### References

- Rogerson SJ, Desai M, Mayor A, Sicuri E, Taylor SM, van Eijk AM. Burden, pathology, and costs of malaria in pregnancy: new developments for an old problem. *Lancet Infect Dis* 2018; **18**: e107–18.
- Rogerson SJ, Unger HW. Pregnancy and malaria: the perfect storm. *Curr Opin Infect Dis* 2022; **35**: 410–16.
- Khan WA, Galagan SR, Prue CS, et al. Asymptomatic *Plasmodium falciparum* malaria in pregnant women in the Chittagong Hill Districts of Bangladesh. *PLoS One* 2014; **9**: e98442.
- Reddy V, Weiss DJ, Rozier J, Ter Kuile FO, Dellicour S. Global estimates of the number of pregnancies at risk of malaria from 2007 to 2020: a demographic study. *Lancet Glob Health* 2023; **11**: e40–47.
- Gore-Langton GR, Cano J, Simpson H, et al. Global estimates of pregnancies at risk of *Plasmodium falciparum* and *Plasmodium vivax* infection in 2020 and changes in risk patterns since 2000. *PLoS Glob Public Health* 2022; **2**: e0001061.
- WHO. World malaria report 2022. Geneva: World Health Organization, 2022.
- WHO. WHO guidelines for malaria—25 November 2022. Geneva: World Health Organization, 2022.
- Hamilton WL, Amato R, van der Pluijm RW, et al. Evolution and expansion of multidrug-resistant malaria in southeast Asia: a genomic epidemiology study. *Lancet Infect Dis* 2019; **19**: 943–51.
- Gilder ME, Hanpithakphong W, Hoglund RM, et al. Primaquine pharmacokinetics in lactating women and breastfed infant exposures. *Clin Infect Dis* 2018; **67**: 1000–07.
- Barber BE, Bird E, Wilkes CS, et al. *Plasmodium knowlesi* malaria during pregnancy. *J Infect Dis* 2015; **211**: 1104–10.
- Sinka ME, Bangs MJ, Manguin S, et al. The dominant *Anopheles* vectors of human malaria in the Asia-Pacific region: occurrence data, distribution maps and bionomic précis. *Parasit Vectors* 2011; **4**: 89.
- Massey NC, Garrod G, Wiebe A, et al. A global bionomic database for the dominant vectors of human malaria. *Sci Data* 2016; **3**: 160014.
- Mueller I, Vantaux A, Karl S, et al. Asia-Pacific ICEMR: Understanding malaria transmission to accelerate malaria elimination in the Asia Pacific region. *Am J Trop Med Hyg* 2022; **107** (suppl): 131–37.
- Bal M, Ghosal J, Das A, et al. Impact of sub-patent malaria during pregnancy on birth-weight in Odisha, India: time-to-event analysis of prospective longitudinal follow-up of a survey. *J Epidemiol Glob Health* 2023; **13**: 23–31.
- Baird JK. Asia-Pacific malaria is singular, pervasive, diverse and invisible. *Int J Parasitol* 2017; **47**: 371–77.
- Vantaux A, Samreth R, Piv E, et al. Contribution to malaria transmission of symptomatic and asymptomatic parasite carriers in Cambodia. *J Infect Dis* 2018; **217**: 1561–68.
- Rijken MJ, McGready R, Boel ME, et al. Malaria in pregnancy in the Asia-Pacific region. *Lancet Infect Dis* 2012; **12**: 75–88.
- Malaria Atlas Project. Malaria Atlas Project. 2020. <https://malariaatlas.org/> (accessed Jan 15, 2023).
- Ryan LM, Mahmood MA, Laurence CO. Incidence of concomitant illnesses in pregnancy in Indonesia: estimates from 1990–2019, with projections to 2030. *Lancet Reg Health West Pac* 2021; **10**: 100139.
- Howard N, Enayatullah S, Mohammad N, et al. Towards a strategy for malaria in pregnancy in Afghanistan: analysis of clinical realities and women's perceptions of malaria and anaemia. *Malar J* 2015; **14**: 431.
- Shannon KL, Khan WA, Sack DA, et al. Subclinical *Plasmodium falciparum* infections act as year-round reservoir for malaria in the hypoendemic Chittagong Hill districts of Bangladesh. *Int J Infect Dis* 2016; **49**: 161–69.
- Singh N, Bharti PK, Singh MP, et al. What is the burden of submicroscopic malaria in pregnancy in central India? *Pathog Glob Health* 2015; **109**: 30–38.
- Singh N, Singh MP, Wylie BJ, et al. Malaria prevalence among pregnant women in two districts with differing endemicity in Chhattisgarh, India. *Malar J* 2012; **11**: 274.
