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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

Expert Opin. Pharmacother. [Early Online]

1. Introduction

Chemotherapy of malaria has become a considerably rapidly changing field. Less than two decades ago, established 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. Most importantly, injectable quinghaosu (artesunate) derivatives are now rapidly becoming the therapeutic backbone of severe falciparum malaria around the globe. Unfortunately, little progress has been made so far on developing marketable tissue schizonticides as possible alternatives to the 8-aminoquinoline primaquine. Furthermore, early evidence of resistance development against the artemisinins [1,2] highlights the need for continuous investment into the development of alternative drug classes.

2. Objectives

This review summarizes the current treatment strategies for malaria and discusses novel developments as far as they are currently undergoing Phase III/IV clinical

10.1517/14656566.2014.944499 © 2014 Informa UK, Ltd. ISSN 1465-6566, e-ISSN 1744-7666

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 conjunction 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 NCT01704 508). Studies evaluating the combination artesunate + sulphadoxine-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 Lanaspa *et al.* [75] showed inadequate 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 artesunates 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 artesunate 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).

Name of study	Registration ID (year) country, status as of March 2014	Antimalarial(s) tested
Study to determine the efficacy of artesunate-mefloquine combination therapy for the treatment of uncomplicated *P. falciparum* Malaria in Thailand	NCT02052323 (2014) Thailand	AS + MQ
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	NCT02020330 (2013) Myanmar	AL (3 days) versus AL (5 days)
Treatment efficacy and malaria TRANSmission after Artemisinin Combination Therapy 2 (TRANSACT2)	NCT01939886 (2013) Tanzania	AL versus AS + MQ
Surveillance and treatment with DHA-piperaquine plus primaquine	NCT01878357 (2013) Indonesia	DHA + PP mass drug administration (MDA) – several time intervals
Effect of oral activated charcoal on parasite clearance rates in response to intravenous artesunate in Malian children with uncomplicated *P. falciparum* Malaria	NCT01955382 (2013)	Oral activated charcoal
Artemisinin-based antimalarial combinations and clinical response in Cameroon	NCT01845701 (2013) Cameroon	AL versus AS + AQ versus DHA + PP
Primaquine's gametocytocidal efficacy in malaria asymptomatic carriers (PRINOGAM)	NCT01838902 (2013) The Gambia	DHA + PP + PQ in different dosages)
The optimal timing of primaquine to prevent malaria transmission after artemisinin-combination therapy	NCT01906788 (2013) Tanzania	AL + PQ (in different dosages)
Safety, tolerability, pharmacokinetics and efficacy of ARCO	NCT01930331 (2013) Tanzania	ARCO versus DHA + PP
A study to find the minimum inhibitory concentration of KAE609 in adult male patients with *P. falciparum* mono-infection (Phase II)	NCT01836458 (2013) Thailand	KAE609
A study to assess efficacy, safety of KAE609 in adult patients with acute malaria mono-infection (Phase II)	NCT01860989 (2013) Thailand	KAE609
Phase IIa primaquine dose-escalation study	NCT01743820 (2012) Mali, Thailand	DHA + PP + PQ (different dosages)
Artemisinin-resistant malaria in Cambodia	NCT01736319 (2012) Cambodia	DHA + PP
Pharmacology of antimalarial therapy with or without antiretroviral therapy	NCT01728961 (2012) Malawi, Uganda	AL
Efficacy of three ACTs for the treatment of *P. falciparum* malaria in Maradi Niger	NCT01755559 (2012) Niger	AL versus DHA + PP versus AS + AQ
Comparing mefloquine-artesunate and DHA-piperaquine in malaria treatment (MMA)	NCT01640587 (2012) Thailand	DHA + PP versus AS + MQ
Improving antimalarial treatment options in Guinea-Bissau - Part A	NCT01704508 (2012) Guinea-Bissau	AL versus DHA + PP
Efficacy, safety and pharmacokinetics of AL dispersible tablet in the treatment of malaria in infants < 5 kg	NCT01619878 (2012) Benin, Burkina Faso, Togo, Nigeria, Congo	AL dispersible tablet
OZ439 Phase IIa study in *P. falciparum*: extended observation (Phase II)	NCT01713621 (2012) Thailand	OZ439
Studies of a candidate aminoquinoline antimalarial (AQ-13)	NCT01614964 (2012) Mali	AQ-13 versus AL
Tracking resistance to artemisinin (TRAC)	NCT01350856 (2011) Multiple countries	AS (two different regimens)
Evaluation of fosmidomycin and clindamycin in the treatment of acute uncomplicated *P. falciparum* malaria	NCT01361269 (2011) (status unknown, probably stopped) Gabon, Mozambique	Fosmidomycin and clindamycin
Impact of artemisinin-based combination therapy and quinine on treatment failure and resistance in uncomplicated malaria (QuinAct)	NCT01374581 (2011) Congo, Uganda	AL versus AS + AQ versus Q + clindamycin

A: Artemether; ACTs: Artemisinin-based combination therapies; AL: Artemether-lumefantrine; AP: Atovaquone-proguanil; AQ: Amodiaquine; ARCO: Artemisinin/naphthoquine; AS: Artesunate; AZ: Azithromycin; CD: Chlorproguanil-dapsone; CQ: Chloroquine; DHA: Dihydroartemisinin; MQ: Mefloquine; PP: Piperaquine; PQ: Piperaquine; Q: Quinine; QC: Quinine + clindamycin; SP: Sulfadoxine-pyrimethamine.

