Malaria: an update on current chemotherapy

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Introduction: Chemotherapy of malaria has become a rapidly changing field. Less than two decades ago, treatment regimens were increasingly bound to fail due to emerging drug resistance against 4-aminoquinolines and sulfa compounds. By now, artemisinin-based combination therapies (ACTs) constitute the standard of care for uncomplicated falciparum malaria and are increasingly also taken into consideration for the treatment of non-falciparum malaria.

Areas covered: This narrative review provides an overview of the state-of-art antimalarial drug therapy, highlights the global portfolio of current Phase III/IV clinical trials and summarizes current developments.

Expert opinion: Malaria chemotherapy remains a dynamic field, with novel drugs and drug combinations continuing to emerge in order to outpace the development of large-scale drug resistance against the currently most important drug class, the artemisinin derivatives. More randomized controlled studies are urgently needed especially for the treatment of malaria in first trimester pregnant women. ACTs should be used for the treatment of imported malaria more consequently. Gaining sufficient efficacy and safety information on ACT use for non-falciparum species including *Plasmodium ovale* and *malariae* should be a research priority. Continuous investment into malaria drug development is a vital factor to combat artemisinin resistance and successfully improve malaria control toward the ultimate goal of elimination.

Keywords: artemisinin combination treatment, malaria, *Plasmodium falciparum*, *Plasmodium knowlesi*, *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium vivax*, pregnancy
Article highlights.

- Artemisinin-based combination therapies (ACTs) constitute the standard of care for uncomplicated falciparum malaria and are increasingly also taken into consideration for the treatment of non-falciparum malaria (Plasmodium vivax, P. ovale, P. malariae and P. knowlesi).
- For severe malaria, intravenous (i.v.) artesunate is superior to quinine; however, i.v. administered quinine remains an option for the treatment of severe malaria particularly if artesunate is unavailable. In the future, should emergence of resistance arise on a large scale before other alternatives become available then i.v. administered quinine will also be an option.
- Artemisinin combination therapy is highly effective for both chloroquine-resistant and chloroquine-sensitive strains of P. vivax malaria. There is also evidence on a smaller scale that it is effective and safe for other non-falciparum species.
- Pregnant women are systematically excluded from clinical trials, resulting in lack of evidence on the safety and efficacy of certain antimalarial drugs. Based on the available clinical data, which show no serious adverse effects of ACTs, the authors advocate conducting controlled clinical trials, including pharmacokinetic studies, for the treatment of malaria with ACT in all trimesters of pregnancy.
- For malaria in returning travelers, ACTs should be most consequently used for the treatment of uncomplicated imported falciparum malaria in view of its favorable adverse effect profile as well as the rapid schizontocidal action.

This box summarizes key points contained in the article.

trials. Preclinical developments and the utilization of antimalarials for malaria chemoprophylaxis in high-risk groups (pregnant women and infants) and for travelers are not in the focus of this review and have been covered recently elsewhere [3–11].

3. Methods

This is a narrative review. Methods of the search strategy and inclusion and exclusion criteria were specified in advance and documented in a protocol. Recommendations made by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group were followed where appropriate [12]. The electronic databases Medline/PubMed, Embase, Cochrane Central Register of Controlled Trials (The Cochrane Library), Biosis Previews and the African Index Medicus were searched in order to identify studies published up to June 2014. In addition, major trial registries were searched to identify ongoing or future trials. The search strategy consisted of free-text words and subject headings related to the treatment of malaria with synthetic drugs. Malaria search terms chosen by consulting a medical subheading (MeSH) thesaurus, and were supplemented with search terms used by Cochrane Database reviews of malaria. For the search, also the function ‘All Fields and Title/Abstract’ was utilized to identify recent, not yet indexed publications. Main search terms were ‘malaria (MeSH)’ and ‘therapeutics (MeSH)’. The search strategy was not limited by language. We did not search the gray literature. The search was restricted to the past 5 years to avoid redundant data and to select more recent evidence. However, related or cited papers of crucial trials and guidelines before this period have also been included. All abstracts were read by the first author, and key articles were indentified based on inclusion criteria and consensus among all authors. Bibliographies of relevant studies retrieved from the studies were checked for additional publications. Selection criteria for inclusion of retrieved studies were as follows; randomized controlled trials (RCTs), meta-analyses, clinical trials, clinical guidelines were included in this review. Case series, case reports and animal studies were excluded. Only trials in Phase III of development and onward were included. The software program EndNote X7.0.2. (Thomson Reuters) was used to manage, de-duplicate and screen the references for eligibility. We did not assess risk of bias in included studies nor did we investigate publication bias.

4. Treatment of uncomplicated Plasmodium falciparum malaria

The causative species, the severity of signs and symptoms as well as patient age, immunity status and other risk determining factors (acute or chronic conditions, pregnancy and/or immune impairment) direct the choice of the most appropriate therapy. In addition, drug therapy should be in conjuction with relevant treatment guidelines and subject to local availability of drugs.

Much evidence from RCTs and meta-analyses is available on the treatment of uncomplicated P. falciparum malaria [13–19]. To overcome the threat of drug resistance of P. falciparum, and to augment treatment efficacy, most malaria-endemic countries have endorsed the World Health Organization (WHO) recommendation and adopted ACTs as first-line therapy for uncomplicated falciparum malaria [20], following establishment of a correct diagnosis of malaria by rapid diagnostic tests. The history of artesunates from ‘household remedy’ against malarial fevers on the Chinese peninsula of Hainan to the modern-day backbone class of antimalarials has been summarized [21]. The artesunate derivate components in combination treatments are active against all stages of the asexual malaria parasites and lead to significantly shorter parasite clearance time than other antimalarials [22]. Moreover, they exhibit some effect on gametocytes, thus reducing the risk of life cycle perpetuation in post-therapeutic patients, which is important when it comes to optimizing malaria control/pre-elimination efforts in malaria-endemic areas [23]. The rationale of administering an ACT, usually over 3 days in total, is twofold; first, administering two or more blood schizontocidal drugs with different modes of action and targets is most often more effective
compared to a single drug. In the event that resistance-conferring polymorphisms preexist, or arise from de novo mutations during treatment to one of the drugs, the mutant and resistant parasite will be probably killed by the still-effective other drug. Secondly, artemisinin derivates should be given in combination since they exhibit an extremely short half-life. Recrudescence may result if given as monotherapy for too short. Artemisinins do have a favorable adverse effects profile [24].

Several artemisinin derivates are available – with no regimen having been unequivocally demonstrated to be superior over the others – including artesunate (water-soluble: for oral, rectal, intramuscular or parenteral use) and artemether (lipid-soluble: for oral, rectal or intramuscular use). These agents are converted to the active agent dihydroartemisinin (DHA), which itself can also be administered directly as in the DHA-piperaquine combination. These drugs differ in their pharmacokinetic and dynamic properties such as stability, bioavailability, metabolism, absorption and excretion. Serious side effects of ACTs have not been reported in humans, although neurotoxicity has been reported in animal studies [25]. ACTs are generally not recommended in the first trimester of pregnancy, on the ground of lack of safety data (see under ‘treatment of malaria in pregnancy’ for details).

ACT options now recommended for treatment of uncomplicated P. falciparum malaria in any order are: artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, artesunate + sulfadoxine-pyrimethamine and DHA + piperaquine (PIP). A wealth of clinical trials have been performed to evaluate the efficacy and safety of artemether-lumefantrine (AL) (26). This combination is well tolerated and regularly yielded cure rates of > 95% for P. falciparum malaria in several trials [27-47]. Several ongoing trials (Table 1) are currently assessing the efficacy of AL compared to the relatively new regimen of DHA + PIP (Phase III: NCT01939886; Phase IV NCT01704508, NCT01755559). Several studies have shown that artesunate in combination with mefloquine is 90 - 100% effective [48-53)]. As well, artesunate in combination with atovaquone-proguanil is highly effective and well-tolerated, as shown among 1596 patients in Thailand with uncomplicated multidrug-resistant falciparum malaria [54]. The recently developed and now marketed fixed-dose ACT is DHA + PIP, with cure rates > 95% [41,55-58]. DHA + PIP is currently under investigation in seven ongoing trials (Phase III: NCT018 45701, NCT01838902; NCT01736319 and NCT01640587; Phase IV: NCT01878357, NCT01755559 and NCT1704 508). Studies evaluating the combination artesunate + sulfadoxine-pyrimethamine for the treatment of uncomplicated malaria show variable efficacies [59-61]. Artesunate-pyronaridine versus other ACTs in adults and children with uncomplicated P. falciparum malaria performed well in six trials [62-68], with a polymerase chain reaction (PCR)-adjusted treatment failure rate at day 28 below the 5% standard set by the WHO [69]. However, further efficacy and safety studies are needed whether this combination is an option as first-line treatment [69].

Recently, the combination artesunate-amodiaquine showed a significantly higher unadjusted adequate clinical and parasitological response compared to AL (58.4 vs 46.1%) at day 28 [70].

The efficacy of the combination of fosmidomycin and clindamycin has been investigated in several trials [71-74] and has been considered as a promising antimalarial combination as alternative to artemisinins. However, results are conflicting and a recent trial conducted by Lanasp et al. [75] showed inadquate efficacy of a new formulation of fosmidomycin-clindamycin combination treatment. Therefore, development of this combination has stalled. However, one Phase II study is still recruiting patients for this combination treatment (NCT01361269). Fosmidomycin-piperaquine appears to be a potential combination of interest and is currently entering clinical testing (G Mombo-Ngoma, personal communication).

A new, not yet marketed, fixed-dose combination of artemisinin-naphthoquine (‘Arco’) has been evaluated in Phase III trials [76-86]. Naphthoquine is a 4-aminoquinoline, synthetic blood schizonticide antimalarial drug with a long half-life (276 h [76]) and is administered orally as a single-dose treatment. A study evaluating the safety and efficacy of artemisinin-naphthoquine versus DHA-piperaquine in adult patients with uncomplicated malaria found a PCR-corrected cure rate of 96.3% (95% CI: 93.6 - 99.0%) in Arco compared to 97.3% (95% CI: 95.0 - 99.6%) in DHP groups [76]. The drug was well tolerated with no adverse reactions. Although a highly effective single-dose treatment for malaria seems to be a breakthrough, concerns have been raised. There is a considerable chance that widespread single-dose use of naphthoquine in this particular combination could generate enough pressure on the malaria parasites resulting in the emergence of increasingly less susceptible mutants and eventually to different levels of parasite resistance [76,77,87].

Other compounds currently under investigation in Phase I and II studies are discussed in appendix 1.

5. Treatment of severe malaria

With the increasing availability of injectable artemesinates in Good Manufacturing Practice (GMP) quality - while availability seems to remain an issue in and outside endemic areas [88,89] - there is widespread acceptance of the SEAQUAMAT [90] and AQUAMAT [91] multicenter trial results that subsequently led to a WHO policy change from intravenously (i.v.) administered quinine to i.v. artesunate (followed by an oral single drug or drug combination [20] as first-line treatment of complicated malaria). Notwithstanding open detail questions, SEAQUAMAT [90] in adult patients from India and across Southeast Asia and AQUAMAT [91] in children across sub-Saharan Africa established the superiority of artemesunate not alone with regard to statistically significant mortality reductions (34.7 - 95% CI 18.5 - 47.6%; p = 0.0002 in SEAQUAMAT; 22.5 - 95% CI 8.1 - 36.9%; p = 0.0022 in AQUAMAT) but also in terms of easier handling (e.g., no rate-controlled infusion, no continuous cardiac monitoring,
### Table 1. Ongoing trials on malaria treatment for uncomplicated *P. falciparum* malaria (date of last search: June 2014).