- Bardaji A, Martínez-Espinosa FE, Arévalo-Herrera M, et al. Burden and impact of *Plasmodium vivax* in pregnancy: a multi-centre prospective observational study. *PLoS Negl Trop Dis* 2017; **11**: e0005606.

- 25 Sohail M, Shakeel S, Kumari S, et al. Prevalence of malaria infection and risk factors associated with anaemia among pregnant women in semiurban community of Hazaribag, Jharkhand, India. *BioMed Res Int* 2015; **2015**: 740512.
- 26 Hirani MM, Vadhvana SK. Study of clinical profile of *P. vivax* malaria in pregnancy. *J Res Med Dent Sci* 2015; **3**: 307–11.
- 27 Kuepfer I, Mishra N, Bruce J, et al. Effectiveness of intermittent screening and treatment for the control of malaria in pregnancy: a cluster randomised trial in India. *BMJ Glob Health* 2019; **4**: e001399.
- 28 Corrêa G, Das M, Kovelamudi R, et al. High burden of malaria and anemia among tribal pregnant women in a chronic conflict corridor in India. *Confl Health* 2017; **11**: 10.
- 29 Qureshi IA, Arlappa N, Qureshi MA. Prevalence of malaria and anemia among pregnant women residing in malaria-endemic forest villages in India. *Int J Gynaecol Obstet* 2014; **127**: 93.
- 30 Garg S, Dewangan M, Barman O. Malaria prevalence in symptomatic and asymptomatic pregnant women in a high malaria-burden state in India. *Trop Med Health* 2020; **48**: 71.
- 31 Poespoprodjo JR, Fobia W, Kenangalem E, et al. Dihydroartemisinin-piperazine treatment of multidrug resistant falciparum and vivax malaria in pregnancy. *PLoS One* 2014; **9**: e84976.
- 32 Ahmed R, Levy EI, Maratina SS, et al. Performance of four HRP-2/pLDH combination rapid diagnostic tests and field microscopy as screening tests for malaria in pregnancy in Indonesia: a cross-sectional study. *Malar J* 2015; **14**: 420.
- 33 Ahmed R, Poespoprodjo JR, Syafruddin D, et al. Efficacy and safety of intermittent preventive treatment and intermittent screening and treatment versus single screening and treatment with dihydroartemisinin-piperazine for the control of malaria in pregnancy in Indonesia: a cluster-randomised, open-label, superiority trial. *Lancet Infect Dis* 2019; **19**: 973–87.
- 34 Qureshi H, Khan MI, Ahmad A, et al. Passive surveillance of malaria in pregnant women, non-pregnant women and children under 5 years of age in Bannu District, Khyber Pakhtunkhwa Pakistan. *Front Med (Lausanne)* 2021; **8**: 751456.
- 35 Briand V, Le Hesran JY, Mayxay M, et al. Prevalence of malaria in pregnancy in southern Laos: a cross-sectional survey. *Malar J* 2016; **15**: 436.
- 36 Harrington WE, Moore KA, Min AM, et al. Falciparum but not vivax malaria increases the risk of hypertensive disorders of pregnancy in women followed prospectively from the first trimester. *BMC Med* 2021; **19**: 98.
- 37 Moore KA, Fowkes FJI, Wiladphaingern J, et al. Mediation of the effect of malaria in pregnancy on stillbirth and neonatal death in an area of low transmission: observational data analysis. *BMC Med* 2017; **15**: 98.
- 38 Stanicic DI, Moore KA, Baiwog F, et al. Risk factors for malaria and adverse birth outcomes in a prospective cohort of pregnant women resident in a high malaria transmission area of Papua New Guinea. *Trans R Soc Trop Med Hyg* 2015; **109**: 313–24.
- 39 Unger HW, Rosanas-Urgell A, Robinson LJ, et al. Microscopic and submicroscopic Plasmodium falciparum infection, maternal anaemia and adverse pregnancy outcomes in Papua New Guinea: a cohort study. *Malar J* 2019; **18**: 302.
- 40 Wini L, Appleyard B, Bobogare A, et al. Intermittent preventive treatment with sulfadoxine-pyrimethamine versus weekly chloroquine for malaria in pregnancy in Honiara, Solomon Islands: a randomised trial. *Malar World J* 2013; **4**: 1–9.
- 41 Carrara VI, Lwin KM, Phyo AP, et al. Malaria burden and artemisinin resistance in the mobile and migrant population on the Thai-Myanmar border, 1999–2011: an observational study. *PLoS Med* 2013; **10**: e1001398.
- 42 Ahmed R, Singh N, ter Kuile FO, et al. Placental infections with histologically confirmed Plasmodium falciparum are associated with adverse birth outcomes in India: a cross-sectional study. *Malar J* 2014; **13**: 232.