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

Name of study	Registration ID (year) country, status as of March 2014	Antimalarial(s) tested
Evaluation of the Riamet® versus Malarone® in the treatment of uncomplicated malaria (MalaRia)	NCT01150344 (2010) France	AP versus AL
Surveillance of effectiveness/safety of AL in patients with malaria	NCT01228344 (2010) United States	AL
Effectiveness of the association of artesunate and mefloquine in the treatment of malaria by *P. falciparum*	NCT01144702 (2010)	AS + MQ
Efficacy, safety and tolerability of DHA-piperaquine for uncomplicated malaria in pregnancy in Ghana (DHAPPQ/MIP)	NCT01231113 (2010) Ghana	DHA + PP
Artesunate plus amodiaquine in malaria in Cote d'Ivoire	NCT01023399 (2009) Ivory Coast	AS + AQ

A: Artemether; ACTs: Artemisinin-based combination therapies; AL: Artemether-lumefantrine; AP: Atovaquone-proguanil; AQ: Amodiaquine; ARCO: Artemisinin/naphthoquine; AS: Artesunate; AZ: Azithromycin; CD: Chlorproguanil-dapsone; CQ: Chloroquine; DHA: Dihydroartemisinin; MQ: Mefloquine; PP: Piperaquine; PQ: Piperaquine; Q: Quinine; QC: Quinine + clindamycin; SP: Sulfadoxine-pyrimethamine.

no frequent plasma glucose monitoring required) and an overall favorable adverse events profile (with regard to neurological consequences of severe malaria, no significant differences between both drugs have been observed). That notwithstanding, i.v. administered quinine remains an option for the treatment of severe malaria particularly if artesunate availability in adequate quality is not warranted yet, or in future, should emergence of resistance arise on a large scale before other alternatives become available. However, while artesunate resistance is not a major issue in practice to date, duration of treatment, a disadvantageous adverse events profile with cinchonism, induction of hypoglycemia and pharmacokinetical properties requiring skilled administration from loading dose to dose adaptation in due course facilitated fairly swift acceptance of a shift from quinine to artesunate as backbone drug against severe falciparum malaria [92]. Intramuscular administration of an oily emulsion of artemether is feasible [93,94], but where possible, preference is given to i.v. administrable artesunate. The intramuscular use of oily artemether might increase risk of neurotoxicity, although the current regimen dosing duration appears to be safe [95]. Although there are no major safety issues with parenteral artesunate, there are some concerns regarding risk of prolonged and/or late hemolysis after high-dose artesunate treatment. Over the past years, up to 25% of patients from several cohorts treated with i.v. artesunate for severe falciparum malaria from Africa (children/malaria-endemic area: Gabon) and Europe (mainly adults, imported malaria) developed in some cases profound delayed hemolytic anemia 7 – 31 days after treatment [96-100]. Up to date, the pathophysiology, causality and dimension of the problem remain to be fully elucidated.

Rectal administration of artesunate prior to referral to/arrival at an appropriately equipped health-care referral unit [101] has been proven to be potentially lifesaving, and all practical problems notwithstanding, repeated rectal administration have been suggested to further improving pre-referral outcomes in cases of suspected malaria [102,103] in settings where prompt adequate diagnosis and treatment may not be at hand. **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 *wallikeri, P. malariae* and *P. knowlesi*. Although the cause of nearly all of the deaths due to malaria is due to *P. falciparum*, non-falciparum

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

Name of study	Registration ID (year) country, status as of March 2014	Antimalarial(s) tested
Intravenous Artesunate and Malaria (IVAS)	NCT01805232 (2013) Sudan	AS versus Q
Malaria Treatment With Injectable ArteSunate (MATIAS)	NCT01828333 (2013) (completed) Democratic Republic of Congo	AS
Superiority of ArTiMist Versus Quinine in Children With Severe Malaria	NCT01258049 (2012) (completed) Burkina Faso, Ghana, Rwanda	Artemether sublingual spray versus Q
Azithromycin Combination Therapy for the Treatment of Severe Malaria	NCT01374126 (2011) (completed) Bangladesh	AS versus AS + Azithromycin
Pharmacokinetics and Pharmacodynamics of Intravenous Artesunate for Severe Malaria Treatment	NCT01122134 (2010) (status unknown) Uganda	AS
Study of SAR97276A in the Treatment of Uncomplicated and Severe Malaria in Adults and Children.	NCT00739206 (2008) (suspended) Benin, Burkina Faso, Gabon	SAR97276A

A: Artemether; AL: Artemether-lumefantrine; AP: Atovaquone-proguanil; AQ: Amodiaquine; AS: Artesunate; AZ: Azithromycin; CD: Chlorproguanil-dapsone; CQ: Chloroquine; DHA: Dihydroartemisinin; MQ: Mefloquine; PQ: Piperaquine; Q: Quinine; QC: Quinine + clindamycin; SP: Sulfadoxine-pyrimethamine.