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Registration ID (year) country, status as of March 2014</th>
<th>Antimalarial(s) tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study to determine the efficacy of artesunate-mefloquine combination therapy for the treatment of uncomplicated <em>P. falciparum</em> Malaria in Thailand</td>
<td>NCT02052323 (2014) Thailand</td>
<td>AS + MQ</td>
</tr>
<tr>
<td>An open-label randomized controlled trial to evaluate the effectiveness and safety of a 3- versus 5-day course of AL for the treatment of uncomplicated falciparum Malaria in Myanmar</td>
<td>NCT02020330 (2013) Myanmar</td>
<td>AL (3 days) versus AL (5 days)</td>
</tr>
<tr>
<td>Treatment efficacy and malaria TRANSMission after Artemisinin Combination Therapy 2 (TRANSACT2)</td>
<td>NCT01939886 (2013) Tanzania</td>
<td>AL versus AS + MQ</td>
</tr>
<tr>
<td>Surveillance and treatment with DHA-piperaquine plus primaquine</td>
<td>NCT01878357 (2013) Indonesia</td>
<td>DHA + PP mass drug administration (MDA) – several time intervals</td>
</tr>
<tr>
<td>Artemisinin-based antimalarial combinations and clinical response in Cameroon</td>
<td>NCT01845701 (2013) Cameroon</td>
<td>AL versus AS + AQ versus DHA + PP</td>
</tr>
<tr>
<td>Primaquine’s gametocytocidal efficacy in malaria asymptomatic carriers (PRINOGAM)</td>
<td>NCT01839902 (2013) The Gambia</td>
<td>DHA + PP + PQ in different dosages</td>
</tr>
<tr>
<td>The optimal timing of primaquine to prevent malaria transmission after artemisinin-combination therapy</td>
<td>NCT01906788 (2013) Tanzania</td>
<td>AL + PQ (in different dosages)</td>
</tr>
<tr>
<td>Safety, tolerability, pharmacokinetics and efficacy of ARCO</td>
<td>NCT01836458 (2013) Tanzania</td>
<td>ARCO versus DHA + PP</td>
</tr>
<tr>
<td>A study to find the minimum inhibitory concentration of KAE609 in adult male patients with <em>P. falciparum</em> mono-infection (Phase II)</td>
<td>NCT01860989 (2013) Thailand</td>
<td>KAE609</td>
</tr>
<tr>
<td>A study to assess efficacy, safety of KAE609 in adult patients with acute malaria mono-infection (Phase II)</td>
<td>NCT01743820 (2012) Mali, Thailand</td>
<td>KAE609</td>
</tr>
<tr>
<td>Phase Ila primaquine dose-escalation study</td>
<td>NCT01736319 (2012) Cambodia</td>
<td>KAE609</td>
</tr>
<tr>
<td>Artemisinin-resistant malaria in Cambodia</td>
<td>NCT01728961 (2012) Malawi, Uganda</td>
<td>AL</td>
</tr>
<tr>
<td>Pharmacology of antimalarial therapy with or without antiretroviral therapy</td>
<td>NCT01755559 (2012) Niger</td>
<td>AL versus DHA + PP versus AS + AQ</td>
</tr>
<tr>
<td>Efficacy of three ACTs for the treatment of <em>P. falciparum</em> malaria in Maradi Niger</td>
<td>NCT01640587 (2012) Thailand</td>
<td>DHA + PP versus AS + MQ</td>
</tr>
<tr>
<td>Improving antimalarial treatment options in Guinea-Bissau - Part A</td>
<td>NCT01619878 (2012) Benin, Burkina Faso, Togo, Nigeria, Congo</td>
<td>AL dispersible tablet</td>
</tr>
<tr>
<td>Efficacy, safety and pharmacokinetics of AL dispersible tablet in the treatment of malaria in infants &lt; 5 kg</td>
<td>NCT01736212 (2012)</td>
<td>OZ439</td>
</tr>
<tr>
<td>OZ439 Phase Ila study in <em>P. falciparum</em>: extended observation (Phase II)</td>
<td>NCT01713621 (2012) Thailand</td>
<td>AQ-13 versus AL</td>
</tr>
<tr>
<td>Studies of a candidate aminoquinoline antimalarial (AQ-13)</td>
<td>NCT01350856 (2011) Multiple countries</td>
<td>AS (two different regimens)</td>
</tr>
<tr>
<td>Tracking resistance to artemisinin (TRAC)</td>
<td>NCT01361269 (2011) (status unknown, probably stopped) Gabon, Mozambique</td>
<td>Fosmidomycin and clindamycin</td>
</tr>
</tbody>
</table>

Table 1. Ongoing trials on malaria treatment for uncomplicated *P. falciparum* malaria (date of last search: June 2014) (continued).

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Registration ID (year)</th>
<th>Antimalarial(s) tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of the Riamet&lt;sup&gt;®&lt;/sup&gt; versus Malarone&lt;sup&gt;®&lt;/sup&gt; in the treatment of uncomplicated malaria (MalaRia)</td>
<td>NCT01150344 (2010)</td>
<td>AP versus AL</td>
</tr>
<tr>
<td>Effectiveness of the association of artesunate and mefloquine in the treatment of malaria by <em>P. falciparum</em></td>
<td>NCT01144702 (2010)</td>
<td>AS + MQ</td>
</tr>
<tr>
<td>Efficacy, safety and tolerability of DHA-piperaquine for uncomplicated malaria in pregnancy in Ghana (DHAPPQ/MIP)</td>
<td>NCT01231113 (2010)</td>
<td>DHA + PP</td>
</tr>
<tr>
<td>Artesunate plus amodiaquine in malaria in Cote d’Ivoire</td>
<td>NCT01023399 (2009)</td>
<td>AS + AQ</td>
</tr>
</tbody>
</table>


Table 2 depicts all currently ongoing trials on chemotherapy of severe falciparum malaria.

While this review focuses on malaria chemotherapy, it ought to be mentioned that in both complicated and uncomplicated disease, there is no room for adjuvant therapies other than unspecific supportive methods such as appropriate rehydration, or administration of (also controversially discussed) antipyretic drugs [104]. An RCT of levamisole hydrochloride (an anthelminthic drug that inhibits cytoadherence in vitro and reduces sequestration) as adjunctive therapy in severe falciparum malaria with high parasitemia showed no benefit in a recent trial [105]. A critical discussion on the value of exchange transfusion [106-108] (or erythrocytapheresis, which is not identical, and the preferred method in some more affluent settings [109]) is on full swing; while there is no evidence for outcome improvement across studies but a recognition of potential benefits in individuals who are critically ill [110], including improvement of the rheological profile, the rapidity of parasite clearance as encountered with i.v. artesunates shifts the debate toward it being increasingly judged upon as contraindicated. For example, the recently revised German guidelines for the treatment of malaria [111] go as far as considering exchange transfusion as contraindicated, whereas others such as the Dutch guidelines, for example, do not go that far.

6. Treatment of non-falciparum malaria

Non-falciparum malaria refers to disease due to infection with *Plasmodium* spp. other than *P. falciparum*; namely *P. vivax*, *P. ovale* subspecies curtisi and wallokeri, *P. malariae* and *P. knowlesi*. Although the cause of nearly all of the deaths due to malaria is due to *P. falciparum*, non-falciparum
quine is a good second-line alternative to chloroquine [115].

reduce the nonspecific symptoms of malaria. Hydroxychloro-

schizonticide with anti-inflammatory action and so helps to

and Severe Malaria in Adults and Children.

Study of SAR97276A in the Treatment of Uncomplicated

and Severe Malaria in Adults and Children.

The combination artesunate-amodiaquine, combined with

Primaquine is contraindicated in pregnant women and

children, as discussed before. Because primaquine is never a
critical or urgent treatment, patients should be screened (for
glucose 6-phosphatase dehydrogenase [G6PD] deficiency)
if this is available in a low-resources setting — if this is available in a low-resources setting — so that the regimen and dosage can be adjusted for those with G6PD deficiency [121]. A recent trial dose-ranging RCT evaluated a single-dose primaquine for clearance of P. falcipa-

rum gametocytes in children with uncomplicated malaria [122]. It was shown that a lower dose (0.4 mg/kg primaquine) had similar gametocyticidal efficacy compared to the reference (0.75 mg/kg). However, these findings are not directly

treatment of non-falciparum malaria consists of treating

the erythrocytic asexual forms that induce symptoms and,

P. vivax, is extremely rare. Of the non-falciparum species,

P. vivax has the largest geographic distribution and burden

disease in terms of health, longevity and socioeconomic
development, and accounts for 40% of malaria cases world-

clearance of uncomplicated malaria [116,117]. In most

esia of disease in terms of health, longevity and socioeconomic
development, and accounts for 40% of malaria cases world-

The variability among P. vivax strains emphasizes that health-
care practitioners are required to consider geographical factors

when initiating drug therapy for P. vivax infection. A recur-

rence of asexual parasitemia < 30 days after starting drug
treatment suggests CRPV; recurrence after 30 days suggests

primaquine-resistant P. vivax. Currently, three alternative
drugs are recommend by the U.S. Centers for Disease Control
and Prevention (CDC) for CRPV; quinine sulfate plus either
doxycycline or tetracycline; atovaquone-proguanil; and meflo-

quine. All three drugs are recommended equivalently and are

succeeded by primaquine, the only licensed hypnozoicidal

drug that is able to reliably prevent relapses and achieve

radical cure. Interestingly, for the therapeutic efficacy of

primaquine (an 8-aminoquinoline) to eradicate hypnozoites

it is shown that a 4-aminoquinoline (e.g., chloroquine or

quine) is needed. Data from > 50 years ago showed that pri-

maquine may exert its beneficial effect when combined with a

4-aminoquinoline drug such as chloroquine [119]. Administra-
tion of a regimen of primaquine concurrently with quinine or

chloroquine showed significantly higher cure rates for P. vivax
malaria compared to primaquine alone [119]. The potential for

synergistic effects has never been evaluated for primaquine

with mefloquine, doxycycline or atovaquone/proguanil [120].

6.1 Treatment (P. ovale, P. vivax and P. malariae)
The treatment of non-falciparum malaria consists of treating

the erythrocytic asexual forms that induce symptoms and,

for infections with P. vivax and P. ovale, assuring eradication of

liver hypnozoites to prevent relapse of infection. Chloro-

quine is highly effective against P. malariae, P. ovale and the

majority of P. vivax infections. Chloroquine, a synthetic

compound of the 4-aminoquinoline group, is a powerful

schizonticide with anti-inflammatory action and so helps to

reduce the nonspecific symptoms of malaria. Hydroxchloro-

quine is a good second-line alternative to chloroquine [115].
The combination artesunate-amodiaquine, combined with

primaquine, is also very effective for blood-stage parasite
clearance of uncomplicated P. vivax malaria [116,117]. In most
malaria guidelines, chloroquine is still the drug of choice for

the treatment of blood forms of all non-falciparum species.
Nevertheless, since the discovery of chloroquine-resistant
P. vivax (CRPV) in the early 1990s, reports of CRPV are
increasing and of a particular problem in the regions of Papua
New Guinea, the Solomon Islands and Indonesia. Sporadi-
cally, CRPV has also been reported from Burma (Myanmar),
India, Vietnam, Turkey, and Central and South America [118].

malarias (P. vivax and P. knowlesi) also carry the risk of severe

and life-threatening illness. Plasmodium knowlesi, a parasite of

macaque monkeys in Southeast Asia, has been identified as

the cause of uncomplicated as well as severe and fatal malaria

in Southeast Asia [112,113]. Severe malaria in

P. malariae, P. ovale and the

Plasmodium species

P. malariae and P. ovale are normally less prevalent, but they
are distributed widely across malaria-endemic areas.

Table 2. Ongoing trials on severe malaria treatment registered online in clinical trial registries (last search June 2014).