- 43 Lufelle E, Umbers A, Ordi J, et al. Risk factors and pregnancy outcomes associated with placental malaria in a prospective cohort of Papua New Guinean women. *Malar J* 2017; **16**: 427.
- 44 Nath J, Mahajan S. A clinical study on pyrexia in pregnancy with special emphasis on fetomaternal outcome. *Int J Sci Res* 2015; **4**: 2071–74.
- 45 Chansamouth V, Thammasack S, Phetsouvanh R, et al. The aetiologies and impact of fever in pregnant inpatients in Vientiane, Laos. *PLoS Negl Trop Dis* 2016; **10**: e0004577.
- 46 Boel ME, Rijken MJ, Leenstra T, et al. Malaria in the post-partum period; a prospective cohort study. *PLoS One* 2013; **8**: e57890.
- 47 Bangal VB, Giri PA. Study of pregnancy outcome in malaria among rural population of Western Maharashtra, India. *Int J Basic Appl Med Sci* 2012; **2**: 108–11.
- 48 Datta M, Biswas J, Dasgupta S, et al. Comparative study on antenatal and perinatal outcome of vivax and falciparum malaria in a tertiary care hospital of Kolkata, India. *J Clin Diagn Res* 2017; **11**: QC01–04.
- 49 Kumari SA. Retrospective study to evaluate the maternal and fetal outcome of malaria in pregnancy. *Int J Toxicol Pharmacol Res* 2021; **11**: 71–77.
- 50 Soomro P, Bhatti N, Abid K. Fetomaternal outcomes among pregnant females suffering from malaria, a study from Interior Sindh, Pakistan. *Pak J Med Res* 2021; **60**: 111–16.
- 51 Chandrashekar VN, Punna K, Dayanand KK, et al. Malarial anemia among pregnant women in the south-western coastal city of Mangaluru in India. *Inform Med Unlocked* 2019; **15**: 100159.
- 52 Guin G, Shaw K, Khare S. Placental malaria prevalence of infestation amongst febrile pregnant women in central India: maternal and perinatal outcome. *J Obstet Gynecol India* 2012; **62**: 25–31.
- 53 Poespoprodjo JR, Fobia W, Kenangalem E, et al. Treatment policy change to dihydroartemisinin-piperazine contributes to the reduction of adverse maternal and pregnancy outcomes. *Malar J* 2015; **14**: 272.
- 54 Nurleila S, Syafruddin D, Elyazar IRF, Baird JK. Serious and fatal illness associated with falciparum and vivax malaria among patients admitted to hospital at West Sumba in eastern Indonesia. *Am J Trop Med Hyg* 2012; **87**: 41–49.
- 55 Chauhan P, Chauhan VK, Shrivastava P. Maternal mortality among tribal women at a tertiary level of care in Bastar, Chhattisgarh. *Glob J Health Sci* 2012; **4**: 132–41.
- 56 Garg P. Study of maternal mortality and complications leading to maternal death in a tertiary centre. *Int J Med Res Review* 2016; **4**: 347–52.
- 57 Sultan S, Kumar A, Bhagchandani D, Dhingre H. Analysis of maternal mortality in a tertiary care centre: a 5 yrs retrospective study. *J Evol Med Dent Sci* 2013; **2**: 1730–37.
- 58 Bhadade R, De' Souza R, More A, Harde M. Maternal outcomes in critically ill obstetrics patients: a unique challenge. *Indian J Crit Care Med* 2012; **16**: 8–16.
- 59 Halder A, Vijayselvi R, Jose R. Changing perspectives of infectious causes of maternal mortality. *J Turk Ger Gynecol Assoc* 2015; **16**: 208–13.
- 60 Paul B, Mohapatra B, Kar K. Maternal deaths in a tertiary health care centre of Odisha: an in-depth study supplemented by verbal autopsy. *Indian J Community Med* 2011; **36**: 213–16.
- 61 Shah P, Shah S, Kutty RV, Modi D. Changing epidemiology of maternal mortality in rural India: time to reset strategies for MDG-5. *Trop Med Int Health* 2014; **19**: 568–75.
- 62 Naik SS, Ghosh S. Comparison of near miss obstetric events and maternal deaths in a tertiary care teaching hospital from Eastern India. *Int J Reprod Contracept Obstet Gynecol* 2018; **7**: 3619–24.
- 63 Satia MN, Panchbudhe SA, Shiloti MP. Maternal mortality due to infectious diseases at a tertiary care centre in India. *Int J Reprod Contracept Obstet Gynecol* 2017; **5**: 2395–401.
- 64 Kanak P, Gautam R, Sharma S, Kharkwal S. Two years retrospective study of causes of maternal mortality in our institution. *Ind J Res* 2016; **5**: 36–37.