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* and *P. ovale* is extremely rare. Of the non-falciparum species, *P. vivax* has the largest geographic distribution and burden of disease in terms of health, longevity and socioeconomic development, and accounts for 40% of malaria cases worldwide [114]. The other two human malaria *Plasmodium* species *P. malariae* and *P. ovale* are normally less prevalent, but they are distributed widely across malaria-endemic areas.

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. Chloroquine 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. Hydroxychloroquine 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 CPRV are increasing and of a particular problem in the regions of Papua New Guinea, the Solomon Islands and Indonesia. Sporadically, CRPV has also been reported from Burma (Myanmar), India, Vietnam, Turkey, and Central and South America [118]. The variability among *P. vivax* strains emphasizes that healthcare practitioners are required to consider geographical factors when initiating drug therapy for *P. vivax* infection. A recurrence 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 mefloquine. 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 quinine) is needed. Data from > 50 years ago showed that primaquine may exert its beneficial effect when combined with a 4-aminoquinoline drug such as chloroquine [119]. Administration 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].

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-phrosphate dehydrogenase [G6PD] deficiency) beforehand – 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. falciparum* gametocytes in children with uncomplicated malaria [122]. It was shown that a lower dose (0.4 mg/kg primaquine) had similar gametocytocidal efficacy compared to the reference (0.75 mg/kg). However, these findings are not directly

Table 3. Clinical studies 2008 – 2013 on treatment of non-falciparum malaria* (*P. vivax, P. ovale* and *P. malariae*).

Source (first author, year of publication, journal) (PubMed ID)	Country (study site), time frame	Study design	Number of patients	Antimalarial(s) tested	Measure of (primary) outcome	Findings
Liu *et al.* (2013) [131]	China	Open-label RCT	n = 251 (*P. vivax)*	AN versus CQ + PQ	Day 42 cure rate	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
Pasaribu et al. (2013) [116]	Thailand	Open-label RCT	n = 331 (*P. vivax*)	DHA + PP + PQ versus AS + AQ + PQ	Day 42 efficacy	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
Senn *et al.* (2013) [128]	Papua New Guinea	Longitudinal prospective effectiveness study	n = 594 (*P. vivax*)	AL	Day 7, 8 and 28 clinical treatment failure rates	Clinical treatment failure rates by 7, 28 and 42 days were 0.2, 2.2 and 12.0%
Sutanto *et al.* (2013) [132]	Indonesia	Randomized, open-label, relapse-controlled trial	n = 116 (*P. vivax*)	PQ + Q versus PQ + DHA + PP Relapse control: only AS	Therapeutic efficacy (follow-up 12 months)	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
Hwang *et al.* (2013) [123]	Ethiopia	Randomized, open-label controlled trial	n = 242 (*P. vivax)*	AL versus CQ	Day 28 efficacy	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
Barber *et al.* (2013) [211]	Malaysia	Prospective study	n = 19 (*P. vivax*)	CQ + PQ or ACT (AS)	NR	Median parasite clearance time (PCT) for *P. vivax* was 2 days. 19 (44%) *P. vivax* patients smear negative by day 1
Abdallah *et al.* (2012) [129]	Sudan	Prospective cohort study	n = 38 (*P. vivax*)	AL	Day 28 cure rate	Day 28, the cure rate was 100 and 88.4% for the per protocol analysis and for the intention to treat analysis, respectively
Mombo-ngoma *et al.* (2012) [130]	Gabon	Prospective cohort study	n = 38 (total) n = 32 mixed	AL	Day 28 adequate clinical and	Day 28 overall cure rate was 100% (95% CI: 91 – 100%) for all species

*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).

Source (first author, year of publication, journal) (PubMed ID)	Country (study site), time frame	Study design	Number of patients	Antimalarial(s) tested	Measure of (primary) outcome	Findings
			infection (*P. ovale* or *P. malariae* with *P. falciparum* n = 7 (*P. malariae* or *P. ovale*)		parasitological response	
Phyo *et al.* (2011) [126]	Thailand	RCT	n = 500 (*P. vivax*)	DHA + PP versus CQ	Day 63 risk of recurrence	Day 28, recurrent infections in 18 of 207 CQ versus 5 of 230 DHA + PP (RR 4.0; 95% CI, 1.51 – 10.58; p = 0.0046). Risk of recurrence day 63: 79.1% (95% CI, 73.5 – 84.8%) in CQ versus 54.9% (95% CI, 48.2% – 61.6%) in DHA + PP ([HR, 2.27; 95% CI, 1.8 – 2.9; p < 0.0001). Both drugs well tolerated
Poravuth *et al.* (2011) [65]	Cambodia, Thailand, India and Indonesia	Randomized, non-inferiority trial (double dummy design)	n = 456 (*P. vivax*)	AS + P versus CQ	Day 14 cure rate in per protocol population	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> 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 < 0.0001). FCT (median 15.9 h and 23.8 h, respectively; p = 0.0017)
Yohannes *et al.* (2011) [124]	Ethiopia	Prospective non-randomized trial	n = 132 (*P. vivax*)	AL versus CQ	Day 28 treatment failure	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 ↓ than CQ; however, the findings were not conclusive, because the AL evening doses were not supervised
Awab *et al.* (2010) [212]	Afghanistan	Open-label randomized non-inferiority trial	n = 536 (*P. vivax*)	DHA + PP versus CQ	Day 56 overall cumulative parasitological failure rate	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

*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).