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Registration ID (year)</th>
<th>Antimalarial(s) tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous Artesunate and Malaria (IVAS)</td>
<td>NCT01805232 (2013) Sudan</td>
<td>AS versus Q</td>
</tr>
<tr>
<td>Malaria Treatment With Injectable ArteSunate (MATIAS)</td>
<td>NCT01828333 (2013) Democratic Republic of Congo</td>
<td>AS</td>
</tr>
<tr>
<td>Superiority of ArTiMist Versus Quinine in Children With Severe Malaria</td>
<td>NCT01258049 (2012) Burkina Faso, Ghana, Rwanda</td>
<td>Artemether sublingual spray versus Q</td>
</tr>
<tr>
<td>Azithromycin Combination Therapy for the Treatment of Severe Malaria</td>
<td>NCT01374126 (2011) Bangladesh</td>
<td>AS versus AS + Azithromycin</td>
</tr>
<tr>
<td>Pharmacokinetics and Pharmacodynamics of Intravenous Artesunate for Severe Malaria Treatment</td>
<td>NCT01122134 (2010) status unknown Uganda</td>
<td>AS</td>
</tr>
<tr>
<td>Study of SAR97276A in the Treatment of Uncomplicated and Severe Malaria in Adults and Children</td>
<td>NCT00739206 (2008) suspended Benin, Burkina Faso, Gabon</td>
<td>SAR97276A</td>
</tr>
</tbody>
</table>

Table 2. Ongoing trials on severe malaria treatment registered online in clinical trial registries (last search June 2014).

<table>
<thead>
<tr>
<th>Source (first author, year of publication, journal) (PubMed ID)</th>
<th>Country (study site), time frame</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Antimalarial(s) tested</th>
<th>Measure of (primary) outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al. (2013) [131]</td>
<td>China</td>
<td>Open-label RCT</td>
<td>n = 251 (P. vivax)</td>
<td>AN versus CQ + PQ</td>
<td>Day 42 cure rate</td>
<td>By day 42, the number of patients free of recurrence was 125 (98.4%; 95% CI, 94.4 – 99.8%) for AN arm and 123 (96.1%; 95% CI, 91.1 – 98.7%) for CQ-PQ, and nonsignificant (p = 0.4496). Compared with CQ-PQ, the side effect of AN was mild.</td>
</tr>
<tr>
<td>Pasaribu et al. (2013) [116]</td>
<td>Thailand</td>
<td>Open-label RCT</td>
<td>n = 331 (P. vivax)</td>
<td>DHA + PP + PQ versus AS + AQ + PQ</td>
<td>Day 42 efficacy</td>
<td>By day 42, AS + PQ: 0/167 recurrent infection versus 1/164 (0.6%; 95% CI, 0.01 – 3.4%) for DHA + PP. Minor adverse events were more frequent with AQ + PP.</td>
</tr>
<tr>
<td>Senn et al. (2013) [128]</td>
<td>Papua New Guinea</td>
<td>Longitudinal prospective effectiveness study</td>
<td>n = 594 (P. vivax)</td>
<td>AL</td>
<td>Day 7, 8 and 28 clinical treatment failure rates</td>
<td>Clinical treatment failure rates by 7, 28 and 42 days were 0.2, 2.2 and 12.0%</td>
</tr>
<tr>
<td>Sutanto et al. (2013) [132]</td>
<td>Indonesia</td>
<td>Randomized, open-label, relapse-controlled trial</td>
<td>n = 116 (P. vivax)</td>
<td>PQ + Q versus PQ + DHA + PP Relapse control: only AS</td>
<td>Therapeutic efficacy (follow-up 12 months)</td>
<td>Relapse in 32 of 41 (78%) only AS (2.71 attacks/person-year), 7 of 36 (19%) PQ + Q (0.23 a/p-y), and 2 of 36 (6%) DHA + PP + PQ (0.06 a/p-y). The efficacy of PQ against relapse was 92% (95% CI 81 – 96%) for Q + PrQ and 98% (95% CI = 91 – 99%) for DHA + PP + PQ.</td>
</tr>
<tr>
<td>Hwang et al. (2013) [133]</td>
<td>Ethiopia</td>
<td>Randomized, open-label controlled trial</td>
<td>n = 242 (P. vivax)</td>
<td>AL versus CQ</td>
<td>Day 28 efficacy</td>
<td>Day 28 cure rates were 75.7% (95% CI 66.8 – 82.5) for AL and 90.8% (95% CI 83.6 – 94.9) for CQ. Day 28 cure rates were genotype adjusted to 91.1% (95% CI 84.1 – 95.1) for AL and to 97.2% (91.6 – 99.1) for CQ.</td>
</tr>
<tr>
<td>Barber et al. (2013) [211]</td>
<td>Malaysia</td>
<td>Prospective study</td>
<td>n = 19 (P. vivax)</td>
<td>CQ + PQ or ACT (AS)</td>
<td>NR</td>
<td>Median parasite clearance time (PCT) for P. vivax was 2 days. 19 (44%) P. vivax patients smear negative by day 1. Day 28, the cure rate was 100 and 88.4% for the per protocol analysis and for the intention to treat analysis, respectively.</td>
</tr>
<tr>
<td>Abdallah et al. (2012) [129]</td>
<td>Sudan</td>
<td>Prospective cohort study</td>
<td>n = 38 (P. vivax)</td>
<td>AL</td>
<td>Day 28 cure rate</td>
<td>Day 28, the cure rate was 100 and 88.4% for the per protocol analysis and for the intention to treat analysis, respectively.</td>
</tr>
<tr>
<td>Mombo-ngoma et al. (2012) [130]</td>
<td>Gabon</td>
<td>Prospective cohort study</td>
<td>n = 38 (total)</td>
<td>AL</td>
<td>Day 28 adequate clinical and</td>
<td>Day 28 overall cure rate was 100% (95% CI: 91 – 100%) for all species</td>
</tr>
</tbody>
</table>

*Data for Plasmodium knowlesi are not shown in this table.
A: Artemether; ACTs: Artemisinin-based combination therapies; AL: Artemether-lumefantrine; AN: Artemisinin-naphthoquine; AS: Artesunate; CQ: Chloroquine; CR: Cure rate; DHA: Dihydroartemisinin; FCT: Fever clearance time; HR: Hazard ratio; MQ: Mefloquine; P: Pyronaridine; PCT: Parasite clearance time; PP: Piperaquine; PQ: Primaquine; Q: Quinine; RCT: Randomized controlled trial; RR: Relative risk; SP: Sulfadoxine-pyrimethamine.
Table 3. Clinical studies 2008 - 2013 on treatment of non-falciparum malaria* (P. vivax, P. ovale and P. malariae) (continued).

<table>
<thead>
<tr>
<th>Source (first author, year of publication, journal) (PubMed ID)</th>
<th>Country (study site), time frame</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Antimalarial(s) tested</th>
<th>Measure of (primary) outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phyto et al. (2011) [126]</td>
<td>Thailand</td>
<td>RCT</td>
<td>n = 500 (P. vivax)</td>
<td>DHA + PP versus CQ</td>
<td>Parasitological response</td>
<td>Day 63 risk of recurrence</td>
</tr>
<tr>
<td>Poravuth et al. (2011) [65]</td>
<td>Cambodia, Thailand, India and Indonesia</td>
<td>Randomized, non-inferiority trial (double dummy design)</td>
<td>n = 456 (P. vivax)</td>
<td>AS + P versus CQ</td>
<td>Day 14 cure rate in per protocol population</td>
<td>Day 14 CR: 99.5%, (217/218; 95%CI 97.5 - 100) AS + P versus 100% (209/209; 95%CI 98.3, 100) CQ. P = non-inferior to CQ; treatment difference -0.5% (95%CI -2.6, 1.4) AS + P CR&gt; non-inferior to CQ for D21, 28, 35 and 42. PCT: shorter for AS + P (median 23.0 h) versus CQ (32.0 h; p &lt; 0.0001). FCT (median 15.9 h and 23.8 h, respectively; p = 0.0017)</td>
</tr>
<tr>
<td>Yohannes et al. (2011) [124]</td>
<td>Ethiopia</td>
<td>Prospective non-randomized trial</td>
<td>n = 132 (P. vivax)</td>
<td>AL versus CQ</td>
<td>Day 28 treatment failure</td>
<td>Day 28 cumulative incidence treatment failure of 7.5% (95% CI 2.9 - 18.9%) for CQ and 19% (95% CI 11 - 31.6%) for AL. CQ resistance was confirmed in 3 of 5 CQ treatment failures cases. The effectiveness of AL was &lt; than CQ; however, the findings were not conclusive, because the AL evening doses were not supervised</td>
</tr>
<tr>
<td>Awab et al. (2010) [212]</td>
<td>Afghanistan</td>
<td>Open-label randomized non-inferiority trial</td>
<td>n = 536 (P. vivax)</td>
<td>DHA + PP versus CQ</td>
<td>Day 56 overall cumulative parasitological failure rate</td>
<td>Day 56, † recurrent infections in the CQ arm (8.9%, 95% CI 6.0 - 13.1%) than the DHA + PP arm (2.8%, 95% CI 1.4 - 5.8%), a difference in cumulative recurrence rate of 6.1% (two-sided 90% CI +2.6 - +9.7%). Day 28 cure rate was 100% in both groups</td>
</tr>
</tbody>
</table>

*Data for Plasmodium knowlesi are not shown in this table.
A: Artemether; ACTs: Artemisinin-based combination therapies; AL: Artemether-lumefantrine; AN: Artemisinin-naphthoquine; AS: Artesunate; CQ: Chloroquine; CR: Cure rate; DHA: Dihydroartemisinin; FCT: Fever clearance time; HR: Hazard ratio; MQ: Mefloquine; P: Pyronaridine; PCT: Parasite clearance time; PP: Piperaquine; PQ: Primaquine; Q: Quinine; RCT: Randomized controlled trial; RR: Relative risk; SP: Sulfadoxine-pyrimethamine.

<table>
<thead>
<tr>
<th>Source (first author, year of publication, journal) (PubMed ID)</th>
<th>Country (study site), time frame</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Antimalarial(s) tested</th>
<th>Measure of (primary) outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karunajeewa et al. (2008) [180]</td>
<td>Papua New Guinea</td>
<td>Open-label RCT</td>
<td>n = 195 (P. vivax)</td>
<td>CQ + SP versus AS + SP versus DHA + PP versus AL</td>
<td>Day 42 clinical and parasitological response rate: CQ + SP arm 13% (95% CI 4.9 – 26.3), AS + SP arm 33.3% (95% CI 19.1 – 50.2), DHA + PP arm 69.4% (95% CI 51.9 – 83.7) and AL 30.3% (95% CI 14.6 – 48.7)</td>
<td>Day 42 clinical and parasitological response</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Krudsood et al. (2008) [213]</td>
<td>Thailand</td>
<td>RCT</td>
<td>n = 322 (P. vivax)</td>
<td>AS + PQ (6 groups: 1 – 5 PQ for 5, 7, 9, 11 and 14 days, group 6: twice a day for 7 days)</td>
<td>Day 28 cure rates</td>
<td></td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

*Data for Plasmodium knowlesi are not shown in this table.