- 65 Tripathy JP, Mishra S. Causes and predictors of neonatal, post-neonatal and maternal deaths in India: analysis of a nationwide district-level household survey-4 (DLHS-4), 2012–13. *J Trop Pediatr* 2017; **63**: 431–39.
- 66 Bolnga JW, Hamura NN, Umbers AJ, Rogerson SJ, Unger HW. Insights into maternal mortality in Madang Province, Papua New Guinea. *Int J Gynaecol Obstet* 2014; **124**: 123–27.
- 67 De Silva M, Panisi L, Maepioh A, et al. Maternal mortality at the National Referral Hospital in Honiara, Solomon Islands over a five-year period. *Aust N Z J Obstet Gynaecol* 2020; **60**: 183–87.

- 68 McGready R, Boel M, Rijken MJ, et al. Effect of early detection and treatment on malaria related maternal mortality on the north-western border of Thailand 1986-2010. *PLoS One* 2012; 7: e40244.
- 69 Ghike S, Asegoankar P. Why obstetric patients are admitted to intensive care unit? *J South Asian Fed Obstet Gynecol* 2012; 4: 90–92.
- 70 Bahadur BR, Kodey P, Tanniru J, Tirumala S. Study of outcome of obstetric emergencies admitted to the intensive care unit. *Int J Reprod Contracept Obstet Gynecol* 2018; 7: 2090–14.
- 71 McGready R, Lee SJ, Wiladphaingern J, et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. *Lancet Infect Dis* 2012; 12: 388–96.
- 72 Moore KA, Simpson JA, Paw MK, et al. Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study. *Lancet Infect Dis* 2016; 16: 576–83.
- 73 Rijken MJ, De Livera AM, Lee SJ, et al. Quantifying low birth weight, preterm birth and small-for-gestational-age effects of malaria in pregnancy: a population cohort study. *PLoS One* 2014; 9: e100247.
- 74 Moore KA, Simpson JA, Wiladphaingern J, et al. Influence of the number and timing of malaria episodes during pregnancy on prematurity and small-for-gestational-age in an area of low transmission. *BMC Med* 2017; 15: 117.
- 75 Unger HW, Ome-Kaius M, Karl S, et al. Factors associated with ultrasound-aided detection of suboptimal fetal growth in a malaria-endemic area in Papua New Guinea. *BMC Pregnancy Childbirth* 2015; 15: 83.
- 76 Ome-Kaius M, Karl S, Wangnapi RA, et al. Effects of *Plasmodium falciparum* infection on umbilical artery resistance and intrafetal blood flow distribution: a Doppler ultrasound study from Papua New Guinea. *Malar J* 2017; 16: 35.
- 77 Rijken MJ, Moroski WE, Kirichareon S, et al. Effect of malaria on placental volume measured using three-dimensional ultrasound: a pilot study. *Malar J* 2012; 11: 5.
- 78 Rijken MJ, Papageorgiou AT, Thiptharakun S, et al. Ultrasound evidence of early fetal growth restriction after maternal malaria infection. *PLoS One* 2012; 7: e31411.
- 79 Rijken MJ, de Wit MC, Mulder EJ, et al. Effect of malaria in pregnancy on foetal cortical brain development: a longitudinal observational study. *Malar J* 2012; 11: 222.
- 80 Umbers AJ, Unger HW, Rosanas-Urgell A, et al. Accuracy of an HRP-2/panLDH rapid diagnostic test to detect peripheral and placental *Plasmodium falciparum* infection in Papua New Guinean women with anaemia or suspected malaria. *Malar J* 2015; 14: 412.
- 81 Vebiyanti V, Murhandarwati EH, Jokorianto BH. Validity of p-LDH/HRP2-based rapid diagnostic test for the diagnosis of malaria in pregnant women in Maluku. *Trop Med J* 2013; 3: 166–75.
- 82 Unwin VT, Ahmed R, Noviyanti R, et al. Use of a highly-sensitive rapid diagnostic test to screen for malaria in pregnancy in Indonesia. *Malar J* 2020; 19: 28.
- 83 Saito M, Carrara VI, Gilder ME, et al. A randomized controlled trial of dihydroartemisinin-piperaquine, artesunate-mefloquine and extended artemether-lumefantrine treatments for malaria in pregnancy on the Thailand-Myanmar border. *BMC Med* 2021; 19: 132.
- 84 Laochan N, Zalourmis SG, Imwong M, et al. Intervals to *Plasmodium falciparum* recurrence after anti-malarial treatment in pregnancy: a longitudinal prospective cohort. *Malar J* 2015; 14: 221.