Source (first author, year of publication, journal) (PubMed ID)	Country (study site), time frame	Study design	Number of patients	Antimalarial(s) tested	Measure of (primary) outcome	Findings
Karunajeewa *et al.* (2008) [180]	Papua New Guinea	Open-label RCT	n = 195 (*P. vivax*)	CQ + SP versus AS + SP versus DHA + PP versus AL	Day 42 clinical and parasitologic response	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)
Krudsood *et al.* (2008) [213]	Thailand	RCT	n = 322 (*P. vivax*)	AS + PQ (6 groups: 1 – 5 PQ for 5, 7, 9, 11 and 14 days, group 6: twice a day for 7 days)	Day 28 cure rates	Day 28 cure rates were 85, 89, 94, 100 and 96%, respectively

*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.

important for the individual patient, but rather on community level with regard to gametocyte transmission back to the vector.

6.2 ACTs for the treatment of non-falciparum malaria

ACT is 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 chloroquine in the treatment of *P. vivax* in areas with sensitive strains of *P. vivax* for chloroquine [123-125]. Evidence indicates excellent cure rates of DHA + PIP. An RCT in Indonesia compared DHA + PIP with artesunate-amodiaquine where both groups were also given primaquine to clear hypnozoites. DHA + PP reduced the number of relapses by day 42 compared to Artesunate (AS) + Amodiaquine (AQ) (84 participants; relative risk [RR] 0.16, 95% CI 0.05 – 0.49) [117]. DHA was more effective and better tolerated than AQ against *P. vivax* infections. Also, it was noted that PIP decreased the rate of recurrence of *P. vivax* infection, and reduced the risk of *P. vivax* gametocyte carriage and anemia [117]. Even though these data encompass patients with *P. falciparum* at inclusion, and even though recurrence of *P. falciparum* was also lower with DHA + PP, it is likely that this prophylactic property is related to the longer half-life of DHA + PP. Another trial in Indonesia showed DHA + PP (compared to AL) also showed that the number of relapses by day 42 was reduced (126 participants; RR 0.16, 95% CI 0.07 – 0.38). More recent trials confirmed these findings (**Table 3**): An RCT comparing DHA + PP with the standard treatment chloroquine in Thailand demonstrated fever and parasite clearance times to be significantly slower in the chloroquine (CQ) than in the DHA + PP group [126]. The cumulative risk of recurrence with *P. vivax* at 9 weeks was considerably higher in the chloroquine group compared to the artemisinin derivate group (**Table 3**) [126]. A randomized comparison of DHA + PP and AS + AQ, both combined with primaquine in Indonesia in 2013, showed comparable efficacy for blood-stage parasite clearance of uncomplicated *P. vivax* malaria. Of note, DHA + PP was better tolerated [116]. The efficacy of 2- versus 3-day regimens of DHA-piperaquine for uncomplicated malaria (mainly *P. vivax*) was evaluated in Cambodia in an open-label RCT. Cure rate at day 42 was for the 2-day regimen 85% (95% CI 69 – 94%) and for the 3-day regimen 90% (95% CI 75 – 97%) [127]. So far, there are no trials registered comparing DHA + PP and artesunate + mefloquine in *P. vivax* mono-infection. Currently, a comparative study is conducted with DHA + PP with standard malaria treatment (AS + sulfadoxine-pyrimethamine [SP] and CQ) in Afghanistan (NCT00682578). A randomized cluster trial of mass screening and selective treatment using DHA-piperaquine plus primaquine (DHP + PQ) is currently conducted in Indonesia, evaluating an intervention arm with an interval of 6 weeks; 3 months and a control arm without mass