A: Artemether; ACTs: Artemisinin-based combination therapies; AL: Artemether-lumefantrine; AN: Artemisinin-naphthoquine; AS: Artesunate; CQ: Chloroquine; CR: Cure rate; DHA: Dihydroartemisinin; FCT: Fever clearance time; HR: Hazard ratio; MQ: Mefloquine; P: Pyronaridine; PCT: Parasite clearance time; PP: Piperaquine; PQ: Primaquine; Q: Quinine; RCT: Randomized controlled trial; RR: Relative risk; SP: Sulfadoxine-pyrimethamine.

ACTs are highly effective for both chloroquine-resistant and chloroquine-sensitive strains of P. vivax malaria. Currently, the WHO recommends, for areas with CRPV, artemisinin-based therapies, particularly with those partner drugs that have long half-lives. AL reaches comparable cure rates to the current artemisinin monotherapy, with excellent cure rates of DHA + PP. An RCT in Indonesia was conducted with DHA + PP with standard malaria treatment compared to the arm without mass screening and selective treatment using DHA-piperaquine (DHP + PQ) is currently being conducted in Indonesia, evaluating an intervention arm with an interval of 6 weeks; 3 months and a control arm without mass screening and selective treatment. A randomized clade trial of mass screening (NCT00082578). A randomized clade trial of mass screening (NCT00082578). A randomized clade trial of mass screening (NCT00082578). A randomized clade trial of mass screening (NCT00082578). A randomized clade trial of mass screening (NCT00082578). A randomized clade trial of mass screening (NCT00082578).
screening and treatment. Another highly effective ACT for the treatment of non-falciparum malaria is AL, which has been investigated in several randomized and prospective clinical trials [123,128-130]. A new combination (artemisinin-naphthoquine ‘ANQ,’ 3-day regimen), which is not yet marketed, was investigated and compared to chloroquine-primaquine (8-day regimen) in an open-label randomized and non-inferiority design trial in China [131]. By day 42, no significant difference was found in the cure rates: 98.4%; 95% CI 94.4 – 99.8% for the artemisinin-naphthoquine versus 96.1%; 95% CI 91.1 – 98.7% for chloroquine-primaquine. Side effects of this combination were found to be more mild compared to CQ-PQ. This trial demonstrated this new combination ANQ to be an effective blood schizonticide for P. vivax infections and is possibly an alternative for people not willing or able to take primaquine [131]. For the radical treatment of P. vivax and P. ovale, according to the WHO, at least a 14-day course of primaquine is required [20]. The best combinations for the treatment of P. vivax are those containing primaquine when given in antihypnozoite doses [116,132].

Less evidence is available on the treatment of the Plasmodium species P. ovale and P. malariae. It is no understatement that these two species are neglected in malaria research and intervention trials. In the past few years, only one non-randomized prospective cohort study performed in Gabon investigated the therapeutic efficacy and safety of AL for these two species [130]. Day 28, overall cure rates were 100% (95% CI; 91 – 100%) for both species. A limitation of this study, however, is the small number of participants (which is a limit in most settings, and a reason why there is less evidence from clinical trials than for other species) and its non-comparative study design. No ongoing trial (Table 4) is currently evaluating the efficacy and safety for the treatment of these two species, which account for a sizable cause of malaria, especially in sub-Saharan Africa.

6.3 Treatment of P. knowlesi malaria

Plasmodium knowlesi is a zoonotic malaria species originating from Sarawak, Malaysian Borneo. It can cause severe malaria with high morbidity and mortality. Effective treatment is available. Plasmodium knowlesi is highly sensitive to artemisinins and thus ACT combination treatments, variably and moderately sensitive to chloroquine and less sensitive to mefloquine. Therefore, it is recommended that treatment of P. knowlesi malaria is similar to uncomplicated P. falciparum malaria. Further studies investigating the effectiveness of ACTs for P. knowlesi malaria need to be undertaken. Recently, an extensive and comprehensive review and in vitro sensitivity of P. knowlesi was undertaken using a WHO schizont maturation assay [133]. A Phase III trial that will be conducted in the near future is examining whether fixed combination of AL is superior to chloroquine in order to define the optimal treatment for both uncomplicated P. knowlesi infection in both adults and children in this region (NCT02001012).

7. Treatment of malaria in pregnancy

Pregnant women are at increased risk of acquiring malaria and are susceptible to more severe disease. The treatment of malaria in pregnant women poses particular challenges, as the theoretical risks of teratogenicity of antimalarial drugs need to be weighed against the risk of undertreatment [134]. In addition, safety and efficacy data from clinical trials are limited. Knowledge about adequate drug levels in pregnant women is scarce. More pharmacodynamic and pharmacokinetic data are needed to be able to adjust dosages according to body weight and not according to age groups, which allow a large deviation in exact therapeutic drug levels. For pregnant women, there is a need to adapt pharmacokinetic models and safety data need to be collected in a systemic way.

Commonly, the newer the antimalarial drug, the more effective it is (to a certain extent due to the lack of time for drug resistance to emerge). However, less information will be at hand on safety and efficacy in pregnancy, in particular the first trimester, in the early years of usage of a drug/drug combination, as data will only accumulate on inadvertent use particularly in early, on time point of treatment initiation unrecognized pregnancy. Therefore, physicians should base their management on the clinical state of the pregnant patient, geographical data, resistance patterns, national guidelines, experience (of colleagues) and published data concerning safety of the drug in pregnancy. The safety of the mother should always prevail over that of the unborn child. Treatment involves antimalarial drugs and supportive measures preferably after parasitological confirmation by expert microscopy or, in the majority of settings in endemic areas, following a rapid diagnostic immunochromatographic antigen detection test. This will reduce the unnecessary exposure to antimalarials of both the mother and the unborn child. Prevention of malaria during pregnancy involves chemoprophylaxis ‘Intermittent Preventive Treatment in pregnancy (IPTp)’ [135,136] and preventing mosquito bites, for example, with insecticide-treated bednets, are discussed elsewhere [137].

7.1 First trimester

Clinical trials that assess the safety and efficacy of new antimalarial drugs typically exclude pregnant women in the first trimester (gestational age < 14 weeks) of pregnancy. Therefore, evidence is scarce and is based on observational rather than interventional studies (Table 5). Current guidelines consider chloroquine, quinine, clindamycin and proguanil as safe in the first trimester [20]. A drug safety database analysis of 2506 cases of mefloquine exposure during pregnancy or in the pre- and periconception period showed that the birth defect prevalence and fetal loss in maternal, prospectively monitored cases were comparable to background rates [138]. A retrospective evaluation reviewing the effects of mefloquine treatment on pregnant women with suspected hyperreactive malarial splenomegaly showed significant smaller spleens and decreased anemia
and malaria antibody titers without negative consequences on the treated women or their newborns [139].

Although data from animal studies [140-142] suggest that artemisinin drugs are teratogenic in the first trimester of pregnancy, human data are reassuring; a recent systematic review assessing the safety and efficacy of AL against uncomplicated P. falciparum malaria during pregnancy [143] shows no evidence of increased risks in 212 first trimester exposures. Animal studies have demonstrated toxic effects to the unborn fetus due to the depletion of primitive red blood cells at therapeutic doses of artemisinin derivates, and there is also information available that reticulocyte counts are decreased in individuals after the intake of artemisinins [144]. Treatment of malaria in humans in the first trimester with artemisinin drugs was fairly safe [145-150]. A retrospective population-based study that included antenatal records of 17,613 women showed no difference in adverse effects and risk of miscarriage between artemisinin derivates (n = 44) and other drugs [146]. Only one study performed in The Gambia in 2001 was a clinical trial that randomized participants to a single dose of the combination artesunate plus sulfadoxine-pyrimethamine or sulfadoxine-pyrimethamine plus placebo during a mass drug administration. There were no differences for pregnant women (first trimester) exposed to artesunate (n = 77) in the proportion of abortions, stillbirths or infant deaths compared to that of other pregnant women [149].

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Registration ID (year) country, status as of March 2014</th>
<th>Antimalarial(s) tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of chloroquine and primaquine for the treatment of plasmodium vivax malaria in Cruzeiro do Sul, Acre, Brazil</td>
<td>NCT02043652 (2014) Brazil</td>
<td>CQ + PQ (no comparison arm)</td>
</tr>
<tr>
<td>AL versus chloroquine in patients with acute uncomplicated P. Knowlesi malaria: a randomized open-label trial in Sabah, Malaysia (CAN KNOW trial)</td>
<td>NCT02001012 (2013) Sabah, Malaysia</td>
<td>AL versus CQ</td>
</tr>
<tr>
<td>Phase Ia study of ChAd63/MVA PvDBP (vaccine trial for P. vivax)</td>
<td>NCT01816113 (2013) United Kingdom</td>
<td>Vaccine: ChAd63 PvDBP, with or without MVA PvDBP</td>
</tr>
<tr>
<td>Radical cure for P. vivax malaria in Indonesia 2</td>
<td>ISRCTN82366390 (2013) Indonesia</td>
<td>AS + PQ, DHA + PP + PQ, AS + PYR</td>
</tr>
<tr>
<td>Surveillance and treatment with DHA-piperazine plus primaquine</td>
<td>NCT01878357 (2013) Indonesia</td>
<td>DHA + PQ (6 weeks vs 3 months vs control)</td>
</tr>
<tr>
<td>Improving the radical cure of P. vivax malaria: A multicenter randomized comparison of short- and long-course primaquine regimens</td>
<td>NCT01814683 (2013) Afghanistan, Pakistan, Vietnam</td>
<td>14 days PQ versus 7 days PQ versus 14 days placebo</td>
</tr>
<tr>
<td>Comparison of two antimalarial drugs regimens in patient with P. vivax malaria in Thailand</td>
<td>NCT01662700 (2012) Thailand</td>
<td>AS versus CQ</td>
</tr>
<tr>
<td>Ethiopia antimalarial in vivo efficacy study</td>
<td>NCT01680406 (2012) Ethiopia</td>
<td>AL, AL + PQ, CQ, or CQ + PQ</td>
</tr>
<tr>
<td>Efficacy, safety, tolerability and pharmacokinetics of KAF156 in adult patients with acute, uncomplicated P. falciparum or vivax malaria mono-infection</td>
<td>NCT01640574 (2012) Thailand</td>
<td>KAF156 (400 vs 800 mg)</td>
</tr>
<tr>
<td>Comparison between 7 and 14 days primaquine combined with DHA-piperazine or 3 days chloroquine radical cure of P. vivax (BPD)</td>
<td>NCT01376167 (2011) Bangladesh, Brazil, India, Peru, Thailand</td>
<td>TFQ versus PQ (different dosages)</td>
</tr>
<tr>
<td>Phase IIb/III Tafenoquine (TFQ) study in prevention of P. vivax relapse</td>
<td>CTRI/2012/03/002511 (2012) India</td>
<td>CQ versus TFQ (different dosages)</td>
</tr>
<tr>
<td>Study to evaluate the efficacy, safety and tolerability of tafenoquine in subject with P. vivax malaria</td>
<td>NCT01708876 (2012) India</td>
<td>AS + MQ versus CQ</td>
</tr>
<tr>
<td>P. knowlesi trial of artesunate-mefloquine versus chloroquine (ACT KNOW)</td>
<td>CTRI/2011/11/002129 (2011) India</td>
<td>CQ versus artesunate maleate</td>
</tr>
<tr>
<td>Phase III trial of FDC of arterolane maleate and PQP tablets in patients with acute uncomplicated P. vivax malaria</td>
<td>CTRI/2010/09/00411 (2010) India</td>
<td>RPM02/08 versus placebo</td>
</tr>
<tr>
<td>A clinical trial to study the activity RPM 02/08 in patients with P. vivax malaria.</td>
<td>CTRI/200682578 (2008) Afghanistan</td>
<td>DHA + PP versus AS + SP, CQ</td>
</tr>
<tr>
<td>A comparative study of Artekin with standard malarial treatment regimes in Afghanistan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Table 4. Ongoing trials on non-falciparum malaria treatment registered online in clinical trial registries (last search: June 2014).

and malaria antibody titers without negative consequences on the treated women or their newborns [139].