- 85 Saito M, Mansoor R, Wiladphaingern J, et al. Optimal duration of follow-up for assessing antimalarial efficacy in pregnancy: a retrospective analysis of a cohort followed up until delivery on the Thailand-Myanmar border. *Open Forum Infect Dis* 2019; 6: ofz264.
- 86 Saito M, Yotyingaphiram W, Cargill Z, et al. Randomized controlled trial of the electrocardiographic effects of four antimalarials for pregnant women with uncomplicated malaria on the Thailand-Myanmar border. *Antimicrob Agents Chemother* 2021; 65: e02473–20.
- 87 Anvikar AR, Kuepfer I, Mishra V, et al. Efficacy of two artemisinin-based combinations for the treatment of malaria in pregnancy in India: a randomized controlled trial. *Malar J* 2018; 17: 246.
- 88 Saragih SW, Khalid SMT, Malinta U, Wahid I. Effect of artesunate on peripheral parasitaemia in pregnant women with *Plasmodium falciparum* infection. *Indones J Obstet Gynecol* 2017; 5: 135–38.
- 89 Jaroensuk J, Stoesser N, Leimanis ML, et al. Treatment of suspected hyper-reactive malarial splenomegaly (HMS) in pregnancy with mefloquine. *Am J Trop Med Hyg* 2014; 90: 609–11.
- 90 Minn PW, Shewade HD, Kyaw NTT, et al. Quality of malaria treatment provided under 'Better Health Together' project in ethnic communities of Myanmar: how are we performing? *Trop Med Infect Dis* 2019; 4: 140.
- 91 WHO. Global Technical Strategy for malaria 2016–2030. Geneva: World Health Organization, 2015.
- 92 Madjid TH, Romulya AI, Mantilidewi KI, Susiarno H. Determinants of insecticide-treated net use amongst pregnant women with malaria in West Papua, Indonesia. *Andalas Obstet Gynaecol J* 2022; 6: 16–20.
- 93 Maung TM, Tripathy JP, Oo T, et al. Household ownership and utilization of insecticide-treated nets under the Regional Artemisinin Resistance Initiative in Myanmar. *Trop Med Health* 2018; 46: 27.
- 94 Linn SY, Maung TM, Tripathy JP, et al. Barriers in distribution, ownership and utilization of insecticide-treated mosquito nets among migrant population in Myanmar, 2016: a mixed methods study. *Malar J* 2019; 18: 172.
- 95 Aung PL, Win KM, Show KL. Utilization of insecticide-treated bed nets among pregnant women in Myanmar-analysis of the 2015–2016 Demographic and Health Survey. *PLoS One* 2022; 17: e0265262.
- 96 Poosesod K, Parker DM, Meemon N, et al. Ownership and utilization of bed nets and reasons for use or non-use of bed nets among community members at risk of malaria along the Thai-Myanmar border. *Malar J* 2021; 20: 305.
- 97 Kumar R, Farzeen M, Hafeez A, et al. Effectiveness of a health education intervention on the use of long-lasting insecticidal nets for the prevention of malaria in pregnant women of Pakistan: a quasi-experimental study. *Malar J* 2020; 19: 232.
- 98 Kumar R, Farzeen M, Ahmed J, Lal M, Somrongthong R. Predictors of knowledge and use of long-lasting insecticidal nets for the prevention of malaria among the pregnant women in Pakistan. *Malar J* 2021; 20: 347.
- 99 Ahmed SM, Hossain S, Kabir MM, Roy S. Free distribution of insecticidal bed nets improves possession and preferential use by households and is equitable: findings from two cross-sectional surveys in thirteen malaria endemic districts of Bangladesh. *Malar J* 2011; 10: 357.
- 100 Hetzel MW, Gideon G, Lote N, Makita L, Siba PM, Mueller I. Ownership and usage of mosquito nets after four years of large-scale free distribution in Papua New Guinea. *Malar J* 2012; 11: 192.
- 101 Martins JS, Zwi AB, Kelly PM. Did the first Global Fund grant (2003–2006) contribute to malaria control and health system strengthening in Timor-Leste? *Malar J* 2012; 11: 237.
- 102 Unger HW, Ome-Kaius M, Wangnapi RA, et al. Sulphadoxine-pyrimethamine plus azithromycin for the prevention of low birthweight in Papua New Guinea: a randomised controlled trial. *BMC Med* 2015; 13: 9.
- 103 National Department of Health. National Malaria Treatment Protocol (Papua New Guinea). Port Moresby: National Department of Health, 2009.
- 104 Moore BR, Benjamin JM, Tobe R, et al. A randomized open-label evaluation of the antimalarial prophylactic efficacy of azithromycin-piperaquine versus sulfadoxine-pyrimethamine in pregnant Papua New Guinean women. *Antimicrob Agents Chemother* 2019; 63: e00302–19.
