Advances and roadblocks in the Treatment of Malaria

Nicholas White[1] and Borimas Hanboonkunupakarn[2]

[1]Faculty of Tropical Medicine, Mahidol Iniversity
[2]Mahidol University

April 28, 2020

Abstract

The deployment of artesunate for severe malaria and the artemisinin combination therapies (ACTs) for uncomplicated malaria has been a major advance in antimalarial therapeutics. These drugs have reduced treated mortality, accelerated recovery, and reduced treatment failure rates and transmission from the treated infection. These drugs remain highly effective against falciparum malaria in most malaria endemic areas but significant resistance has emerged in the Greater Mekong subregion of Southeast Asia. Resistance to artemisinin was followed by resistance in the ACT partner drugs, and fit multidrug resistant parasite lineages have now spread widely across the region. ACTs are highly effective against P. vivax and the other malaria species. Recent studies show that radical curative regimens of primaquine (to prevent relapse) can be shortened to seven days, and that the newly introduced single dose tafenoquine is an alternative, although the currently recommended dose is insufficient in Southeast Asia and Oceania. Targeted malaria elimination using focal mass treatments with dihydroartemisinin-piperaquine have proved safe and effective malaria elimination accelerators, but progress overall towards malaria elimination is very slow. Indeed since 2015 overall malaria case numbers globally have risen.

Advances and Roadblocks in the Treatment of Malaria

Borimas Hanboonkunupakarn [1]

Nicholas J White* [1,2]

1. Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
2. Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, Oxford University, United Kingdom.

Correspondence: nickw@tropmedres.ac

Summary

The deployment of artesunate for severe malaria and the artemisinin combination therapies (ACTs) for uncomplicated malaria has been a major advance in antimalarial therapeutics. These drugs have reduced treated mortality, accelerated recovery, and reduced treatment failure rates and transmission from the treated infection. These drugs remain highly effective against falciparum malaria in most malaria endemic areas but significant resistance has emerged in the Greater Mekong subregion of Southeast Asia. Resistance to artemisinin was followed by resistance in the ACT partner drugs, and fit multidrug resistant parasite lineages have now spread widely across the region. ACTs are highly effective against *P. vivax* and the other malaria species. Recent studies show that radical curative regimens of primaquine (to prevent relapse) can be shortened to seven days, and that the newly introduced single dose tafenoquine is an alternative, although the currently recommended dose is insufficient in Southeast Asia and Oceania. Targeted malaria elimination using focal mass treatments with dihydroartemisinin-piperaquine have proved safe and effective

malaria elimination accelerators, but progress overall towards malaria elimination is very slow. Indeed since 2015 overall malaria case numbers globally have risen.

Keywords : malaria, antimalarial drugs, artemisinin, resistance

Introduction

The treatment of malaria has improved substantially in the past 15 years, and morbidity and mortality have declined as a result, but significant challenges lie ahead (1). The major advance in antimalarial therapeutics has been the deployment of drugs derived from artemisinin (qinghaosu) (2). This unusual compound (a sesquiterpene lactone peroxide) is derived from the leaves of the plant *Artemesia annua.* The derivatives of artemisinin; dihydroartemisinin (DHA), artesunate and artemether now form the cornerstone of current antimalarial treatment. They are the most rapidly acting of available antimalarial drugs and they are very well tolerated, but resistance has now emerged in Southeast Asia and it has spread, and there are worrying early reports from other regions. These drugs are partnered in fixed-dose combinations (artemisinin combination therapies) with more slowly eliminated antimalarial drugs for the treatment of uncomplicated malaria. New antimalarial drugs are on the horizon, but they are unlikely to become generally available within the next few years, so current treatments must rely upon the artemisinin derivatives. This review presents some of the recent advances in antimalarial therapeutics and some of the obstacles to progress in controlling and eliminating malaria.

Advance 1: Improvements in the treatment of severe malaria

In the two largest randomized controlled trials conducted in patients hospitalised with severe falciparum malaria artesunate was shown to reduce mortality substantially. The mortality reduction (95% confidence interval) was 34.7% (18·5 to 47·6%) in Southeast Asian adults and children and 22.5% (8·1 to 36·9%) in African children (3,4) (Figure 1). In African children it can be difficult to distinguish severe malaria from bacterial sepsis with incidental parasitaemia. In those children with a high likelihood of having severe malaria based on parasite biomass estimation the reduction in mortality was the same (i.e. one third) as observed in the Asian series (5). Artesunate was also better tolerated (less hypoglycaemia) and easier to administer (intravenous injection rather than controlled rate infusion, and no pain and local toxicity following intramuscular injection) than the previous "gold-standard" treatment quinine. Importantly there were also less neurological sequelae in the survivors so lives were not saved at the expense of neurological deficits. Artemether is nearly as active as artesunate *in-vitro* against *P. falciparum* but, being an oil-based intramuscular injection, is slowly and erratically absorbed from the intramuscular injection site in-vivo (particularly in shocked patients) (6). In contrast the water soluble artesunate is rapidly and reliably absorbed. This probably explains why the severe malaria mortality following artemether is higher than that following artesunate treatment (7,8). Community based pre-referral rectal artesunate was also shown to reduce malaria attributable mortality by 25% in children unable to take oral antimalarial medications (9) Since these trials reported artesunate has become the generally recommended first line treatment for severe malaria (1) and usage has increased substantially, although unfortunately quinine is still the only available parenteral antimalarial in some malaria endemic areas.

Following drug administration the DHA derivatives are rapidly and reliably converted back to DHA in-vivo which is then very rapidly eliminated ($t_{1/2} < 1$ hour) mainly by glucuronidation (10), yet they are highly efficacious when given once daily (11). The main pathological process in severe falciparum malaria is the sequestration of erythrocytes containing mature forms of the parasite in the vascular beds of vital organs (5,12). This reduces microcirculatory blood flow and probably markedly disturbs endothelial function. The key pharmacodynamic effect of the artemisinin derivatives, which mediates the life-saving advantage over quinine, is their action in killing the younger circulating stages of *P. falciparum* before they sequester (12). Unfortunately, this property is reduced markedly in artemisinin resistance.

Apart from the prompt initiation of renal replacement therapies (preferably haemofiltration) in acute kidney injury (12,13), no adjuvant therapies have proved beneficial and many (including aspirin, corticosteroids, heparin, mannitol, high dose phenobarbitone, anti-TNF antibody and rapid fluid loading) were found to be

harmful in severe malaria (12,14).