Although data from animal studies [140-142] suggest that artemisinin drugs are teratogenic in the first trimester of pregnancy, human data are reassuring; a recent systematic review assessing the safety and efficacy of AL against uncomplicated P. falciparum malaria during pregnancy [143] shows no evidence of increased risks in 212 first trimester exposures. Animal studies have demonstrated toxic effects to the unborn fetus due to the depletion of primitive red blood cells at therapeutic doses of artemisinin derivates, and there is also information available that reticulocyte counts are decreased in individuals after the intake of artemisinins [144]. Treatment of malaria in humans in the first trimester with artemisinin drugs was fairly safe [145-150]. A retrospective population-based study that included antenatal records of 17,613 women showed no difference in adverse effects and risk of miscarriage between artemisinin derivates (n = 44) and other drugs [146]. Only one study performed in The Gambia in 2001 was a clinical trial that randomized participants to a single dose of the combination artesunate plus sulfadoxine-pyrimethamine or sulfadoxine-pyrimethamine plus placebo during a mass drug administration. There were no differences for pregnant women (first trimester) exposed to artesunate (n = 77) in the proportion of abortions, stillbirths or infant deaths compared to that of other pregnant women [149]. A prospective cohort
expertise in interpreting the available evidence. This has resulted in a substantial body of work on the safety and efficacy of antimalarial drugs in pregnancy, particularly in the context of the first trimester.

7.2 Second and third trimester

Much more evidence from observational as well as interventional trials is available on the use of artemisinin combination treatment in the second and third trimester of pregnancy. A recent review of the safety and efficacy of AL against uncomplicated P. falciparum malaria during pregnancy from studies conducted in 1989 – 2011 showed no evidence of increased risks (890 second/third trimester exposures), supporting the WHO recommendation to treat uncomplicated falciparum malaria with ACT known to be effective in the region in second and third trimester pregnancy. Also, treatment with artesunate plus clindamycin to be given for 7 days, or quinine plus clindamycin also for 7 days is possible. For severe P. falciparum malaria, i.v. administration of artesunate to the mother is the preferable treatment. The poor tolerability and longer duration of treatment with quinine augments the risk of poor compliance, and therefore the risk of treatment failure and the development of drug resistance.

Several artemisinin derivatives, alone or in combination with other antimalarials in the second and third trimester of pregnancy in Tanzania [153], Thailand [145,154] and Malawi (Table 5) [155]. No trials have compared the efficacy of artesunate + clindamycin in first trimester pregnant women. The WHO only recommends ACTs in the first trimester if it is the only treatment available, or if treatment with quinine plus clindamycin fails or uncertainty of compliance with a 7-day treatment exists. This, however, is in sharp contrast with daily practice: a population-based survey of other antimalarials, are evaluated as efficacious and safe in second and third trimester pregnancy. AL has been shown to be efficacious in pregnant women with uncomplicated P. falciparum malaria in Thailand [154,157]. Only one study [159] compared the efficacy of AL with quinine, although quinine was previously the first-line WHO recommended treatment for malaria in pregnant women and is still the first-line drug for malaria in the first trimester of pregnancy. An open-label RCT performed in Uganda showed a day 28 cure rate of AL of 100%, where it was compared to chlorproguanil-dapsone (cure rate also 100%). Parasite and fever clearance time were comparable, and the treatment was well tolerated. However, these results are in contrast to findings from Thailand where the day 42 cure rate for AL was only 82% for the intention to treat population. This significant risk of recurrence of infection was most probable because of low plasma concentrations during pregnancy of both artemether and lumefantrine at day 7 [154]. As for other antimalarial drugs, plasma concentrations of artemether and its metabolite DHA, and lumefantrine, are lowered in pregnant women [157,160-162]. This raises the question of whether the standard adult dose should be modified for pregnant women. A pharmacokinetics study in 103 pregnant women with uncomplicated P. falciparum malaria treated with AL suggested that in order to maintain optimal lumefantrine concentrations the duration of AL in pregnant women should be prolonged without danger for the neonate. The maintenance treatment of CRPV (from Papua New Guinea and Indonesia) remains unclear, but repetitive mefloquine or quinine can be considered. A recent systematic review showed no increased risk for the unborn child due to mefloquine use during pregnancy [156]. Whether primaquine can be safely administered during lactation is currently under investigation (NCT 01780753) but is at present advised to be avoided during breastfeeding, along with tetracycline and doxycycline (Table 6).
### Table 5. Clinical studies in 1997 - 2013 on treatment of malaria in pregnancy.

<table>
<thead>
<tr>
<th>Source (first author, year of publication, journal) (PubMed ID)</th>
<th>Country (study site), time frame</th>
<th>Study design</th>
<th>Number of pregnant women with malaria, <em>Plasmodium spp.</em></th>
<th>Trimester</th>
<th>Antimalarial(s) tested</th>
<th>Measure of (primary) outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosha et al. (2014) [151]</td>
<td>Tanzania 2012 – 2013</td>
<td>Prospective observational cohort study</td>
<td>n = 1783, n = use of antimalarial 1 trimester: n = 172 (AL), n = 78 (Quinine), n = 66 (SP), n = 11 (AQ)</td>
<td>1</td>
<td>AL, Q, SP, AQ</td>
<td>Miscarriage, stillbirth, premature death, congenital anomalies</td>
<td>Quinine exposure in first trimester was associated with an increased risk of miscarriage/stillbirth (OR 2.5; 1.3 – 5.1) and premature birth (OR 2.6; 1.3 – 5.3) as opposed to AL with (OR 1.4; 0.8 – 2.5) for miscarriage/stillbirth and (OR 0.9; 0.5 – 1.8) for preterm birth. Congenital anomalies were identified in four exposure groups namely AL only (1/164 [0.6%]), quinine only (1/70 [1.4%]), SP (2/66[3.0%]) and non-antimalarial exposure group (19/1464 [1.3%]).</td>
</tr>
<tr>
<td>McGready et al. (2012)* [146]</td>
<td>Thailand 1986 – 2000</td>
<td>Population-based retrospective study</td>
<td>n = 17,613, n = 44 (exposure to ACTs) Infection with <em>P. falciparum</em> and/or <em>P. vivax</em></td>
<td>1</td>
<td>Q, CQ (for <em>P. vivax</em>) AS, MQ</td>
<td>Outcome of pregnancy of malaria in first trimester + outcome after Rx</td>
<td>16,668 (95%) had no malaria during pregnancy 945 (5%) had one episode in the first trimester. The odds of miscarriage in women with asymptomatic malaria (adj. OR 2.70, 95% CI 2.04 – 3.59) and symptomatic malaria (3.99, 3.10 – 5.13), and were similar for <em>P. falciparum</em> and <em>P. vivax</em>. The risk of miscarriage was similar for women treated with CQ (92 [26%] of 354), Q (95 [27%] of 355) or AS (20 [31%] of 64, p = 0.71)</td>
</tr>
</tbody>
</table>