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

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

Name of study	Registration ID (year) country, status as of March 2014	Antimalarial(s) tested
Efficacy of chloroquine and primaquine for the treatment of plasmodium vivax malaria in Cruzeiro do Sul, Acre, Brazil	NCT02043652 (2014) Brazil	CQ + PQ (no comparison arm)
AL versus chloroquine in patients with acute uncomplicated *P. Knowlesi* malaria: a randomized open-label trial in Sabah, Malaysia (CAN KNOW trial)	NCT02001012 (2013) Sabah, Malaysia	AL versus CQ
Phase Ia study of ChAd63/MVA PvDBP (vaccine trial for *P. vivax*)	NCT01816113 (2013) United Kingdom	Vaccine: ChAd63 PvDBP, with or without MVA PvDBP
Radical cure for *P. vivax* malaria in Indonesia 2	ISRCTN82366390 (2013) Indonesia	AS + PQ, DHA + PP + PQ, AS + PYR
Surveillance and treatment with DHA-piperaquine plus primaquine	NCT01878357 (2013) Indonesia	DHA + PQ (6 weeks vs 3 months vs control)
Improving the radical cure of *P. vivax* malaria: A multicenter randomized comparison of short- and long-course primaquine regimens	NCT01814683 (2013) Afghanistan, Pakistan, Vietnam	14 days PQ versus 7 days PQ versus 14 days placebo
Comparison of two antimalarial drugs regimens in patient with *P. vivax* malaria in Thailand	NCT01662700 (2012) Thailand	AS versus CQ
Ethiopia antimalarial *in vivo* efficacy study	NCT01680406 (2012) Ethiopia	AL, AL + PQ, CQ, or CQ + PQ
Efficacy, safety, tolerability and pharmacokinetics of KAF156 in adult patients with acute, uncomplicated *P. falciparum* or *vivax* malaria mono-infection	NCT01753323 (2012) Thailand	KAF156 (400 vs 800 mg)
Comparison between 7 and 14 days primaquine combined with DHA-piperaquine or 3 days chloroquine radical cure of *P. vivax* (BPD)	NCT01640574 (2012) Thailand	DHA versus CQ
Phase IIB/III Tafenoquine (TFQ) study in prevention of *P. vivax* relapse	NCT01376167 (2011) Bangladesh, Brazil, India, Peru, Thailand	TFQ versus PQ (different dosages)
Study to evaluate the efficacy, safety and tolerability of tafenoquine in subject with *P. vivax* malaria	CTRI/2012/03/002511 (2012) India	CQ versus TFQ (different dosages)
P. knowlesi trial of artesunate-mefloquine versus chloroquine (ACT KNOW)	NCT01708876 (2012)	AS + MQ versus CQ
Phase III trial of FDC of arterolane maleate and PQP tablets in patients with acute uncomplicated *P. vivax* malaria	CTRI/2011/11/002129 (2011) India	CQ versus arterolane maleate
A clinical trial to study the activity RPM 02/08 in patients with *P. vivax* malaria.	CTRI/2010/091/000411 (2010) India	RPM02/08 versus placebo
A comparative study of Artekin with standard malarial treatment regimes in Afghanistan	NCT00682578 (2008) Afghanistan	DHA + PP versus AS + SP, CQ

AL: Artemether-lumefantrine; AS: Artesunate; CQ: Chloroquine; DHA: Dihydroartemisinin; MQ: Mefloquine; PP: Piperaquine; PQ: Primaquine; PYR: Pyronaridine tetraphosphate; TFQ: Tafenoquine.

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

study conducted in Zambia evaluated the safety of AL in women (n = 106) during their first trimester of pregnancy. No particular risks were identified in terms of perinatal morbidity, malformations or developmental impairment in women exposed to AL [150]. This study confirmed findings of an earlier observational study with 62 women exposed to artemisinin derivates [148]. In Tanzania, 319 pregnant women using antimalarials in their first trimester were described in an observational study [151]. Most of them (53.9%) used AL. Quinine showed an increased risk of stillbirth and premature birth as opposed to AL. No significant difference between congenital anomalies was found between the antimalarial drugs (AL, Q, SP, AQ). Globally, 555 first trimester artemisinin derivate exposures are documented in clinical trials with known pregnancy outcomes (**Table 5**). Many more have been reported in population-based surveys [152]. However, the question is whether this number is too small or sufficient enough to draw any significant conclusions on the efficacy and safety of ACTs in first trimester pregnancy malaria treatment. Currently, the WHO recommends quinine plus clindamycin to be given for 7 days for uncomplicated *P. falciparum* malaria (given adequate safety data and low cost) or artesunate plus clindamycin for 7 days if this treatment fails. However, this latter recommendation is pragmatic and based on modest evidence; no randomized clinical trial has compared the efficacy of artesunate in pregnant women in their first trimester of pregnancy. Several trials did show high cure rates of artesunate 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 on self-reported antimalarial drugs showed that almost half of the malaria episodes in the first trimester are treated with ACTs, without obvious disadvantages compared to other antimalarial drugs [152], a survey that is probably a good representation of clinical practice in sub-Saharan Africa. Hitherto, human data suggest that ACTs are safe in the first trimester, so the use of ACTs for the treatment of first trimester malaria in RCTs appears to be justifiable, as obtaining high-quality data from a controlled trial appears to be superior than collecting evidence from retrospective analysis of possibly insufficiently documented anecdotal evidence. So far, women in their first trimester of pregnancy remain excluded.

Primaquine is contraindicated in pregnancy as it can cause a hemolytic anemia in persons with G6PD deficiency, and with the G6PD status of the unborn child naturally remaining unknown. Consequently, pregnant women should receive a treatment of chloroquine (if chloroquine sensitive) or another drug as described above, and then continue once weekly with chloroquine until after delivery, when primaquine can be given 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**).

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 [143] 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 [20]. 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 derivates, alone or in combination with 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], Uganda [158]. 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

Table 5. Clinical studies in 1997 – 2013 on treatment of malaria in pregnancy.