Advance 2: **Better treatments for uncomplicated falciparum malaria**

The main advance in the treatment of falciparum malaria has been the replacement of the failing monotherapies chloroquine and sulfadoxine-pyrimethamine by artemisinin combination therapies (ACTs) (1). These three-day regimens combine an artemisinin derivative with a more slowly eliminated partner drug (Figure 2A). Four ACTs were recommended originally; artesunate combined with sulfadoxine-pyrimethamine (SP), amodiaquine or mefloquine, and artemether combined with lumefantrine. More recently dihydroartemisinin-piperaquine and artesunate-pyronaridine have been introduced (1,15). All except artesunate-SP are available in combined formulations and all but artemether-lumefantrine are taken once daily. These drugs are all rapidly effective and generally well tolerated (1, 10, 16). Early concerns over potential neurotoxicity and teratogenicity have receded with increasing evidence of safety (12). Worries over piperaquine cardiotoxicity (QT prolongation - risk of Torsade de Pointes) have also declined with large meta-analyses showing no increase in the rate of sudden death (17). ACTs are now recommended as first line treatment for all patients with falciparum malaria, including in pregnancy (1). Costs have been reduced, and generics developed. Hundreds of millions of treatments are dispensed annually.

The main current concern is ensuring access to diagnosis and effective treatment and emerging resistance in *Plasmodium falciparum* to the artemisinin derivatives. Artemisinin resistance manifests as slowing of parasite clearance because of reduced ring stage (the younger asexual forms) parasite susceptibility (18). The discovery of a parasite molecular marker, mutations in the propeller region of the kelch gene on chromosome 13, has greatly facilitated characterization and epidemiological assessments. (19, 20) Reduced parasite killing in artemisinin resistant malaria infections places greater selective "pressure" on the ACT partner drug, This is because the number of parasites which remain after the artemisinin component in an ACT has been eliminated is many orders of magnitude greater - and the probability of selecting resistant mutants is correspondingly higher (Figure 2A). Indeed ACT partner drug resistance has followed artemisinin resistance in the Greater Mekong subregion of Southeast Asia (21-24). Fortunately artemisinin resistant *P. falciparum* are still largely confined to this one region (25), although there are increasing reports that clusters of kelch mutant parasites have been identified elsewhere (27,27). One potential solution is to deploy triple artemisinin combination treatments (TACTs) which combine an artemisinin derivative with two slowly eliminated antimalarials (23). This solves the pharmacokinetic mismatch whereby the rapidly eliminated artemisinin component leaves the slowly eliminated partner drug "unprotected" for days or weeks after the second post-treatment asexual parasite cycle (i.e. >3 days after starting the ACT). With TACTs there are now two slowly eliminated partner drugs providing mutual protection against the selection of resistance (Figure 2B). The two TACTs under current development artemether-lumefantrine -amodiaquine and dihydroartemisinin-piperaquine-mefloquine exploit reciprocal susceptibilities whereby resistance to one of the slowly eliminated components is associated with increased susceptibility to the other. In large scale trials TACTs have proved well tolerated, safe and highly effective (24).

Advance 3: **Chemoprevention in malaria endemic areas**

For many years pregnant women living in a malaria endemic region were advised to take chloroquine chemoprophylaxis to reduce the adverse effects of falciparum malaria on the developing foetus (mainly low birthweight), but as chloroquine resistance worsened chemoprophylaxis was replaced by intermittent presumptive treatment with sulphadoxine-pyrimethamine (IPT-SP) (1). This involves giving full treatment doses at intervals. Although preventive efficacy is much greater than treatment efficacy against resistant *P. falciparum* , IPT-SP is threatened by worsening resistance – both to the antifol and the sulphonamide components (28). There is increasing evidence that dihydroartemisinin-piperaquine (DP) provides excellent antimalarial chemoprevention for approximately one month, is well tolerated, and appears safe in pregnancy (29, 30). IPT is imperfect chemoprophylaxis. In order to provide continuous suppressive prophylaxis DP needs to be given at least monthly, and preferably weekly (31). The IPT-SP concept has also been advocated in infants, where treatment doses of SP are to be given together with the routine EPI vaccines at the ages of 2, 3 and 9 months. This is not widely practiced as the benefits are relatively small, and SP resistance is

widespread. A more effective strategy, which is now implemented widely across the Sahel region of Africa (where there is intense malaria transmission largely confined to the 3-4 month rainy season), is seasonal malaria chemoprevention (SMC) with monthly administration of treatment doses of amodiaquine together with SP to all children aged between 6 and 59 months (1, 32). SMC prevents symptomatic reinfection and substantially reduces the malaria burden. Adding azithromycin to amodiaquine and SP provides no additional benefit (33). Resistance to both components of SMC is widespread in East Africa but whether resistance is impacting on the chemoprophylactic activity of SMC is uncertain currently – more information is needed on this critical point to guide policy.

Advances 4: Mass treatment as a malaria elimination accelerator

Where malaria transmission is low the prospects for elimination increase. In the Greater Mekong subregion (GMS), which harbours the most drug resistant *P. falciparum* in the world, there is a general consensus that the only way to counter multi-drug resistance effectively is to eliminate all falciparum malaria. This is an area of low seasonal malaria transmission and targeted malaria elimination, even in the most remote and inaccessible areas, has been very effective (34, 35). The key to successful elimination is the support of village health workers in every village (usually 300-800 people) to provide diagnosis of malaria with a rapid diagnostic test, and treatment with an effective ACT (36). In foci of higher transmission (sometimes called "hot spots'), where a significant proportion of the healthy population have asymptomatic parasitaemias, mass treatments with dihydroartemisinin-piperaquine have proved very effective and well tolerated "accelerators" of elimination (34,35).