A: Artemether; ACTs: Artemisinin-based combination therapies; adj.: Adjusted; AE: Adverse events; AL: Artemether-lumefantrine; AO: Adverse outcomes; AP: Atovaquone-proguanil; AQ: Amodiaquine; AS: Artesunate; AZ: Azithromycin; CD: Chloroquine-dapsone; CQ: Chloroquine; CR: Clearance/cure rate; DHA: Dihydroartemisinin; FCT: Fever clearance time; HR: Hazard Ratio; Hz: Hemozoin (malaria pigment); ITT: Intention to treat; LBW: Low birth weight; MQ: Mefloquine; NIT: Non-inferiority trial; OL: Open label; OT: Observational trial; PCT: Parasite clearance time; PCR: Polymerase chain reaction; PE: Parasitological efficacy; PF: Pharmacokinetics; PQ: Piperaquine; RCT: Randomized controlled trial; RR: Recrudescence rate; SP: Sulfadoxine-pyrimethamine.
<table>
<thead>
<tr>
<th>Source (first author, year of publication, journal) (PubMed ID)</th>
<th>Country (study site), time frame</th>
<th>Study design</th>
<th>Number of pregnant women with malaria, <em>Plasmodium</em> spp.</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Manyando et al. (2010) [150]</td>
<td>Zambia 2004 – 2008</td>
<td>Prospective cohort study</td>
<td>n = 1001  n = 106 exposed to artemisinin derivates</td>
<td>1</td>
<td>AL (n = 495), SP (n = 506)</td>
<td>Incidence of perinatal mortality; gestational age at delivery and birth weight</td>
<td>Perinatal mortality (AL 4.2%; SP 5.0%); early neonatal mortality (each group 2.3%); stillbirths (AL 1.9%; SP 2.7%); preterm deliveries (AL 14.1%; SP 17.4% of fetuses); and gestational age-adjusted LBW (AL 9.0%; SP 7.7%). Infant birth defect incidence was 1.8% AL and 1.6% SP, excluding umbilical hernia. Abortion occurred in 4.5% of women treated with AL during their first trimester; none were reported in the 133 women exposed to SP and/or Q during their first trimester.</td>
</tr>
<tr>
<td>Adam et al. (2009) [148]</td>
<td>Sudan 2006 – 2008</td>
<td>Prospective observational study</td>
<td>n = 62 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>1</td>
<td>A (n = 48), AS + SP (n = 11) and AL (n = 3)</td>
<td>Pregnancy outcome, malformations</td>
<td>Two cases of miscarriage in A group (while receiving Q for second malaria attack). No congenital malformations were detected, no preterm labor, no maternal deaths were recorded during the follow-up, and none of the babies died (follow-up 1 year) 28 days parasite reappearance rate. Following Q was 28.7% (60/209) for primary treatments and 44% (11/25) for re-treatments.</td>
</tr>
<tr>
<td>McGready et al. (2002) [214]</td>
<td>Thailand 1995 – 2000</td>
<td>Prospective treatment clinical trial</td>
<td>n = 300 Uncomplicated <em>P. falciparum</em> and <em>P. vivax</em> malaria</td>
<td>1</td>
<td>Q (for <em>P. falciparum</em>) (n = 246) + CQ (for <em>P. vivax</em>) (n = 130)</td>
<td>Day 28 parasite reappearance rate</td>
<td>28 days parasite reappearance rate. Following Q was 28.7% (60/209) for primary treatments and 44% (11/25) for re-treatments.</td>
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<tr>
<th>Source (first author, year of publication, journal) (PubMed ID)</th>
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<th>Trimester</th>
<th>Antimalarial(s) tested</th>
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<tbody>
<tr>
<td>McGready et al. (2001) [145]</td>
<td>Thailand 1992–2000</td>
<td>Prospective treatment clinical trial</td>
<td>n = 461</td>
<td>1, 2 and 3</td>
<td>AS (n = 528) or A (n = 11)</td>
<td>Artemisinin failure rate</td>
<td>For <em>P. vivax</em>, the reappearance rate for all episodes by day 28 was 4.5% (5/111). Also, more tinnitus and maternal anemia for Q. Pregnancies exposed to Q or CQ and carried to term did not have increased rates of congenital abnormality, stillbirth or LBW. The cumulative artemisinin failure rate for primary infections was 6.6% (95% CI 1.0 – 12.3), compared with the re-treatment failure rate of 21.7% (95% CI 15.4 – 28.0; P &lt; 0.004). The artemisinins were well tolerated with no evidence of adverse effects. Birth outcomes did not differ significantly to community rates for abortion, stillbirth, congenital abnormality and mean gestation at delivery. There was no difference in the proportion of abortions, stillbirths or infant deaths among those exposed or not exposed to the drugs. No teratogenic or harmful effect of gestational exposure to AS and SP were detected.</td>
</tr>
<tr>
<td>Deen et al. (2001) [149]</td>
<td>The Gambia 1999</td>
<td>Observational study</td>
<td>n = 287 (+172 nonexposed women)</td>
<td>1, 2 and 3</td>
<td>AS + SP</td>
<td>Pregnancy outcomes, congenital malformations</td>
<td></td>
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<td>Tarning et al. (2012) [215]</td>
<td>Thailand</td>
<td>Pharmacokinetic and -dynamic study</td>
<td>n = 27 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>AQ</td>
<td>Plasma conc. Recurrent infections</td>
<td>Amodiaquine treatment ↓ the risk of recurrent infections from 22.2 to 7.4% at day 35. No dose adjustments are required in pregnancy</td>
</tr>
<tr>
<td>Tarning et al. (2012) [174]</td>
<td>Thailand</td>
<td>Pharmacokinetics study</td>
<td>n = 48 (24 pregnant and 24 matched nonpregnant) Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>DHA and PQ</td>
<td>Pharmacokinetics parameters</td>
<td>The main pharmacokinetic finding was an unaltered total exposure to PQ but reduced exposure to DHA in pregnant compared to nonpregnant women. The shorter terminal elimination half-life of PQ and lower exposure to DHA will shorten the posttreatment prophylactic effect and might affect cure rates</td>
</tr>
<tr>
<td>Rulisa et al. (2012) [163]</td>
<td>Rwanda</td>
<td>Pharmacovigilance study with matched nonexposed control group</td>
<td>n = 1072 (controls; without malaria, no exposition AL n = 978) Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>AL</td>
<td>Pregnancy outcomes, congenital malformations and AE</td>
<td>Outcomes for AL and controls respectively; abortions: 1.3 and 0.4%; perinatal mortality 3.7 and 2.8%; stillbirth 2.9 and 2.4%; neonatal death (less than or equal to) 7 days after birth 0.5 and 0.4%; premature delivery 0.7 and 0.3%; congenital malformations 0.3 and 0.3%. Obstetric complication ↑ in AL group: OR (95% CI): 1.38 (0.95 - 2.01), in primigravidae (OR (95% CI) 2.65 (1.71 - 4.12)</td>
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<td>Muehlenbachs <em>et al.</em> (2012) [216]</td>
<td>Uganda 2006 - 2009</td>
<td>Prospective study (efficacy data published earlier by Piola 2010)</td>
<td>n = 304; AL: n = 97, Q = 98 placental biopsies</td>
<td>2 and 3</td>
<td>AL versus Q</td>
<td>Placental Hz by histology. Clearance curves Hz</td>
<td>AL was associated with decreased rates of moderate-to-high grade Hz deposition (13.3 vs 25.8%), which remained significant after correcting for gravidity, time of infection, reinfection and parasitemia. Histology may be considered as a informative outcome in pregnancy malaria trials.</td>
</tr>
<tr>
<td>Tarning <em>et al.</em> (2012) [164]</td>
<td>Uganda 2008</td>
<td>Pharmacokinetics study</td>
<td>n = 21 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>A and DHA</td>
<td>Plasma concentrations of the drug after last dose</td>
<td>The treatment was well tolerated, and there were no cases of recurrent malaria. A and DHA exposures were lower than that reported in nonpregnant populations.</td>
</tr>
<tr>
<td>Adam <em>et al.</em> (2012) [217]</td>
<td>Sudan 2007 - 2008</td>
<td>Pharmacokinetics study</td>
<td>n = 12 (+12 controls nonpregnant) uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>PQ</td>
<td>Plasma drug concentration</td>
<td>Pregnant women had a significantly higher total drug exposure and longer time to maximal concentration. There was no other significant difference observed in PQ pharmacokinetics between pregnant and nonpregnant women.</td>
</tr>
<tr>
<td>Sangare <em>et al.</em> (2011) [152]</td>
<td>Uganda 2008</td>
<td>Population-based survey on self-reported antimalarial drugs</td>
<td>n = 334</td>
<td>1, 2 and 3</td>
<td>AL, Q and others</td>
<td>Self-reported use of anti-malarial drugs</td>
<td>First trimester (n = 126 episodes): Q: 5.6%; AL: 42.1%; SP: 23% SP + CQ 4.8% (other: 24.5%).</td>
</tr>
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<tr>
<td>Rijken et al. (2011) [173]</td>
<td>Thailand 2008</td>
<td>Pharmacokinetics study</td>
<td>n = 25 (+24 controls nonpregnant) Uncomplicated <em>P. falciparum</em></td>
<td>2 and 3</td>
<td>DHA + PQ</td>
<td>Plasma drug concentration</td>
<td>Second and third trimester (n = 478 episodes): Recommended antimalarials were used according to the guidelines in only 30.1% of all second and third trimester episodes. There are no clinically important differences in the pharmacokinetics of DHA or PQ between pregnant and nonpregnant women. The same women were studied again at 3 months postpartum; there were no clinically relevant differences in the pharmacokinetics of amodiaquine and desethylamodiaquine between pregnant (n = 24) and postpartum (n = 18) women. Pharmacokinetic modeling suggests that pregnant women have accelerated DHA clearance compared to nonpregnant women receiving orally administered AS. This study suggests higher AS doses would be required to maintain similar DHA levels in pregnant women as achieved in nonpregnant controls.</td>
</tr>
<tr>
<td>Rijken et al. (2011) [165]</td>
<td>Thailand 2007 - 2008</td>
<td>Pharmacokinetics study</td>
<td>n = 24 Uncomplicated <em>P. vivax</em> malaria</td>
<td>2 and 3</td>
<td>AQ (n = 24)</td>
<td>Plasma concentrations</td>
<td></td>
</tr>
<tr>
<td>Morris et al. (2011) [218]</td>
<td>Democratic Republic of Congo Date: NR</td>
<td>Population pharmacokinetics study</td>
<td>n = 26 n = 25 controls (nonpregnant) Uncomplicated <em>P. falciparum</em></td>
<td>2 and 3</td>
<td>AS and DHA</td>
<td>Pharmacokinetic and variability parameters</td>
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<tr>
<td>Piola et al. (2010) [159]</td>
<td>Uganda 2006 - 2009</td>
<td>OL, NIT, RCT</td>
<td>n = 304 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>AL (n = 152) compared to Q (n = 152)</td>
<td>Cure rate at day 42 (PCR-confirmed)</td>
<td>Day 42 cure rate: AL 99.3% (n = 137/138), Q 97.6% (n = 122/125). Difference 1.7% (lower limit of 95% CI = 0.9%). There were 290 AE in the Q group and 141 in the AL group. 16 patients lost to follow up, 25 excluded from the analysis.</td>
</tr>
<tr>
<td>Nyunt et al. (2010) [219]</td>
<td>Zambia, Sudan, Mali, Mozambique Date: NR</td>
<td>Pharmacokinetics study</td>
<td>n = 98 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>SP (n = 98)</td>
<td>Plasma concentrations</td>
<td>SP pharmacokinetic parameters differed significantly among the study sites and due to this inconsistency no recommendations could be made for any dose adjustments.</td>
</tr>
<tr>
<td>Karunajeewa et al. (2010) [220]</td>
<td>Papua New Guinea 2006</td>
<td>Pharmacokinetics study</td>
<td>n = 30 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>CQ (n = 30)</td>
<td>Plasma concentrations</td>
<td>Pregnant subjects had significantly lower area under the plasma concentration-time curve for both CQ (35,750 vs 47,892 µg h/liter, p &lt; 0.001) and desethylchloroquine (23,073 vs 41, 584 µg h/liter, p &lt; 0.001), reflecting significant differences in elimination half-lives and in volumes of distribution and clearances relative to bioavailability.</td>
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<td>Tarning et al. (2009) [221]</td>
<td>Thailand 2009</td>
<td>Pharmacokinetics study</td>
<td>n = 103 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>Lumefantrine in AL</td>
<td>Plasma concentration and treatment failure rate</td>
<td>Day 7, 40% (n = 41/103) plasma concentrations of &lt; 355 ng/ml (which corresponds to approximately &lt; 280 ng/ml in venous plasma), a threshold previously associated with an increased risk of therapeutic failure in nonpregnant patients in this area. The treatment failure rate 16.5% (95% CI 9.9 – 25.1)</td>
</tr>
<tr>
<td>Mutabingwa et al. (2009) [153]</td>
<td>Tanzania 2004 – 2006</td>
<td>RCT with 4 regimes</td>
<td>n = 272 Non-severe <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>SP (n = 28) CD(n = 81) SP + AQ (n = 80) AQ + AS (n = 83)</td>
<td>Parasitological failure by day 28</td>
<td>Day 28 parasitological failure rates were 4/26 (15%, 95% CI 4 – 35) in the SP, 18/77 (23%, 95% CI 14 – 34) in the CD, 1/73 (1% 95% CI 7 – 0.001) in the SP + AQ and 7/75 (9% 95% CI 4 – 18) in the AQ + AS arms, respectively</td>
</tr>
<tr>
<td>McGready et al. (2008) [154]</td>
<td>Thailand 2004 – 2006</td>
<td>OL-RCT</td>
<td>n = 252 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>AL (n = 125) AS (n = 128)</td>
<td>PCR-adjusted cure rates assessed at delivery or by day 42</td>
<td>Day 42 CR for the ITT population: AS 89.2% (82.3 – 96.1%) and AL 82.0% (74.8 – 89.3%), p = 0.054 (ITT); and AS 89.7% (82.6 – 96.8%) and AL 81.2% (73.6 – 88.8%), p = 0.031 (per-protocol population)</td>
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<td>Kaye et al. (2008) [158]</td>
<td>Uganda 2006</td>
<td>OL-RCT</td>
<td>n = 114</td>
<td>2 and 3</td>
<td>AL (n = 49) CD (n = 49)</td>
<td>Clinical and parasitological response assessed on days 0, 1, 2, 4, 7, 14 and 28</td>
<td>Day 28 CR: AL 100%, CD 100%. Parasite and fever clearance time were comparable. The adverse effects were comparable between the two groups. Ten participants lost to follow up, and three developed severe malaria and were given Q therapy.</td>
</tr>
<tr>
<td>Kalilani et al. (2007) [155]</td>
<td>Malawi 2003 – 2004</td>
<td>Pilot, OL-RCT with three treatment groups</td>
<td>n = 141 with uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>SP (n = 47) SP + AZ (n = 47) SP + AS (n = 47)</td>
<td>Incidence of AO, PCT, FCT and RR</td>
<td>PF: SP + AS 14.3% (peripheral parasitemia at delivery) (n = 101), 11.4% (placental parasitemia by microscopy) (n = 99) and 44.8% (placental parasitemia by histology) (n = 70) compared to 30.3, 16.1 and 47.8% for SP; 27.3, 27.3 and 50.0% for SP + AZ. Recrudescence episodes of malaria were less frequent with SP-AZ (HR 0.19 [95% CI 0.06 - 0.63]) and SP-AS (HR 0.25 [95% CI 0.10 - 0.65]) compared with SP. All treatment regimens were well tolerated.</td>
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<th>Source (first author, year of publication, journal) (PubMed ID)</th>
<th>Country (study site), time frame</th>
<th>Study design</th>
<th>Number of pregnant women with malaria, <em>Plasmodium</em> spp.</th>
<th>Trimester</th>
<th>Antimalarial(s) tested</th>
<th>Measure of (primary) outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tagbor <em>et al.</em> (2006) [166]</td>
<td>Ghana 2003 – 2004</td>
<td>RCT with four treatment groups</td>
<td>n = 900 <em>P. falciparum</em> infection</td>
<td>2 and 3</td>
<td>CQ (n = 225) SP (n = 225) AQ (n = 225) AQ + SP (n = 225) AL (n = 13)</td>
<td>PCR-corrected parasitological failure by day 28</td>
<td>Day 28 parasitological failure: 14% CQ, 11% SP, 3% AQ, 0% AQ + SP (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Mcgready <em>et al.</em> (2006) [157]</td>
<td>Thailand 2004</td>
<td>Pharmacokinetics</td>
<td>n = 13 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>AL (n = 13)</td>
<td>Plasma concentrations</td>
<td>Pregnancy is associated with reduced plasma concentrations of both artemether and lumefantrine</td>
</tr>
<tr>
<td>Mcgready <em>et al.</em> (2006) [223]</td>
<td>Thailand 2000 – 2001</td>
<td>Pharmacokinetics study</td>
<td>n = 24 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>DHA following AS</td>
<td>Plasma concentrations</td>
<td>The kinetics of DHA are modified by pregnancy. The plasma levels of the active antimalarial metabolite DHA are lower than reported in nonpregnant adults</td>
</tr>
<tr>
<td>Na-Bangchang <em>et al.</em> (2005) [222]</td>
<td>Thailand, Zambia 2000 – 2001</td>
<td>Pharmacokinetics and dynamics</td>
<td>n = 26 with uncomplicated <em>P. falciparum</em> malaria</td>
<td>3</td>
<td>AP</td>
<td>Clinical and parasitological efficacy by day 28; pharmacokinetics</td>
<td>The 28-day cure rates were 100%. The pharmacokinetics of atovaquone and cycloguanil appeared to be influenced by the pregnancy status, resulting in an approximately twofold decrease in C-max and AUC</td>
</tr>
<tr>
<td>McGready <em>et al.</em> (2005) [168]</td>
<td>Thailand 2001 – 2003</td>
<td>OL-RCT</td>
<td>n = 81 with uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>A + AP (n = 39) Q (n = 42) (7 days)</td>
<td>Day 63 cumulative cure rate</td>
<td>Day 63 cure rate (PCR-adjusted) (95% CI) of 63.4% (46.9 - 77.4%) (26/41) for Q and 94.9% (81.37 - 99.11%) (37/39) for A + AP. There were no significant difference in birth weight, duration of gestation or congenital abnormality rates in</td>
</tr>
</tbody>
</table>