- 105 Webster J, Ansariadi, Burdam FH, et al. Evaluation of the implementation of single screening and treatment for the control of malaria in pregnancy in Eastern Indonesia: a systems effectiveness analysis. *Malar J* 2018; 17: 310.
- 106 Hill J, Landuwulang CUR, Ansariadi, et al. Evaluation of the national policy of single screening and treatment for the prevention of malaria in pregnancy in two districts in Eastern Indonesia: health provider perceptions. *Malar J* 2018; 17: 309.
- 107 Paintain L, Hill J, Ahmed R, et al. Cost-effectiveness of intermittent preventive treatment with dihydroartemisinin-piperaquine versus single screening and treatment for the control of malaria in pregnancy in Papua, Indonesia: a provider perspective analysis from a cluster-randomised trial. *Lancet Glob Health* 2020; 8: e1524–33.
- 108 Hoyt J, Landuwulang CUR, Ansariadi, et al. Intermittent screening and treatment or intermittent preventive treatment compared to current policy of single screening and treatment for the prevention of malaria in pregnancy in Eastern Indonesia: acceptability among health providers and pregnant women. *Malar J* 2018; 17: 341.



- 109 Sabin L, Hecht EMS, Brooks MI, et al. Prevention and treatment of malaria in pregnancy: what do pregnant women and health care workers in East India know and do about it? *Malar J* 2018; **17**: 207.
- 110 Webster J, Mishra VK, Anvikar AR, et al. Evaluation of implementation of intermittent screening and treatment for control of malaria in pregnancy in Jharkhand, India. *Am J Trop Med Hyg* 2020; **102**: 1343–50.
- 111 Lim S, Yasuoka J, Poudel KC, Ly P, Nguon C, Jimba M. Promoting community knowledge and action for malaria control in rural Cambodia: potential contributions of Village Malaria Workers. *BMC Res Notes* 2012; **5**: 405.
- 112 Lover AA, Sutton BA, Asy AJ, Wilder-Smith A. An exploratory study of treated-bed nets in Timor-Leste: patterns of intended and alternative usage. *Malar J* 2011; **10**: 199.
- 113 Andrew EV, Pell C, Angwin A, et al. Knowledge, attitudes, and practices concerning malaria in pregnancy: results from a qualitative study in Madang, Papua New Guinea. *PLoS One* 2015; **10**: e0119077.
- 114 Burger RJ, Visser BJ, Grobusch MP, van Vugt M. The influence of pregnancy on the pharmacokinetic properties of artemisinin combination therapy (ACT): a systematic review. *Malar J* 2016; **15**: 99.
- 115 Olafuyi O, Coleman M, Badhan RKS. The application of physiologically based pharmacokinetic modelling to assess the impact of antiretroviral-mediated drug-drug interactions on piperazine antimalarial therapy during pregnancy. *Biopharm Drug Dispos* 2017; **38**: 464–78.
- 116 Rijken MJ, McGready R, Jullien V, et al. Pharmacokinetics of amodiaquine and desethylamodiaquine in pregnant and postpartum women with *Plasmodium vivax* malaria. *Antimicrob Agents Chemother* 2011; **55**: 4338–42.
- 117 Tarning J, Chotsiri P, Jullien V, et al. Population pharmacokinetic and pharmacodynamic modeling of amodiaquine and desethylamodiaquine in women with *Plasmodium vivax* malaria during and after pregnancy. *Antimicrob Agents Chemother* 2012; **56**: 5764–73.
- 118 Klotzrogge F, McGready R, Hanpithakpong W, et al. Lumefantrine and desbutyl-Lumefantrine population pharmacokinetic-pharmacodynamic relationships in pregnant women with uncomplicated *Plasmodium falciparum* malaria on the Thailand-Myanmar border. *Antimicrob Agents Chemother* 2015; **59**: 6375–84.
- 119 Tarning J, Rijken MJ, McGready R, et al. Population pharmacokinetics of dihydroartemisinin and piperazine in pregnant and nonpregnant women with uncomplicated malaria. *Antimicrob Agents Chemother* 2012; **56**: 1997–2007.
- 120 Rijken MJ, McGready R, Phyo AP, et al. Pharmacokinetics of dihydroartemisinin and piperazine in pregnant and nonpregnant women with uncomplicated falciparum malaria. *Antimicrob Agents Chemother* 2011; **55**: 5500–06.
- 121 Benjamin JM, Moore BR, Salman S, et al. Population pharmacokinetics, tolerability, and safety of dihydroartemisinin-piperazine and sulfadoxine-pyrimethamine-piperazine in pregnant and nonpregnant Papua New Guinean women. *Antimicrob Agents Chemother* 2015; **59**: 4260–71.