Obstacles 1: The emergence and spread of antimalarial drug resistance

There is resistance in *Plasmodium falciparum* to all currently used antimalarial drugs but there is substantial variation in the geographic distribution and degree of reduced susuceptibility. The most resistant parasites are found in the eastern greater Mekong subregion of Southeast Asia. Multidrug resistant *P. falciparum* is also prevalent in parts of South America. In general *P.falciparum* in Africa is more sensitive with higher levels of resistance in East compared with West Africa (37). Resistance is generally less in the other malarias although antifol resistance in *P.vivax* is widespread and chloroquine resistance in *P. vivax* is found throughout Indonesia and Papua New Guinea (38). Antifol resistance in both *P.falciparum* and *P.vivax* results from stepwise accumulation of mutations in the *dhfr* gene encoding the drug target dihydrofolate reductase , (S108N, N51I, C59R) and sulphonamide resistance results from accumulation of mutations in the *dhps*gene encoding the drug target dihydropteroate synthase (A437G,K540E, A581G). In general, the more of these mutations there are more resistant is the *P. falciparum* infection (39). The highest level of antifol resistance is conferred by the *Pfdhfr* I164L mutation (found in Southeast Asia and South America). This renders parasites completely resistant to pyrimethamine. Resistance to chloroquine and the structurally related antimalarials which interfere with haem detoxification results from mutations in the transporter *Pfcrt* , and to a lesser extent mutations in *Pfmdr* (notably N86Y, N1042D, S1034C, and D1246Y). Positions 72 to 76 are mutated in the *Pfcrt*of most *P. falciparum* (causing 4-aminoquinoline resistance) with K76T being consistently mutant in the five major haplotypes (CVIET, SVMNT, SVIET, CVMNT and CVTNT) (39). Recently downstream mutations from the chloroquine resistance locus have been strongly associated with piperaquine resistance (23,39). Copy number increase in wild type*Pfmdr* is the main identified genetic association with mefloquine and lumefantrine resistance (22). Atovaquone resistance arises readily as a result of mutations in the mitochondrial multicopy cytochrome b gene (usually at position 268; Y268S or Y268N).

From a therapeutic perspective high level resistance precludes use of chloroquine and sulphadoxine-pyrimethamine alone in most areas (1). Amodiaquine alone is also not sufficiently efficacious in many parts of the tropics but still contributes significantly to efficacy in combinations - and artesunate-amodiaquine remains efficacious in Central and West Africa. Significant resistance to mefloquine and piperaquine is prevalent only in the Greater Mekong subregion (GMS) of Southeast Asia. Fortunately in these areas artemether-lumefantrine and artesunate-pyronaridine currently remain highly effective (24, 40). It is an ominous precedent that the eastern GMS is the same area from which resistance to chloroquine and sulphadoxine-pyrimethamine arose and then spread to India and Africa (at a cost of millions of lives), and it is where resistance to the artemisinin

drugs has arisen first.

Obstacles 2: Artemisinin resistance

Artemisinin resistance was found first near the Thailand-Cambodia border. It manifests by slowing of parasite clearance which reflects reduced "ring stage" killing (1). In falciparum malaria the young ring stage parasites in the first third of the 48 hour asexual life cycle circulate in the blood stream before the infected erythrocytes adhere to vascular endothelium (cytoadherence) – a process called sequestration. This does not occur to a significant extent with the other human malarias. Sequestration is considered central to the potentially lethal pathology of falciparum malaria, and the life saving benefit of the artemisinin derivatives (Figure 1) results from reducing sequestration by killing the ring stage parasites (12). The pharmacodynamic effect is best measured in-vivo from the log-linear decline in parasite densities which follows a variable lag phase. The slope provides the parasite clearance rate and thus a half-life. Parasite clearance half-lives over 5 hours are generally associated with artemisinin resistance (18,20) (Figure 3). When artemisinin resistance was recognised first it was observed there were multiple independent mutations in the *Pf* kelch gene propeller region but in recent years successful artemisinin resistant parasite lineages have outcompeted the other parasites and spread across large areas (37). In the Eastern GMS a parasite lineage bearing the C580Y mutation has predominated, whereas in Myanmar a lineage bearing the F446I mutation has spread over large distances (41, 42) (Figure 4). The F446I mutation confers a lower degree of resistance (in terms of parasite clearance) than many of the other propeller mutants. This may reflect a lesser fitness cost and thus greater competitive advantage in areas of higher transmission. These artemisinin resistant parasites have then acquired resistance to the ACT partner drugs -piperaquine (in the Eastern GMS) and mefloquine (along the Thailand-Myanmar border). This has resulted in increasing rates of ACT failure (21-23) forcing Governments to change their first-line treatment policies. There is serious concern that these resistant parasites could spread westward, or that artemisinin resistance could emerge de-novo elsewhere, and derail global aspirations to control and eliminate malaria.

Obstacles 3: Underuse of primaquine

Primaquine is a very important antimalarial as both a single dose gametocytocide in falciparum malaria, and in multiple dose "radical cure" regimens to prevent relapse in vivax and ovale malaria (1), but it is underused. This is because of concerns over haemolytic toxicity in glucose-6-phosphate dehydrogenase (G6PD) deficiency (43). Gene frequencies for X-linked G6PD deficiency average 8-10% in tropical areas (although prevalences are lower in vivax malaria), but screening tests to identify G6PD deficient patients are not widely available. Relapses are recurrences of malaria which follow complete cure of the blood stage infection. They derive from dormant parasite forms (hypnozoites) which persist in the liver. Hypnozoites are resistant to all current antimalarial drugs except the 8-aminoquinolines (8-AQ) (1). Without radical cure relapse rates vary between 20% and 80%. Relapse is a major cause of morbidity and mortality in higher transmission settings (44). Primaquine has usually been given in 7 or 14 day "radical cure" courses. As these cause predictable haemolysis in G6PD deficient patients, G6PD testing is recommended (1,43). The recent development of rapid screening tests is a significant advance which should enable wider safe use of primaquine for radical cure, and thereby make elimination a more achievable target. Recent very large studies confirm that the treatment courses even for the higher dose primaquine regimens (total 7mg/kg) can be condensed into a one week course. With G6PD testing to exclude deficient patients these are well tolerated , and if these adhered to, radical curative efficacy is very high (>95%) (45, 46).

Until recently primaquine was used in a single 0.75mg base/kg dose (45mg adult dose) as a *P. falciparum* gametocytocide to reduce transmissibility of the treated infection. This was given in addition to the standard three day ACT for treatment. Re-evaluation of the transmission blocking dose-response relationship for primaquine indicates that the same gametocytocidal effect is obtained with a dose three times lower (0.25mg base/kg) with obviously less haemolytic risk. This obviates the need for G6PD testing- so this has now become the recommended dose (1,47).