Source (first author, year of publication, journal) (PubMed ID)	Country (study site), time frame	Study design	Number of pregnant women with malaria, *Plasmodium* spp.	Trimester	Antimalarial(s) tested	Measure of (primary) outcome	Findings
Mosha *et al.* (2014) [151]	Tanzania 2012 – 2013	Prospective observational cohort study	n = 1783 n = use of antimalarial 1 trimester n = 172 (AL) n = 78 (Quinine) n = 66 (SP) n = 11 (AQ)	1	AL, Q, SP, AQ	Miscarriage, stillbirth, premature death, congenital anomalies	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%])
McGready *et al.* (2012)* [146]	Thailand 1986 – 2000	Population-based retrospective study	n = 17,613 n = 44 (exposure to ACTs) Infection with *P. falciparum* and/or *P. vivax*	1	Q, CQ (for *P. vivax*) AS, MQ	Outcome of pregnancy of malaria in first trimester + outcome after Rx	16,668 (95%) had no malaria during pregnancy and 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 *P. falciparum* and *P. vivax*. 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)

First trimester: first 12 weeks, second trimester: weeks 13 – 28, third trimester 28-delivery.

*Part of data of in McGready 2002 and McGready 2001.

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 5. Clinical studies in 1997 – 2013 on treatment of malaria in pregnancy (continued).

Source (first author, year of publication, journal) (PubMed ID)	Country (study site), time frame	Study design	Number of pregnant women with malaria, *Plasmodium* spp.	Trimester	Antimalarial(s) tested	Measure of (primary) outcome	Findings
Manyando *et al.* (2010) [150]	Zambia 2004 – 2008	Prospective cohort study	n = 1001 n = 106 exposed to artemisinin derivates	1	AL (n = 495), SP (n = 506)	Incidence of perinatal mortality; gestational age at delivery and birth weight	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
Adam *et al.* (2009) [148]	Sudan 2006 – 2008	Prospective observational study	n = 62 Uncomplicated *P. falciparum* malaria	1	A (n = 48), AS + SP (n = 11) and AL (n = 3)	Pregnancy outcome, malformations	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)
McGready *et al.* (2002) [214]	Thailand 1995 – 2000	Prospective treatment clinical trial	n = 300 Uncomplicated *P. falciparum* and *P. vivax* malaria	1	Q (for *P. falciparum*) (n = 246) + CQ (for *P. vivax*) (n = 130)	Day 28 parasite reappearance rate	28 days parasite reappearance rate following Q was 28.7% (60/209) for primary treatments and 44% (11/25) for re-treatments.

First trimester: first 12 weeks, second trimester: weeks 13 – 28, third trimester 28-delivery.

*Part of data of in McGready 2002 and McGready 2001.

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Table 5. Clinical studies in 1997 – 2013 on treatment of malaria in pregnancy (continued).

Source (first author, year of publication, journal) (PubMed ID)	Country (study site), time frame	Study design	Number of pregnant women with malaria, *Plasmodium* spp.	Trimester	Antimalarial(s) tested	Measure of (primary) outcome	Findings
							For *P. vivax*, 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 LWB
McGready *et al.* (2001) [145]	Thailand 1992 – 2000	Prospective treatment clinical trial	n = 461 n = 42 (first trimester artemisinin derivates) Uncomplicated *P. falciparum* malaria	1, 2 and 3	AS (n = 528) or A (n = 11) 57.5% (n = 310) received earlier Q or MQ	Artemisinin failure rate	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; P0.004). 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
Deen *et al.* (2001) [149]	The Gambia 1999	Observational study	n = 287 (+172 nonexposed women) n = 77 exposed to ACTs Uncomplicated *P. falciparum*	1, 2 and 3	AS + SP	Pregnancy outcomes, congenital malformations	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

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Tarning *et al.* (2012) [215]	Thailand Date: NR	Pharmacokinetic and -dynamic study	n = 27 Uncomplicated *P. falciparum* malaria	2 and 3	AQ	Plasma conc. Recurrent infections	Amodiaquine treatment ↓ the risk of recurrent infections from 22.2 to 7.4% at day 35. No dose adjustments are required in pregnancy
Tarning *et al.* (2012) [174]	Thailand Date: NR	Pharmacokinetics study	n = 48 (24 pregnant and 24 matched nonpregnant) Uncomplicated *P. falciparum* malaria	2 and 3	DHA and PQ	Pharmacokinetics parameters	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
Rulisa *et al.* (2012) [163]	Rwanda 2007 – 2009	Pharmacovigilance study with matched nonexposed control group	n = 1072 (controls; without malaria, no exposition AL n = 978) Uncomplicated *P. falciparum* malaria	2 and 3	AL	Pregnancy outcomes, congenital malformations and AE	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)

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Muehlenbachs *et al.* (2012) [216]	Uganda 2006 – 2009	Prospective study (efficacy data published earlier by Piola 2010)	n = 304; AL: n = 97, Q = 98 placental biopsies	2 and 3	AL versus Q	Placental Hz by histology. Clearance curves Hz	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
Tarning *et al.* (2012) [164]	Uganda 2008	Pharmacokinetics study	n = 21 Uncomplicated *P. falciparum* malaria	2 and 3	A and DHA	Plasma concentrations of the drug after last dose	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
Adam *et al.* (2012) [217]	Sudan 2007 – 2008	Pharmacokinetics study	n = 12 (+12 controls nonpregnant) uncomplicated *P. falciparum* malaria	2 and 3	PQ	Plasma drug concentration	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
Sangare *et al.* (2011) [152]	Uganda 2008 – 2009	Population-based survey on self-reported antimalarial drugs	n = 334	1, 2 and 3	AL, Q and others	Self-reported use of anti-malaria drugs	First trimester (n = 126 episodes): Q: 5.6%; AL: 42.1%; SP: 23% SP + CQ 4.8% (other: 24.5%).