- 122 Klotzrogge F, McGready R, Phyo AP, et al. Opposite malaria and pregnancy effect on oral bioavailability of artesunate—a population pharmacokinetic evaluation. *Br J Clin Pharmacol* 2015; **80**: 642–53.
- 123 Salman S, Baiwog F, Page-Sharp M, et al. Optimal antimalarial dose regimens for chloroquine in pregnancy based on population pharmacokinetic modelling. *Int J Antimicrob Agents* 2017; **50**: 542–51.
- 124 McGready R, Phyo AP, Rijken MJ, et al. Artesunate/dihydroartemisinin pharmacokinetics in acute falciparum malaria in pregnancy: absorption, bioavailability, disposition and disease effects. *Br J Clin Pharmacol* 2012; **73**: 467–77.
- 125 Moore BR, Benjamin JM, Auyeung SO, et al. Safety, tolerability and pharmacokinetic properties of coadministered azithromycin and piperazine in pregnant Papua New Guinean women. *Br J Clin Pharmacol* 2016; **82**: 199–212.
- 126 Chotsiri P, Gutman JR, Ahmed R, et al. Piperazine pharmacokinetics during intermittent preventive treatment for malaria in pregnancy. *Antimicrob Agents Chemother* 2021; **65**: e01150–20.
- 127 Salman S, Baiwog F, Page-Sharp M, et al. Optimal antimalarial dose regimens for sulfadoxine-pyrimethamine with or without azithromycin in pregnancy based on population pharmacokinetic modeling. *Antimicrob Agents Chemother* 2017; **61**: e02291–16.
- 128 National Malaria and Leishmaniasis Control Program. National malaria treatment guideline (Afghanistan). Kabul: National Malaria and Leishmaniasis Control Program, Ministry of Public Health, the Islamic Republic of Afghanistan, 2017.
- 129 National Malaria and Leishmaniasis Control Program. National strategic plan 'from malaria control to elimination in Afghanistan' 2018–21. Kabul: National Malaria and Leishmaniasis Control Program, Ministry of Public Health, the Islamic Republic of Afghanistan, 2017.
- 130 National Malaria Elimination & Aedes Transmitted Disease Control Program. Revised malaria treatment regimen—2017 (6th version) Bangladesh. Dhaka: National Malaria Elimination & Aedes Transmitted Disease Control Program, Ministry of Health & Family Welfare, 2017.
- 131 National Malaria Elimination Programme. National strategic plan for malaria elimination in Bangladesh (2021–2025) Dhaka: National Malaria Elimination Programme, Directorate General of Health Services, Ministry of Health & Family Welfare, 2020.
- 132 Vector-borne Diseases Control Program. National guidelines on diagnosis and treatment of malaria in Bhutan (5th edition). Gelephu: Vector-borne Diseases Control Program, Department of Public Health, Gelephu, 2019.
- 133 Vector-borne Diseases Control Program. Strategic plan for elimination of malaria and prevention of re-introduction in Bhutan 2020–25. Gelephu: Vector-borne Diseases Control Program, Department of Public Health, 2020.
- 134 National Center for Malaria Control. National treatment guidelines for malaria in Cambodia. Phnom Penh: National Center for Malaria Control, Parasitology and Entomology, The Ministry of Health, the Kingdom of Cambodia, 2014.
- 135 Ministry of Health. Cambodia malaria elimination action framework 2021–25. Phnom Penh: Ministry of Health, Kingdom of Cambodia, 2020.
- 136 National Malaria Programme. National malaria elimination strategy 2018–22. Pyongyang: National Malaria Programme, Ministry of Public Health, 2017.
- 137 National Institute of Malaria Research & National Vector Borne Disease Control Programme. Guidelines for diagnosis and treatment of malaria in India. New Delhi: National Institute of Malaria Research & National Vector Borne Disease Control Programme, 2014.
- 138 National Vector Borne Disease Control Programme. National framework for malaria elimination in India (2016–30). New Delhi: Directorate of National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, 2016.
- 139 Directorate General of Disease Prevention and Control. Malaria case management pocket book (Indonesia). Jakarta: Directorate General of Disease Prevention and Control, Ministry of Health, 2020.
- 140 Ministry of Health. National strategic plan for malaria control and elimination 2016–20 (Laos). Vientiane: Ministry of Health, 2016.
- 141 Center of Malarialogy, Parasitology and Entomology. National guidelines for the treatment of malaria (Laos). Vientiane: Department of Communicable Diseases Control, Ministry of Health, 2022.
- 142 Vector Borne Disease Section. National strategic plan for elimination of Malaria 2010–20 (Malaysia). Kuala Lumpur: Vector Borne Disease Section, Disease Control Division, Ministry of Health Malaysia, 2010.