Obstacle 4: Medicine quality

Poor medicine quality is often ignored in discussions of disease control but the problem is massive, and it affects particularly the antimalarial drugs. In many countries the private sector is main source of antimalarials and there is weak regulation of pharmaceuticals (48). A recent systematic review and meta-analysis estimated that 12·4% of antibiotics and 19·1% of antimalarials in low-income and middle-income countries were substandard or falsified, with an estimated economic impact ranging from US$10 billion to $200 billion (49).

Obstacles 5: Political roadblocks and funding gaps

Discussion of roadblocks would be incomplete without considering the political dimension. Although malaria has a reasonable global profile in comparison with the "neglected tropical diseases" it is often low in National Health priorities, particularly in Asia and the Americas where it is predominantly a disease of the poor or marginalized. Much of the funding for malaria control comes from International Agencies such as the Global Fund to fight AIDS, TB and Malaria (GFATM) and the President's Malaria Initiative (PMI) or from bilateral donors. Whereas the world was doing very well in reducing malaria morbidity and mortality in the decade between 2005 and 2015, the total number of malaria cases has increased steadily since then (50). There has been no in-depth analysis to explain this reversal, and no clear evidence that providing more funding without reforms will reverse this trend.

Advances 5: Tafenoquine

For over 60 years primaquine has been the only widely available drug in the 8-aminoquinoline class. In the past year, after a long and difficult gestation, the slowly eliminated 8-AQ tafenoquine was registered and launched. Tafenoquine is a well tolerated single dose treatment which solves the problem of potentially poor adherence (51,52). Like the other 8-aminoquinolines tafenoquine also causes oxidant haemolysis in G6PD deficiency. However the rapidly eliminated primaquine can be stopped in case of haemolysis in a G6PD deficient patient, thereby limiting the consequent anaemia – whereas tafenoquine continues to cause haemolysis for weeks. Thus tafenoquine has the advantage of simplicity and reliability of dosing, but at the expense of an increased risk of serious haemolysis. Currently available rapid screening tests identify individuals who have 30-40% of normal erythrocyte G6PD activity which identifies all male hemizygotes and female homozygotes, but they do not identify the majority of female heterozygotes (whose blood contains a mixture of G6PD deficient and normal erythrocytes). Safe use of tafenoquine therefore requires development and deployment of simple quantitative G6PD screening tests which can identify individuals with <70% of normal red G6PD activity in blood samples. These are under development, but they are not yet ready for roll out. In East Asia and Oceania relapse is the main cause of vivax illness, a major contributor to morbidity and mortality, and a major obstacle to elimination. The dose of tafenoquine currently recommended (300mg adult dose) is too low for this populous region, where a large proportion of the world's relapses occur. In the pre-registration clinical trials tafenoquine 300mg proved inferior to a sub-optimal dose of primaquine (52) (Figure 5). Unfortunately there are no plans currently to rectify this.

Advances 6: New antimalarials in development

Several new antimalarial drugs are in clinical development (53). These include

1. cipargamin, a spiroindolone compound that is more rapidly acting (in terms of accelerating parasite clearance) than artemisinins. It inhibits PfATPase4.
2. artefenomel, a synthetic peroxide which is more stable and more slowly eliminated arterolane.
3. Ganaplacide, a potent imidazolopiperazine compound with an unknown mode of action;
4. P218, a dihydrofolate reductase inhibitor with preserved activity against prevalent antifol resistant parasites.
5. DSM265, a slowly acting dihydroorotate dehydrogenase inhibitor
6. Ferroquine, an aminoquinoline compound with similarities to chloroquine but activity against chloroquine resistant parasites.
7. MMV390048 is a novel aminopyridine antimalarial compound that inhibits *Plasmodium* phosphatidylinositol-4-kinase (PI4K)

Most of these drugs are in phase 2 testing, and so if some of these compounds do proceed successfully to phase 3 studies and regulatory approval, likely in combinations, and these new combination therapies are well tolerated, effective and affordable they will be a welcome addition to the antimalarial armamentarium. But this is will not happen in the next few years. This means that current antimalarial treatment strategies must make use of the currently available medicines.

References

1. World Health Organisation. Guidelines for the treatment of malaria. 3rd Edition. WHO, Geneva, 2015.
2. A Detailed Chronological Record of Project 523 and the Discovery and Development of Qinghaosu (Artemisinin). ed Zhan JianFang Translation Arnold K, Arnold M. Strategic Book Publishing & Rights Agency, LLC.
3. Dondorp A, Nosten F, Stepniewska K, Day N, White NJ; South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005; **366** : 717–25.
4. Dondorp A M, Fanello CE, Hendriksen ICE, Gomes E, Seni A, Chhaganlal KD, Bojang K, Olaosebikan R, Anunobi N, Maitland K, Kivaya E, Agbenyega T, Nguah SB, Evans J, Gesase S, Kahabuka C, Mtove G, Nadjm B, Deen J, Mwanga-Amumpaire J, Nansumba M, Karema C, Umulisa N, Uwimana A, Mokuolu OA, Adedoyin TO, Johnson WBR, Tshefu AK, Onyamboko MA, Sakulthaew T, Pan-Ngum W, Silamut K, Stepniewska K, Woodrow C, Bethell D, Wills B, Oneko M, Peto T, von Seidlein L, Day NPJ, White NJ, for the AQUAMAT group. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet 2010; **376** : 1647-1657.
5. White NJ, Turner GD, Day NP, Dondorp AM. Lethal malaria: Marchiafava and Bignami were right. J Infect Dis. 2013; 208: 192-8.
6. Hien TT, Davis TM, Chuong LV, Ilett KF, Sinh DX, Phu NH, Agus C, Chiswell GM, White NJ, Farrar J. Comparative pharmacokinetics of intramuscular artesunate and artemether in patients with severe falciparum malaria. Antimicrob Agents Chemother. 2004;48: 4234-9.
7. Artemether-Quinine Meta-analysis Study Group. A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria. Trans R Soc Trop Med Hyg. 2001; 95: 637-50.
8. Phu NH, Tuan PQ, Day N, Mai NT, Chau TT, Chuong LV, Sinh DX, White NJ, Farrar J, Hien TT. Randomized controlled trial of artesunate or artemether in Vietnamese adults with severe falciparum malaria. Malar J 2010; **9** : e97.
9. Gomes MF, Faiz MA, Gyapong JO, Warsame M, Agbenyega T, Babiker A, Baiden F,Yunus EB, Binka F, Clerk C, Folb P, Hassan R, Hossain MA, Kimbute O, Kitua A, Krishna S, Makasi C, Mensah N, Mrango Z, Olliaro P, Peto R, Peto TJ, Rahman MR, Ribeiro I, Samad R, White NJ; Study 13 Research Group. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial.*Lancet* 2009; **373** : 557-66.
10. Sugiarto SR, Davis TME, Salman S. Pharmacokinetic considerations for use of artemisinin-based combination therapies against falciparum malaria in different ethnic populations. Expert Opin Drug Metab Toxicol. 2017; 13: 1115-1133.
11. White NJ, Watson J, Ashley EA. Split dosing of artemisinins does not improve antimalarial therapeutic efficacy. Sci Rep. 2017;7:12132.
12. World Health Organisation. Severe Malaria. Trop Med Int Hlth 2014;**19** (Supplement 1): 1-131.
13. Phu NH, Hien TT, Mai NT, Chau TT, Chuong LV, Loc PP, Winearls C, Farrar J, White N, Day N. Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. N Engl J Med. 2002 Sep 19;347(12):895-902.
14. Maitland K. Severe Malaria in African Children - The Need for Continuing Investment. N Engl J Med. 2016; 375: 2416-2417.
15. West African Network for Clinical Trials of Antimalarial Drugs (WANECAM). Pyronaridine-artesunate or dihydroartemisinin-piperaquine versus current first-line therapies for repeated treatment of uncom-