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							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
Rijken *et al.* (2011) [173]	Thailand 2008	Pharmacokinetics study	n = 25 (+24 controls nonpregnant). Uncomplicated *P. falciparum*	2 and 3	DHA + PQ	Plasma drug concentration	There are no clinically important differences in the pharmacokinetics of DHA or PQ between pregnant and nonpregnant women
Rijken *et al.* (2011) [165]	Thailand 2007 – 2008	Pharmacokinetics study	n = 24 Uncomplicated *P. vivax* malaria	2 and 3	AQ (n = 24)	Plasma concentrations	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
Morris *et al.* (2011) [218]	Democratic Republic of Congo Date: NR	Population pharmacokinetics study	n = 26 n = 25 controls (nonpregnant) Uncomplicated *P. falciparum*	2 and 3	AS and DHA	Pharmacokinetic and variability parameters	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

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Piola *et al.* (2010) [159]	Uganda 2006 – 2009	OL, NIT, RCT	n = 304 Uncomplicated *P. falciparum* malaria	2 and 3	AL (n = 152) compared to Q (n = 152)	Cure rate at day 42 (PCR-confirmed)	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
Nyunt *et al.* (2010) [219]	Zambia, Sudan,Mali, Mozambique Date: NR	Pharmacokinetics study	n = 98 Uncomplicated *P. falciparum* malaria	2 and 3	SP (n = 98)	Plasma concentrations	SP pharmacokinetic parameters differed significantly among the study sites and due to this inconsistency no recommendations could be made for any dose adjustments
Karunajeewa *et al.* (2010) [220]	Papua New Guinea 2006	Pharmacokinetics study	n = 30 Uncomplicated *P. falciparum* malaria	2 and 3	CQ (n = 30)	Plasma concentrations	Pregnant subjects had significantly lower area under the plasma concentration-time curve for both CQ (35,750 vs 47,892 μg h/liter, $p < 0.001$) and desethylchloroquine (23,073 vs 41, 584 μg h/liter, $p < 0.001$), reflecting significant differences in elimination half-lives and in volumes of distribution and clearances relative to bioavailability

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Tarning *et al.* (2009) [221]	Thailand 2009	Pharmacokinetics study	n = 103 Uncomplicated *P. falciparum* malaria	2 and 3	Lumefantrine in AL	Plasma concentration and treatment failure rate	Day 7, 40% (n = 41/103) plasma concentrations of < 355 ng/ml (which corresponds to approximately < 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)
Mutabingwa *et al.* (2009) [153]	Tanzania 2004 – 2006	RCT with 4 regimes	n = 272 Non-severe *P. falciparum* malaria	2 and 3	SP (n = 28) CD(n = 81) SP + AQ (n = 80) AQ + AS (n = 83)	Parasitological failure by day 28	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
McGready *et al.* (2008) [154]	Thailand 2004 – 2006	OL-RCT	n = 252 Uncomplicated *P. falciparum* malaria	2 and 3	AL (n = 125) AS (n = 128)	PCR-adjusted cure rates assessed at delivery or by day 42	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)

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Kaye *et al.* (2008) [158]	Uganda 2006	OL-RCT	n = 114	2 and 3	AL (n = 49) CD (n = 49)	Clinical and parasitological response assessed on days 0, 1, 2, 4, 7, 14 and 28	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
Kalilani *et al.* (2007) [155]	Malawi 2003 – 2004	Pilot, OL-RCT with three treatment groups	n = 141 with uncomplicated *P. falciparum* malaria	2 and 3	SP (n = 47) SP + AZ (n = 47) SP + AS (n = 47)	Incidence of AO, PCT, FCT and RR	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. Recrudescent 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

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Tagbor *et al.* (2006) [166]	Ghana 2003 – 2004	RCT with four treatment groups	n = 900 *P. falciparum* infection	2 and 3	CQ (n = 225) SP (n = 225) AQ (n = 225) AQ + SP (n = 225)	PCR-corrected parasitological failure by day 28	Day 28 parasitological failure: 14% CQ, 11% SP, 3% AQ, 0% AQ + SP ($p < 0.0001$)
Mcgready *et al.* (2006) [157]	Thailand 2004	Pharmacokinetics	n = 13 Uncomplicated *P. falciparum* malaria	2 and 3	AL (n = 13)	Plasma concentrations	Pregnancy is associated with reduced plasma concentrations of both artemether and lumefantrine
Mcgready *et al.* (2006) [223]	Thailand 2000 – 2001	Pharmacokinetics study	n = 24 Uncomplicated *P. falciparum* malaria	2 and 3	DHA following AS	Plasma concentrations	The kinetics of DHA are modified by pregnancy. The plasma levels of the active antimalarial metabolite DHA are lower than reported in nonpregnant adults
Na-Bangchang *et al.* (2005) [222]	Thailand, Zambia 2000 –2001	Pharmacokinetics and dynamics	n = 26 with uncomplicated *P. falciparum* malaria	3	AP	Clinical and parasitological efficacy by day 28; pharmacokinetics	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
McGready *et al.* (2005) [168]	Thailand 2001 –2003	OL-RCT	n = 81 with uncomplicated *P. falciparum* malaria	2 and 3	A + AP (n = 39) Q (n = 42) (7 days)	Day 63 cumulative cure rate	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