- 143 Vector Borne Disease Section. Management guidelines of malaria in Malaysia. Kuala Lumpur: Vector Borne Disease Section, Disease Control Division, Ministry of Health, 2013.
- 144 National Malaria Control Programme. Guidelines for malaria diagnosis and treatment in Myanmar. Rangoon: National Malaria Control Programme, Department of Public Health, Ministry of Health and Sports, Republic of the Union of Myanmar, 2015.
- 145 National Malaria Control Programme. Addendum: guidelines for malaria diagnosis and treatment in Myanmar. Rangoon: National Malaria Control Programme, Department of Public Health, Ministry of Health and Sports, Republic of the Union of Myanmar, 2018.
- 146 Epidemiology and Disease Control Division. National malaria treatment protocol 2019 (Nepal). Kathmandu: Epidemiology and Disease Control Division, Department of Health Services, Ministry of Health and Population, Government of Nepal, 2019.



- 147 Epidemiology and Disease Control Division. National malaria strategic plan 2014–25 (updated 2020; Nepal). Kathmandu: Epidemiology and Disease Control Division, Department of Health Services, Ministry of Health and Population, Government of Nepal, 2020.
- 148 Directorate of Malaria Control. National malaria case management guidelines (Pakistan). Islamabad: Directorate of Malaria Control, Ministry of National Health Services, 2018.
- 149 Ejov M. National strategic plan for malaria elimination in Pakistan 2021–35. Islamabad: Directorate of Malaria Control, Ministry of National Health Services, Regulations & Coordination, 2020.
- 150 Papua New Guinea National Department of Health. National malaria strategic plan 2014–18. Port Moresby, Papua New Guinea: Papua New Guinea National Department of Health, 2014.
- 151 National Program for the Control and Elimination of Malaria. National strategic plan for the control and elimination of malaria in the Philippines (2020–22). Manila: National Program for the Control and Elimination of Malaria, Department of Health, 2020.
- 152 Department of Health. Philippine clinical practice guidelines for the diagnosis, treatment, prevention, and control of malaria in adults and special risk groups. Manila: Department of Health, 2018.
- 153 Korea Disease Control and Prevention Agency. Korea Disease control and prevention agency malaria treatment guideline. Seoul: Korea Disease Control and Prevention Agency, South Korea Ministry of Health, 2022.
- 154 Ministry of Health & Medical Services. Solomon Islands 2018 malaria case management guideline. Honiara: Ministry of Health & Medical Services, 2018.
- 155 Department of Disease Control. Medical practice guidelines for the treatment of malaria patients in Thailand. Bangkok: Department of Disease Control, Ministry of Public Health, 2019.
- 156 Ministry of Health. Timor-Leste malaria treatment guideline. Dili: Ministry of Health, 2017.
- 157 Ministry of Health. National strategic plan for malaria elimination 2017–21 (Timor-Leste). Dili: Ministry of Health, 2017.
- 158 Malaria and Vector Borne Diseases Control Program. National malaria strategic plan 2021–25 (Vanuatu). Port Vila: Malaria and Vector Borne Diseases Control Program, Ministry of Health, 2021.
- 159 Malaria and Vector Borne Diseases Control Program. Vanuatu malaria diagnosis and treatment guidelines 2021 (version 2). Port Vila: National Malaria and Vector Borne Diseases Control Program, Ministry of Health, 2021.
- 160 Ministry of Health. Guidelines for malaria diagnosis, treatment, and prevention (Vietnam). Hanoi: Ministry of Health, 2016.
- 161 Ministry of Health. National strategic plan on malaria control and elimination 2021–25 (Vietnam). Hanoi: Ministry of Health, 2020.
- 162 Madanitsa M, Barsosio HC, Minja DTR, et al. Effect of monthly intermittent preventive treatment with dihydroartemisinin-piperaquine with and without azithromycin versus monthly sulfadoxine-pyrimethamine on adverse pregnancy outcomes in Africa: a double-blind randomised, partly placebo-controlled trial. *Lancet* 2023; **401**: 1020–36.
- 163 Unger HW, Wangnapi RA, Ome-Kaius M, et al. Azithromycin-containing intermittent preventive treatment in pregnancy affects gestational weight gain, an important predictor of birthweight in Papua New Guinea—an exploratory analysis. *Matern Child Nutr* 2016; **12**: 699–712.
- 164 Roh ME, Kuile FOT, Rerolle F, et al. Overall, anti-malarial, and non-malarial effect of intermittent preventive treatment during pregnancy with sulfadoxine-pyrimethamine on birthweight: a mediation analysis. *Lancet Glob Health* 2020; **8**: e942–53.

Copyright © 2023 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license.