plicated malaria: a randomised, multicentre, open-label, longitudinal, controlled, phase 3b/4 trial. Lancet. 2018; 391: 1378-1390.
16. Smithuis F, Kyaw MK, Phe O, Win T, Aung PP, Oo AP, Naing AL, Nyo MY, Myint NZ, Imwong M, Ashley E, Lee SJ, White NJ. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. Lancet Infect Dis 2010; **10** : 673-81.
17. Chan XHS, Win YN, Mawer LJ, Tan JY, Brugada J, White NJ. Risk of sudden unexplained death after use of dihydroartemisinin-piperaquine for malaria: a systematic review and Bayesian meta-analysis. Lancet Infect Dis. 2018 Aug;18(8):913-923.
18. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, Lwin KM, Ariey F,Hanpithakpong W, Lee SJ, Ringwald P, Silamut K, Imwong M, Chotivanich K, Lim P, Herdman T, An SS, Yeung S, Singhasivanon P, Day NP, Lindegårdh N, Socheat D, White NJ. Artemisinin resistance in*Plasmodium falciparum* malaria. N Engl J Med 2009; **361** : 455-67.
19. Ariey F, Witkowski B, Amaratunga C, Beghain J, Langlois AC, Khim N, Kim S, Duru V, Bouchier C, Ma L, Lim P, Leang R, Duong S, Sreng S, Suon S, Chuor CM, Bout DM, Ménard S, Rogers WO, Genton B, Fandeur T, Miotto O, Ringwald P, Le Bras J, Berry A, Barale JC, Fairhurst RM, Benoit-Vical F, Mercereau-Puijalon O, Ménard D. A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. Nature. 2014; 505: 50-5.
20. Ashley EA, Dhorda M, Fairhurst RM, Amaratunga C, Lim P, Suon S, Sreng S, Anderson JM, Mao S, Sam B, Sopha C, Chuor CM, Nguon C, Sovannaroth S,Pukrittayakamee S, Jittamala P, Chotivanich K, Chutasmit K, Suchatsoonthorn C, Runcharoen R, Hien TT, Thuy-Nhien NT, Thanh NV, Phu NH, Htut Y, Han KT, Aye KH, Mokuolu OA, Olaosebikan RR, Folaranmi OO, Mayxay M, Khanthavong M, Hongvanthong B, Newton PN, Onyamboko MA, Fanello CI, Tshefu AK, Mishra N, Valecha N, Phyo AP, Nosten F, Yi P, Tripura R, Borrmann S, Bashraheil M, Peshu J, Faiz MA, Ghose A, Hossain MA, Samad R, Rahman MR, Hasan MM, Islam A, Miotto O, Amato R, MacInnis B, Stalker J, Kwiatkowski DP, Bozdech Z, Jeeyapant A, Cheah PY, Sakulthaew T, Chalk J, Intharabut B, Silamut K, Lee SJ, Vihokhern B, Kunasol C, Imwong M, Tarning J, Taylor WJ, Yeung S, Woodrow CJ, Flegg JA, Das D, Smith J, Venkatesan M, Plowe CV, Stepniewska K, Guerin PJ, Dondorp AM, Day NP, White NJ; Tracking Resistance to Artemisinin Collaboration (TRAC). Spread of artemisinin resistance in*Plasmodium falciparum* malaria. N Engl J Med 2014; **371** : 411-23.
21. Amaratunga C, Lim P, Suon S, Sreng S, Mao S, Sopha C, Sam B, Dek D, Try V, Amato R, Blessborn D, Song L, Tullo GS, Fay MP, Anderson JM, Tarning J, Fairhurst RM. Dihydroartemisinin-piperaquine resistance in*Plasmodium falciparum* malaria in Cambodia: a multisite prospective cohort study. Lancet Infect Dis. 2016;16(3):357-65.
22. Phyo AP, Ashley EA, Anderson TJ, Bozdech Z, Carrara VI, Sriprawat K, Nair S, White MM, Dziekan J, Ling C, Proux S, Konghahong K, Jeeyapant A, Woodrow CJ, Imwong M, McGready R, Lwin KM, Day NP, White NJ, Nosten F. Declining efficacy of artemisinin combination therapy against*P. falciparum* malaria on the Thai-Myanmar Border (2003-2013): The role of parasite genetic factors. Clin Infect Dis 2016;**63** : 784-91.
23. van der Pluijm RW, Imwong M, Chau NH, Hoa NT, Thuy-Nhien NT, Thanh NV, Jittamala P, Hanboonkunupakarn B, Chutasmit K, Saelow C, Runjarern R, Kaewmok W, Tripura R, Peto TJ, Yok S, Suon S, Sreng S, Mao S, Oun S, Yen S, Amaratunga C, Lek D, Huy R, Dhorda M, Chotivanich K, Ashley EA, Mukaka M, Waithira N, Cheah PY, Maude RJ, Amato R, Pearson RD, Gonçalves S, Jacob CG, Hamilton WL, Fairhurst RM, Tarning J, Winterberg M, Kwiatkowski DP, Pukrittayakamee S, Hien TT, Day NP, Miotto O, White NJ, Dondorp AM. Determinants of dihydroartemisinin-piperaquine treatment failure in *Plasmodium falciparum* malaria in Cambodia, Thailand, and Vietnam: a prospective clinical, pharmacological, and genetic study. Lancet Infect Dis. 2019;**19** : 952-961.
24. van der Pluijm RW, Tripura R, Hoglund RM, Pyae Phyo A, Lek D, Ul Islam A, Anvikar AR, Satpathi P, Satpathi S, Behera PK, Tripura A, Baidya S, Onyamboko M, Chau NH, Sovann Y, Suon S, Sreng S, Mao S, Oun S, Yen S, Amaratunga C, Chutasmit K, Saelow C, Runcharern R, Kaewmok W, Hoa NT, Thanh NV, Hanboonkunupakarn B, Callery JJ, Mohanty AK, Heaton J, Thant M, Gantait K, Ghosh