A: Artemether; ACTs: Artemisinin-based combination therapies; adj.: Adjusted; AE: Adverse events; AL: Artemether-lumefantrine; AO: Adverse outcomes; AP: Atovaquone-proguanil; AQ: Amodiaquine; AS: Artesunate; AZ: Azithromycin; CD: Chlorproguanil-dapsone; CQ: Chloroquine; CR: Clearance/cure rate; DHA: Dihydroartemisinin; FCT: Fever clearance time; HR: Hazard Ratio; Hz: Hemozoin (malaria pigment); ITT: Intention to treat; LBW: Low birth weight; MQ: Mefloquine; NIT: Non-inferiority trial; OL: Open label; OT: Observational trial; PCT: Parasite clearance time; PCR: Polymerase chain reaction; PE: Parasitological efficacy; PF: Parasitological failure; PK: Pharmacokinetics; PQ: Piperaquine; Q: Quinine; QC: Quinine + clindamycin; RCT: Randomized controlled trial; RR: Recrudescence rate; SP: Sulfadoxine-pyrimethamine.

<table>
<thead>
<tr>
<th>Source (first author, year of publication, journal) (PubMed ID)</th>
<th>Country (study site), time frame</th>
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<th>Number of pregnant women with malaria, <em>Plasmodium</em> spp.</th>
<th>Trimester</th>
<th>Antimalarial(s) tested</th>
<th>Measure of (primary) outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam et al. (2004) [169]</td>
<td>Sudan 1998 – 2001</td>
<td>Prospective non-comparative clinical trial</td>
<td>n = 40 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>MQ</td>
<td>Clinical efficacy, adverse effects</td>
<td>Recrudescence or reinfection occurred on day 14 in one patient (2.5%). One baby with LBW. There was no abortion, no stillbirth and no congenital abnormality in the newborn children and no maternal death.</td>
</tr>
<tr>
<td>McGready et al. (2003) [161]</td>
<td>Thailand 1999 – 2001</td>
<td>OT</td>
<td>n = 27 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>A + AP</td>
<td>Day 42 cure rate: 96% (95% CI 89 – 100). The treatment was well tolerated, and no evidence was found of toxicity for the mothers and the fetus. Day 42 cure rate: 100% for QC versus 100% for AS. The AS regimen was also associated with less gametocyte carriage; the average person-gametocyte-weeks for A was 3 (95% CI 0 – 19) and for QC was 39 (95% CI 21 – 66) per 1000 person-weeks, respectively (p &lt; 0.01)</td>
<td></td>
</tr>
<tr>
<td>McGready et al. (2001) [167]</td>
<td>Thailand 1997 – 2000</td>
<td>RCT</td>
<td>n = 129 Acute uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>QC (n = 65) AS (n = 64)</td>
<td>Day 42 cure rate</td>
<td></td>
</tr>
</tbody>
</table>


A: Artemether; ACTs: Artemisinin-based combination therapies; adj.: Adjusted; AE: Adverse events; AL: Artemether-lumefantrine; AO: Adverse outcomes; AP: Atovaquone-proguanil; AQ: Amodiaquine; AS: Artesunate; AZ: Azithromycin; CD: Chlorproguanil-dapsone; CQ: Chloroquine; CR: Clearance/Cure rate; DHA: Dihydroartemisinin; FCT: Fever clearance time; HR: Hazard Ratio; HZ: Hemoglobin (malaria pigment); ITT: Intention to treat; LBW: Low birth weight; MQ: Mefloquine; NT: Non-inferiority trial; OL: Open label; OT: Observational trial; PCT: Parasite clearance time; PCR: Polymerase chain reaction; PE: Parasitological efficacy; PF: Parasitological failure; PK: Pharmacokinetics; PQ: Piperaquine; Q: Quinine; QC: Quinine + clindamycin; RCT: Randomized controlled trial; RR: Recrudescence rate; SP: Sulfadoxine-pyrimethamine.
### Table 5. Clinical studies in 1997 - 2013 on treatment of malaria in pregnancy (continued).

<table>
<thead>
<tr>
<th>Source (first author, year of publication, journal) (PubMed ID)</th>
<th>Country (study site), time frame</th>
<th>Study design</th>
<th>Number of pregnant women with malaria, <em>Plasmodium</em> spp.</th>
<th>Trimester</th>
<th>Antimalarial(s) tested</th>
<th>Measure of (primary) outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGready et al. (2000) [170]</td>
<td>Thailand 1995 – 1997</td>
<td>RCT</td>
<td>n = 108 Uncomplicated <em>P. falciparum</em> malaria</td>
<td>2 and 3</td>
<td>MQ + AS (n = 65) Q (n = 41)</td>
<td>Day 63 cure rates</td>
<td>Day 63 cure rates were 98.2% (95% CI 94.7 – 100) for MQ + AS and 67.0% (95% CI 43.3 – 90.8) for Q p = 0.001. The MQ + AS regimen was also associated with less gametocyte carriage; the average person-gametocyte-weeks for MQ + AS was 2.3 (95% CI 0 – 11) and for Q was 46.9 (95% CI 26 – 78) per 1000 person-weeks, respectively (p &lt; 0.001). MQ + AS was significantly better tolerated. Both groups 100% by day 14 and 28; however, one person in the A group was retreated. There was no correlation between initial parasite density and parasite or fever clearance times in the two groups. Both treatment regimens were well tolerated.</td>
</tr>
</tbody>
</table>


**A:** Artemether; **ACTs:** Artemisinin-based combination therapies; **adj.:** Adjusted; **AE:** Adverse events; **AL:** Artemether-lumefantrine; **AO:** Adverse outcomes; **AP:** Atovaquone-proguanil; **AQ:** Amodiaquine; **AS:** Artesunate; **AZ:** Azithromycin; **CD:** Chlorproguanil-dapsone; **CQ:** Chloroquine; **CR:** Clearance/cure rate; **DHA:** Dihydroartemisinin; **FCT:** Fever clearance time; **HR:** Hazard Ratio; **Hz:** Hemoglobin (malaria pigment); **ITT:** Intention to treat; **LBW:** Low birth weight; **MQ:** Mefloquine; **NT:** Non-inferiority trial; **OL:** Open label; **OT:** Observational trial; **PCT:** Parasite clearance time; **PCR:** Polymerase chain reaction; **PE:** Parasitological efficacy; **PF:** Parasitological failure; **PK:** Pharmacokinetics; **PQ:** Piperaquine; **Q:** Quinine; **QC:** Quinine + clindamycin; **RCT:** Randomized controlled trial; **RR:** Recrudescence rate; **SP:** Sulfadoxine-pyrimethamine.
Table 6. Ongoing trials on malaria treatment in pregnant women registered online in clinical trial registries (date of last search: June 2014).

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Registration ID (year)</th>
<th>Antimalarial(s) tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison of two regimens of artemether-lumefantrine for the treatment of malaria in pregnancy (ALN5P)</td>
<td>NCT01916954 (2013)</td>
<td>AL (3 days) versus AL (5 days)</td>
</tr>
<tr>
<td>Antimalarial pharmacology in children and pregnant women in Uganda</td>
<td>Democratic Republic of Congo NCT01717885 (2012)</td>
<td>AL in combination with anti-HIV Rx</td>
</tr>
<tr>
<td>Comparison of the safety, efficacy and tolerability of artemether-lumefantrine and artesunate amodiaquine in Nigerian pregnant women with acute uncomplicated falciparum malaria</td>
<td>NCT01916954 (2013)</td>
<td>AS + AQ versus AL</td>
</tr>
<tr>
<td>Randomized trial of three artemisinin combination therapy for malaria in pregnancy (DMA)</td>
<td>NCT01054248 (2010)</td>
<td>AS + MQ, AL, DHA + PQ</td>
</tr>
<tr>
<td>Safe and efficacious artemisinin-based combination treatments for African pregnant women with malaria (PREGACT)</td>
<td>NCT00852423 (2009)</td>
<td>DHA + PQ, AS + MQ, AS + AQ, AL</td>
</tr>
<tr>
<td>A Phase II/III randomized clinical trial of the efficacy and safety of artesunate sulphadoxine pyrimethamine and artesunate mefloquine to treat uncomplicated falciparum malaria in pregnancy</td>
<td>Burkina Faso NCT01231113 (2010)</td>
<td>AS + AQ, AL</td>
</tr>
<tr>
<td>Study of pharmacokinetics and pharmacodynamics of artesunate in pregnant women in the Democratic Republic of Congo</td>
<td>NCT01916954 (2013)</td>
<td>AS + MQ</td>
</tr>
<tr>
<td></td>
<td>Burkin Faso NCT01231113 (2010)</td>
<td>AS</td>
</tr>
<tr>
<td></td>
<td>Democratic Republic of Congo NCT00538382 (2007)</td>
<td>AS</td>
</tr>
</tbody>
</table>


to 5 days. Further studies are needed to collect pharmacokinetic data in pregnant women after an extended regimen or dose adjustment to investigate whether an adjusted course is warranted. A comparison of two regimens of AL (3 vs 5 days) is currently under investigation in the Democratic Republic of Congo (NCT01916954). In a pharmacovigilance study with 978 exposures to AL and follow-up until delivery, no specific safety concerns related to AL for uncomplicated falciparum malaria were described [165]. However, there were slightly more obstetric complications in the treatment group (compared to a matched, nonexposed control group); this could have been caused by the treatment itself or more probably have been caused by the malaria episode itself. Further assessment of possible obstetric complications is required. A population-based survey on self-reported antimalarial drugs showed that AL was the most widely used drug in the treatment of malaria in the second or third trimester of pregnancy (any use of AL 43.3%; 207/478 episodes). AL is currently being investigated in Thailand and several other African countries (Phase III: NCT01054248, NCT01916954, NCT01717885, NCT00852423 and PACTR2010020001862624) (Table 6).