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							newborns or in growth and developmental parameters of infants monitored for 1 year
Adam *et al.* (2004) [169]	Sudan 1998 – 2001	Prospective non-comparative clinical trial	n = 40 Uncomplicated *P. falciparum* malaria	2 and 3	MQ	Clinical efficacy, adverse effects	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
McGready *et al.* (2003) [161]	Thailand 1999 – 2001	OT	n = 27 Uncomplicated *P. falciparum* malaria	2 and 3	A + AP	Day 42 cure rate	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
McGready *et al.* (2001) [167]	Thailand 1997 – 2000	RCT	n = 129 Acute uncomplicated *P. falciparum* malaria	2 and 3	QC (n = 65) AS (n = 64)	Day 42 cure rate	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 ($p < 0.01$)

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McGready *et al.* (2000) [170]	Thailand 1995 – 1997	RCT	n = 108 Uncomplicated *P. falciparum* malaria	2 and 3	MQ + AS (n = 65) Q (n = 41)	Day 63 cure rates	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 < 0.001). MQ + AS was significantly better tolerated
Sowunmi *et al.* (1998) [171]	Nigeria 1994 – 1997	RCT	n = 45 Uncomplicated *P. falciparum* malaria	2 and 3	A (n = 23) A + MQ (n = 22)	Day 14 and 28 cure rates, parasite and fever clearance time	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

First trimester: first 12 weeks, second trimester: weeks 13 – 28, third trimester 28-delivery.

*Part of data of in McGready 2002 and McGready 2001.

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 6. Ongoing trials on malaria treatment in pregnant women registered online in clinical trial registries (date of last search: June 2014).

Name of study	Registration ID (year) country, status as of March 2014	Antimalarial(s) tested
Comparison of two regimens of artemether-lumefantrine for the treatment of malaria in pregnancy (ALN5P)	NCT01916954 (2013) Democratic Republic of Congo	AL (3 days) versus AL (5 days)
Antimalarial pharmacology in children and pregnant women in Uganda	NCT01717885 (2012) Uganda	AL in combination with anti-HIV Rx
Efficacy, safety and tolerability of dihydroartemisinin-piperaquine for uncomplicated malaria in pregnancy in Ghana: an open-label, randomized controlled, non-inferiority trial	NCT01231113 (2010) Ghana	Drug: AS + AQ versus DHA + PQ
Comparison of the safety, efficacy and tolerability of artemether-lumefantrine and artesunate amodiaquine in Nigerian pregnant women with acute uncomplicated falciparum malaria	PACTR2010020001862624 (2010) Nigeria	AS + AQ versus AL
Randomized trial of three artemisinin combination therapy for malaria in pregnancy (DMA)	NCT01054248 (2010) Thailand	AS + MQ, AL, DHA + PQ
Safe and efficacious artemisinin-based combination treatments for African pregnant women with malaria (PREGACT)	NCT00852423 (2009) Burkina Faso, Ghana, Malawi and Zambia	DHA + PQ, AS + MQ, AS + AQ, AL
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	CTRI/2009/091/001055 (2008) India	AS + MQ versus AS + SP
Pharmacokinetic of mefloquine-artesunate in *Plasmodium falciparum* malaria infection in pregnancy	NCT00701961 (2008) Burkina Faso	AS + MQ
Study of pharmacokinetics and pharmacodynamics of artesunate in pregnant women in the Democratic Republic of Congo	NCT00538382 (2007) Democratic Republic of Congo	AS

AL: Artemether-lumefantrine; AQ: Amodiaquine; AS: Artesunate; DHA: Dihydroartemisinin; MQ: Mefloquine; PQ: Piperaquine; SP: Sulfadoxine-pyrimethamine.

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 [163]. 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 9% 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 [166]. 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 (PACTR20100 20001862624 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 artesunate-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 hypoglycemia 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 advised to not combine mefloquine with other potentially neurotoxic agents such as the artemisinin antimalarials [172]. That notwithstanding, a pharmacokinetic Phase II/III study investigating the combination mefloquine with artesunate in Burkina Faso is underway (NCT00701961).

DHA-PIP was highly effective in women with uncomplicated *P. falciparum* malaria in Thailand [173,174]. However, all published studies evaluating DHA plus PIP are pharmacokinetic studies, and the first RCTs from both African and Asia are conducted at the time of writing (Phase III: NCT012 31113 and NCT00852423). In conclusion, the current recommended treatment for malaria in the second or third trimester of pregnancy is a locally effective ACT (AL, artesunate-amodiaquine, artesunate-mefloquine, artesunate-sulfadoxine-pyrimethamine), but do not (yet) include DHA plus PIP due to the lack of data. For the women who breastfeed, standard antimalarial treatment for adults (including ACTs) is recommended, except for dapsone, primaquine and tetracyclines [20].

8. Treatment of malaria in children

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-piperaquine 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) [39,183,186-196], 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 ACTs, 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 comparably 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 countries 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 derivates 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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Supplementary materials available online

Appendix 1