T, Amato R, Pearson RD, Jacob CG, Gonçalves S, Mukaka M, Waithira N, Woodrow CJ, Grobusch MP, van Vugt M, Fairhurst RM, Cheah PY, Peto TJ, von Seidlein L, Dhorda M, Maude RJ, Winterberg M, Thuy-Nhien NT, Kwiatkowski DP, Imwong M, Jittamala P, Lin K, Hlaing TM, Chotivanich K, Huy R, Fanello C, Ashley E, Mayxay M, Newton PN, Hien TT, Valecha N, Smithuis F, Pukrittayakamee S, Faiz A, Miotto O, Tarning J, Day NPJ, White NJ, Dondorp AM; Tracking Resistance to Artemisinin Collaboration. Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated Plasmodium falciparum malaria: a multicentre, open-label, randomised clinical trial. Lancet. 2020 Mar 11. pii: S0140-6736(20)30552-3. doi: 10.1016/S0140-6736(20)30552-3. [Epub ahead of print]

25. Ménard D, Khim N, Beghain J, Adegnika AA, Shafiul-Alam M, Amodu O, Rahim-Awab G, Barnadas C, Berry A, Boum Y, Bustos MD, Cao J, Chen JH, Collet L, Cui L, Thakur GD, Dieye A, Djallé D, Dorkenoo MA, Eboumbou-Moukoko CE, Espino FE, Fandeur T, Ferreira-da-Cruz MF, Fola AA, Fuehrer HP, Hassan AM, Herrera S, Hongvanthong B, Houzé S, Ibrahim ML, Jahirul-Karim M, Jiang L, Kano S, Ali-Khan W, Khanthavong M, Kremsner PG, Lacerda M, Leang R, Leelawong M, Li M, Lin K, Mazarati JB, Ménard S, Morlais I, Muhindo-Mavoko H, Musset L, Na-Bangchang K, Nambozi M, Niaré K, Noedl H, Ouédraogo JB, Pillai DR, Pradines B, Quang-Phuc B, Ramharter M, Randrianarivelojosia M, Sattabongkot J, Sheikh-Omar A, Silué KD, Sirima SB, Sutherland C, Syafruddin D, Tahar R, Tang LH, Touré OA, Tshibangu-wa-Tshibangu P, Vigan-Womas I, Warsame M, Wini L, Zakeri S, Kim S, Eam R, Berne L, Khean C, Chy S, Ken M, Loch K, Canier L, Duru V, Legrand E, Barale JC, Stokes B, Straimer J, Witkowski B, Fidock DA, Rogier C, Ringwald P, Ariey F, Mercereau-Puijalon O; KARMA Consortium. A Worldwide Map of*Plasmodium falciparum* K13-Propeller Polymorphisms. N Engl J Med. 2016 Jun 23;374(25):2453-64.
26. Tacoli C, Gai PP, Bayingana C, Sifft K, Geus D, Ndoli J, Sendegeya A, Gahutu JB, Mockenhaupt FP. Artemisinin Resistance-Associated K13 Polymorphisms of *Plasmodium falciparum* in Southern Rwanda, 2010-2015. Am J Trop Med Hyg. 2016; 95(5): 1090-1093.
27. Chenet SM, Akinyi Okoth S, Huber CS, Chandrabose J, Lucchi NW, Talundzic E, Krishnalall K, Ceron N, Musset L, Macedo de Oliveira A, Venkatesan M, Rahman R, Barnwell JW, Udhayakumar V. Independent Emergence of the *Plasmodium falciparum* Kelch Propeller Domain Mutant Allele C580Y in Guyana. J Infect Dis. 2016; 213: 1472-5.
28. Taylor SM, Levitt B, Freedman B, Madanitsa M, Thwai KL, Kalilani-Phiri L, Khairallah C, Mwapasa V, Ter Kuile FO, Meshnick SR. Interactions between antenatal sulfadoxine-pyrimethamine, drug-resistant Plasmodium falciparum parasites and delivery outcomes in Malawi. J Infect Dis. 2020 Mar 28. pii: jiaa145. doi: 10.1093/infdis/jiaa145.
29. Ahmed R, Poespoprodjo JR, Syafruddin D, Khairallah C, Pace C, Lukito T, Maratina SS, Asih PBS, Santana-Morales MA, Adams ER, Unwin VT, Williams CT, Chen T, Smedley J, Wang D, Faragher B, Price RN, ter Kuile FO. Efficacy and safety of intermittent preventive treatment and intermittent screening and treatment versus single screening and treatment with dihydroartemisinin-piperaquine for the control of malaria in pregnancy in Indonesia: a cluster-randomised, open-label, superiority trial. Lancet Infect Dis. 2019;19(9):973-987.
30. Muhindo MK, Jagannathan P, Kakuru A, Opira B, Olwoch P, Okiring J, Nalugo N, Clark TD, Ruel T, Charlebois E, Feeney ME, Havlir DV, Dorsey G, Kamya MR. Intermittent preventive treatment with dihydroartemisinin-piperaquine and risk of malaria following cessation in young Ugandan children: a double-blind, randomised, controlled trial. Lancet Infect Dis. 2019;19(9):962-972.
31. Permala J, Tarning J, Nosten F, White NJ, Karlsson MO, Bergstrand M. Prediction of Improved Antimalarial Chemoprevention with Weekly Dosing of Dihydroartemisinin-Piperaquine. Antimicrob Agents Chemother. 2017;61.pii: e02491-16.
32. Ndiaye JLA, Ndiaye Y, Ba MS, Faye B, Ndiaye M, Seck A, Tine R, Thior PM, Atwal S, Beshir K, Sutherland C, Gaye O, Milligan P. Seasonal malaria chemoprevention combined with community case management of malaria in children under 10 years of age, over 5 months, in south-east Senegal: A cluster-randomised trial. PLoS Med 2019;16:e1002762.
33. Chandramohan D, Dicko A, Zongo I, Sagara I, Cairns M, Kuepfer I, Diarra M, Barry A, Tapily A,

Nikiema F, Yerbanga S, Coumare S, Thera I, Traore A, Milligan P, Tinto H, Doumbo O, Ouedraogo JB, Greenwood B. Effect of Adding Azithromycin to Seasonal Malaria Chemoprevention. N Engl J Med. 2019; 380: 2197-2206.