Another drug that demonstrated to be highly effective is amodiaquine. A pharmacokinetic study conducted in Thailand reduced the risk of recurrent *P. falciparum* infections from 22.2 to 7.4% at day 35 in 27 women [164]. This study also implied that no dose adjustments are required in pregnancy. This study supports previous research that there were no clinically relevant differences in the pharmacokinetics of amodiaquine and desethylamodiaquine between pregnant and postpartum women [165]. Amodiaquine was shown to be highly effective combined with sulfadoxine-pyrimethamine or artesunate in an RCT in Tanzania [153]. By day 28, parasitological failure rates were 1% in the sulfadoxine-pyrimethamine-amodiaquine group and 3% in the amodiaquine-artesunate group. In a large RCT in Ghana, amodiaquine alone (n = 225) had a 3% PCR-corrected parasitological failure rate by day 28, compared to 0 in combination with sulfadoxine-pyrimethamine [156]. Amodiaquine is relatively safe and well tolerated; however, some side effects such as dizziness and nausea have been reported. Amodiaquine is currently under investigation in a clinical Phase III trial in Ghana (NCT01231113), where it is combined with artesunate and compared with DHA plus PIP. Two other Phase III trials are currently underway evaluating amodiaquine in pregnant women in Africa (PACTR2010020001862624 and NCT00852423).

Safety and efficacy data on quinine are widely available and not discussed in detail here. A randomized trial performed > 10 years ago, compared artesunate versus quinine plus clindamycin for the treatment of *P. falciparum* malaria, reported no difference in efficacy with 100% of the women in each
treatment regimen cured [167]. Efficacy data from a more recent randomized trial on the Thai-Burmese border showed that 63.4% (95% CI: 46.9 – 77.4%) of pregnant women (second and third trimester) with uncomplicated P. falciparum malaria who received a 7-day course of quinine monotherapy were cured, based on PCR-corrected parasite clearance at day 63 of follow-up or delivery [168]. This was in contrast with considerably higher proportion of cure rates in the arm with 3 days of arsunate-atovaquone-proguanil (94.9%; 95% CI: 81.37, -99.11%). The low cure rates of 63.4% of quinine [168] may be explained by a combination of resistance of P. falciparum and by the pharmacokinetic properties of quinine during pregnancy. Furthermore, quinine is not well tolerated and often causes symptoms of cinchonism, and it can cause severe hypoglycaemia with high insulin levels.

Extensive clinical experience of prophylactic use of mefloquine in the first trimester of pregnancy showed no increased risks or teratogenic effects [156]. Experience with a high dose as treatment is limited to three studies (Table 5): A high cure rate has been reported in Sudan (recrudescence or reinfection in 2.5%; 1/40) [169], Thailand (mefloquine in combination with artesunate a cure rate of 98.2% by day 63) [170] and Nigeria (in combination with artemether cure rate of 100% by day 14 and day 28) [171]. The treatment is generally well tolerated, and only minor adverse effects were reported. As for the use of mefloquine in nonpregnant individuals, safety concerns have been raised regarding the occurrence of neuropsychiatric disorders as adverse effects. A literature review suggested that females are at greater risk to develop neurotoxicity and it was disordered as adverse effects. A literature review suggested that there have been raised regarding the occurrence of neuropsychiatric disorders as adverse effects. A literature review suggested that these disorders are common adverse events. A literature review suggested that these disorders are common adverse events.

Malaria is, on a global scale, a pediatric disease [175]. Very much different from many other diseases, almost all clinical drug development trials have been performed in children in endemic areas, with treatment outcomes being extrapolated from those trials to inform treatment strategies for adults in malaria-endemic areas, as well as for children and adults exporting malaria to non-endemic, affluent countries. That notwithstanding, the most appropriate choice of combination therapy needs to take age and age-specific pharmacokinetic and -dynamic factors, body weight and specific pediatric risk factors (e.g., among others, the problems of administering tetracyclines to younger children) into account. AL is the ACT most commonly used for the treatment of uncomplicated malaria in children. AL has been demonstrated to be safe when compared with other antimalarials such as quinine, sulphadoxine-pyrimethamine and chloroquine [176]. Several combinations have been investigated. Firstly, AL has been compared with dihydroartemisinin-piperazine in 11 studies [40,41,56,177-185], involving 5958 children. No drug-related deaths were identified, and the risk of serious adverse events for AL was not significantly different for DHA + PP [176]. Other trials compared AL with artesunate-amodiaquine (13 studies, 6018 children) [39,183,186-190], with chlorproguanil-dapsone-artesunate (three studies, 3366 children) [183,188,197], with artesunate-mefloquine (two studies, 476 children) [198,199] and with artesunate-azithromycin (one study, 261 children) [200]. Regarding the safety and tolerability of AL, the authors of a recent systematic review [176] demonstrate cough as the most common adverse event in children treated with AL. Other frequently reported adverse effects are gastrointestinal symptoms such as vomiting, abdominal pain and diarrhea. Headache and anemia were also described as common adverse events.

9. Treatment of malaria as an imported condition

Whereas most cases of malaria remain to be pediatric in endemic countries, most imported cases are in adults – yet our treatment strategies are everywhere based on data predominantly obtained from clinical trials conducted in young children in Africa. There is a wealth of national guidelines in place in the various countries where malaria is regularly encountered as an imported condition. Whereas those vary in some detail, atovaquone-proguanil, mefloquine and ACT’s, with AL dominating and DHA-PIP now entering the Northern, affluent markets, are regularly featuring in various order of appearance with regard to preference [111,201-203]. In Europe, atovaquone-proguanil ranges high in many non-endemic countries among the preferred therapies for uncomplicated falciparum malaria [204], despite the fact that the slow action inherent to this drug combination, with comparatively long parasite and fever clearance times, regularly leads to misperceptions about possible resistance, and to prolonged disease episodes compared to ACTs. Special recommendations for the treatment of children/pregnant women apply throughout all guidelines. A recently introduced black box warning regarding mefloquine use for the therapy of uncomplicated falciparum malaria [205] will reduce its use as treatment for uncomplicated malaria further. However, for some indications (high-risk groups, such as long-term travelers,
VFR travelers and families with small children), there is currently no replacement for mefloquine available or in the pipeline [206]. In our view, ACTs should most consequently be used for the treatment of uncomplicated imported falciparum malaria in view of its favorable adverse events profile as well as the rapid schizontocidal action.

There is also an increasing debate on whether to continue with non-ACTs (chloroquine in the first place, mostly followed by primaquine administration in non-G6PD-deficient individuals) for non-falciparum species (except for P. knowlesi) therapy as far as susceptibility is assumed. In some non-endemic countries, first shifts away from chloroquine for vivax and ovale malaria treatment toward ACTs on basis of good tolerance and swift clinical improvement due to quick parasite and fever clearance times can be observed [111], mainly based on data from malaria-endemic areas and based on expert opinion, as controlled trials being tedious to carry out at least in non-endemic countries.

With the prospects of increased availability of GMP-conform artesunates in non-malaria-endemic countries improving, there is an increasing shift toward adopting i.v. artesunate in place of i.v. quinine as chemotherapeutic backbone for the treatment of severe falciparum malaria. While controlled trials on the scale of the trials in Asia and Africa are not possible due to small patient numbers [207], there is evidence from small case series [98] as well as growing expert opinion in favor of parenteral artesunate use [208].

Due to space constraints, it is not possible to elaborate in detail on differences in all the factors that may influence clinical presentation and clinical course of malaria in patients in endemic versus those encountered in non-endemic areas, and possible (maybe only subtle) consequences for the choice of antimalarial treatment; a subject that would warrant a paper on its own.

10. Conclusion

Malaria chemotherapy remains a dynamic field, with novel drugs and drug combinations continue to emerge in order to outpace the development of large-scale drug resistance against the currently most important drug class, the artesunates. Continuous investment into malaria drug development is a vital contribution to combat artemisinin resistance and successfully improve malaria control toward the ultimate elimination goal.

11. Expert opinion

Knowledge about adequate drug levels in children and pregnant women is scarce. More pharmacodynamic and pharmacokinetic data are needed to be able to adjust dosages according to body weight and not according to age groups, which allow a large deviation in exact therapeutic drug levels, especially among children. For pregnant women, there is a need to adapt pharmacokinetic models and safety data need to be collected in a systemic way. We see a need to discuss openly, in view of the complexity of the ethical aspects of the issue, whether women should be excluded per se from these RCTs, as long as sufficient observational safety data for the drug under investigation are available. Researchers may argue it is unfeasible and unlikely they will intentionally expose pregnant women to potential teratogenic drugs; the only alternative to RCTs are sensitive pharmacovigilance systems for the monitoring of outcomes of unintentional first trimester exposures, but these need to be developed first and have many (practical) limitations. Another argument not to include consenting pregnant women in their first trimester in clinical trials is that in view of the widespread use of AL for the treatment of female adults of child-bearing age, a substantial number of women will be unintentionally exposed to an artemisinin derivate early in pregnancy. In areas with high transmission, people might receive as many as three treatments of artemisinin derivate every year, there is a 17% chance of the unborn child to be exposed during the putative sensitive period from week 3 to 9 weeks after conception. This may affect 8.5 million unborn children each year [209]. An important note is that, due to such an early susceptible period in pregnancy, fetal deaths due to ACTs could be easily overlooked, because women may not yet know they are pregnant. Data suggest that a large proportion of women have malaria at the time of their first antenatal care visit [210], another reason that highlights the importance of further studies into the safety and efficacy of ACTs for its potential use in the first trimester.

Furthermore, and despite constraints in case numbers in individual sites, it is somewhat surprising that almost none of the past and ongoing clinical trials investigate ACTs for non-falciparum species, particularly P. vivax that causes the same complications as P. falciparum malaria, although less frequent and less severe. Treatment of non-falciparum malaria in pregnant women is nearly the same as for nonpregnant adults. Following treatment of infection due to P. ovale or P. vivax, nonpregnant patients, if not returning to an endemic region, are treated with primaquine to prevent relapse by eradicating hypnozoite forms that may remain dormant in the liver. For future trials, it is important to recognize that if primaquine is coadministered with a blood schizontocidal agent, the total effect is a sum of the synergistic efficacy of the schizontocidal drug and primaquine.

Furthermore, more consequent use of ACTs for the treatment of important malaria in order to capitalize outside endemic areas on reduced parasite and fever clearance times resulting in patients improving in the shortest possible period of time after diagnosis and treatment initiation should become a priority.

In the future, one important research area will be to further explore avenues toward identifying drug combinations that may further reduce the duration of treatment and allow reduction on the total number of doses administered; with single-dose regimens being the sought-after ‘magic bullet’ (which from today’s perspective may remain unsuitable for routine use for quite a while).
Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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**Malaria**
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Supplementary materials available online

Appendix 1