34. Landier J, Parker DM, Thu AM, Lwin KM, Delmas G, Nosten FH; Malaria Elimination Task Force Group. Effect of generalised access to early diagnosis and treatment and targeted mass drug administration on*Plasmodium falciparum* malaria in Eastern Myanmar: an observational study of a regional elimination programme. *Lancet*2018; **391** : 1916-1926.
35. von Seidlein L, Peto TJ, Landier J, Nguyen TN, Tripura R, Phommasone K, Pongvongsa T, Lwin KM, Keereecharoen L, Kajeechiwa L, Thwin MM, Parker DM, Wiladphaingern J, Nosten S, Proux S, Corbel V, Tuong-Vy N, Phuc-Nhi TL, Son DH, Huong Thu PN, Tuyen NTK, Tien NT, Dong LT, Hue DV, Quang HH, Nguon C, Davoeung C, Rekol H, Adhikari B, Henriques G, Phongmany P, Suangkanarat P, Jeeyapant A,Vihokhern B, van der Pluijm RW, Lubell Y, White LJ, Aguas R, Promnarate C, Sirithiranont P, Malleret B, Rénia L, Onsjö C, Chan XH, Chalk J, Miotto O, Patumrat K, Chotivanich K, Hanboonkunupakarn B, Jittmala P, Kaehler N, Cheah PY, Pell C, Dhorda M, Imwong M, Snounou G, Mukaka M, Peerawaranun P, Lee SJ, Simpson JA, Pukrittayakamee S, Singhasivanon P, Grobusch MP, Cobelens F, Smithuis F, Newton PN, Thwaites GE, Day NPJ, Mayxay M, Hien TT, Nosten FH, Dondorp AM, White NJ. The impact of targeted malaria elimination with mass drug administrations on falciparum malaria in Southeast Asia: A cluster randomised trial. PLoS Med 2019;**16** : e1002745.
36. McLean ARD, Wai HP, Thu AM, Khant ZS, Indrasuta C, Ashley EA, Kyaw TT, Day NPJ, Dondorp A, White NJ, Smithuis FM. Malaria elimination in remote communities requires integration of malaria control activities into general health care: an observational study and interrupted time series analysis in Myanmar. BMC Med. 2018; **16** : e183.
37. Worldwide Antimalarial Resistance Network. https://www.wwarn.org/
38. Price RN, von Seidlein L, Valecha N, Nosten F, Baird JK, White NJ. Global extent of chloroquine-resistant Plasmodium vivax: a systematic review and meta-analysis. Lancet Infect Dis. 2014; 14:982-91.
39. Ross LS, Fidock DA. Elucidating Mechanisms of Drug-Resistant*Plasmodium falciparum* . Cell Host Microbe. 2019; 26: 35-47.
40. Leang R, Khim N, Chea H, Huy R, Mairet-Khedim M, Mey Bouth D, Dorina Bustos M, Ringwald P, Witkowski B. Efficacy and Safety of Pyronaridine-Artesunate plus Single-Dose Primaquine for the Treatment of Malaria in Western Cambodia. Antimicrob Agents Chemother. 2019;63. pii: e01273-19.
41. Imwong M, Suwannasin K, Kunasol C, Sutawong K, Mayxay M, Rekol H, Smithuis FM, Hlaing TM, Tun KM, van der Pluijm RW, Tripura R, Miotto O, Menard D, Dhorda M, Day NP, White NJ, Dondorp AM. The spread of artemisinin-resistant *Plasmodium falciparum* in the Greater Mekong Subregion: a molecular epidemiology observational study. Lancet Infect Dis. 2017: 17: 491-497.
42. Imwong M, Dhorda M, Tun KM, Thu AM, Phyo AP, Proux S et al. Molecular epidemiology of resistance to current antimalarial drugs in the Greater Mekong Subregion: an observational study. Lancet Infect Dis, in press.
43. Recht J, Ashley EA, White NJ. Safety of 8-aminoquinoline antimalarial medicines. World Health Organisation, Geneva, 2014.
44. Dini S, Douglas NM, Poespoprodjo JR, Kenangalem E, Sugiarto P, Plumb ID, Price RN, Simpson JA. The risk of morbidity and mortality following recurrent malaria in Papua, Indonesia: a retrospective cohort study. BMC Med. 2020; 18: e28.
45. Taylor WRJ, Thriemer K, von Seidlein L, Yuentrakul P, Assawariyathipat T, Assefa A, Auburn S, Chand K, Chau NH, Cheah PY, Dong LT, Dhorda M, Degaga TS, Devine A, Ekawati LL, Fahmi F, Hailu A, Hasanzai MA, Hien TT, Khu H, Ley B, Lubell Y, Marfurt J, Mohammad H, Moore KA, Naddim MN, Pasaribu AP, Pasaribu S, Promnarate C, Rahim AG, Sirithiranont P, Solomon H, Sudoyo H, Sutanto I, Thanh NV, Tuyet-Trinh NT, Waithira N, Woyessa A, Yamin FY, Dondorp A, Simpson JA, Baird JK, White NJ, Day NP, Price RN. Short-course primaquine for the radical cure of*Plasmodium vivax* malaria: a multicentre, randomised, placebo-controlled non-inferiority trial. Lancet. 2019; **394** : 929-938.
46. Taylor AR, Watson JA, Chu CS, Puaprasert K, Duanguppama J, Day NPJ, Nosten F, Neafsey DE,

Buckee CO, Imwong M, White NJ. Resolving the cause of recurrent *Plasmodium vivax* malaria probabilistically. Nat Commun. 2019; **10** : e5595.
47. White NJ, Li GQ, Q Gao, Luzzatto L. Rationale for recommending a lower dose of primaquine (0.25mg base/kg) as a *Plasmodium falciparum*gametocytocide in populations where G6PD deficiency is common. Malaria J 2012; **11** : e418.
48. Newton PN, Bond KC; Oxford Statement signatories. Global access to quality-assured medical products: the Oxford Statement and call to action. Lancet Glob Health. 2019; 7: e1609-e1611.
49. Ozawa S, Evans DR, Bessias S, Haynie DG, Yemeke TT, Laing SK, Herrington JE. Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. JAMA Netw Open. 2018; 1: e181662.World health Organisation. World Malaria Report 2019. Geneva.
50. World Health Organisation. World Malaria Report 2019.
51. Lacerda MVG, Llanos-Cuentas A, Krudsood S, Lon C, Saunders DL, Mohammed R, Yilma D, Batista Pereira D, Espino FEJ, Mia RZ, Chuquiyauri R, Val F, Casapía M, Monteiro WM, Brito MAM, Costa MRF, Buathong N, Noedl H, Diro E, Getie S, Wubie KM, Abdissa A, Zeynudin A, Abebe C, Tada MS, Brand F, Beck H-P, Angus B, Duparc S, Kleim J-P, Kellam LM, Rousell VM, Jones SW, Hardaker E, Mohamed K, Clover DD, Fletcher K, Breton JJ, Ugwuegbulam CO, Green JA, Koh GCKW. Single-Dose Tafenoquine to Prevent Relapse of *Plasmodium vivax* Malaria. N Engl J Med. 2019; 380:215-228.
52. Llanos-Cuentas A, Lacerda MVG, Hien TT, Vélez ID, Namaik-larp C, Chu CS, Villegas MF, Val F, Monteiro WM, Brito MAM, Costa MRF, Chuquiyauri R, Casapía M, Nguyen CH, Aruachan S, Papwijitsil R, Nosten FH, Bancone G, Angus B, Duparc S, Craig G, Rousell VM, Jones SW, Hardaker E, Clover DD, Kendall L, Mohamed K, Koh GCKW, Wilches VM, Breton JJ, Green JA. Tafenoquine versus Primaquine to Prevent Relapse of Plasmodium vivax Malaria. N Engl J Med. 2019; 380: 229-241.
53. Ashley EA, Phyo AP. Drugs in Development for Malaria. Drugs. 2018; 78: 861-879.

Legends to Figures

Figure 1: Mortality by treatment arm in randomized comparative controlled trials in strictly defined severe falciparum malaria (which together enrolled 2874 adults and 7424 children). The size of the circle is approximately proportional to the size of the trial and the error bars are 95% confidence intervals. The adults were enrolled mainly in Southeast Asia and the children in Africa (4,5,7,8).

Figure 2: In artemisinin combination treatments (2A: left panel) the three day artemisinin regimen in sensitive infections (AS) results in rapid parasite killing and consequent decline in parasitaemia. The logarithmic scale vertical axis shows the total number of parasites in the body of an adult with approximately 2% parasitaemia. The ACT partner drug has only approximately 1000 parasites to remove in this example (green triangle). In contrast in an artemisinin resistant infection (AR) there is much less parasite killing initially and the ACT partner drug now has approximately 100 million parasites to remove with a substantially greater risk of treatment failure (recrudescence) and thus selective pressure to the emergence of partner drug resistance. In the right panel (2B) with TACTs there are now two slowly eliminated drugs providing a potentially greater antimalarial effect in resistant infections and ensuring mutual protection against the emergence of resistance. The detection limit (dashed line) is the limit for microscopy to identify a malaria infection.

Figure 3: The parasite clearance half-lives associated with*Pf* kelch mutations in patients with acute falciparum malaria studied in the TRAC1 study (20). WT= wild type (note parasite clearance half-lives can still be much longer than 5 hours in *Pf* kelch wild-type infections). Mutations in the "propeller "region are usually associated with slow parasite clearance, the phenotypic hallmark of artemisinin resistance, although there is substantial inter-individual variation and some mutations (A578S: pink arrow) are clearly not associated with artemisinin resistance. In the GMS parasite lineages associated with the F446I mutation have spread widely in Myanmar, and a lineages associated with C580Y was common along the Thailand-Myanmar border before targeted elimination activities. In the Eastern GMS lineages associated with R539T and C580Y both spread but in recent years the C580Y lineage (termed *Pf* Pailin) has dominated. Modified from Ashley et al

(20) with permission.

Figure 4

The spread of artemisinin resistant *P. falciparum* parasite lineages across the Greater Mekong subregion (GMS). A single long*pfKelch* C580Y haplotype (from -50 to +31·5kb either side of the Pfkelch gene), which emerged in Western Cambodia in 2008 (*Pf* Pailin), has spread across the Eastern GMS. In Myanmar C580Y parasites of a different lineage have spread widely and a single*pfKelch* F446I haplotype which probably originated in the North of Myanmar has spread widely across the country; modified from Imwong et al (42) with permission.

Figure 5

Individual patient meta-analysis (52) of freedom from recurrence of*P. vivax* malaria (relapse prevention) in the two pivotal phase 3 studies in adults which compared tafenoquine single dose (300mg) with a low dose primaquine regimen (15mg base day for 14 days) (46,47). The dashed vertical line represents the prespecified noninferiority margin of an odds ratio for recurrence of 1.45 (tafenoquine vs. primaquine). In Southeast Asia, which has high relapse rates, tafenoquine was significantly inferior (orange highlighting) to the low dose primaquine regimen (which is considered inferior to a high dose (30mg base/day) primaquine regimen); modified from Llanos-Cuentas et al (52) with permission.

Hosted file

`Fig 1 BJCP.pptx` available at https://authorea.com/users/312614/articles/443169-advances-and-roadblocks-in-the-treatment-of-malaria

Hosted file

`Fig 2 BJCP.pptx` available at https://authorea.com/users/312614/articles/443169-advances-and-roadblocks-in-the-treatment-of-malaria

Hosted file

`Fig 3 BJCP.pptx` available at https://authorea.com/users/312614/articles/443169-advances-and-roadblocks-in-the-treatment-of-malaria

Hosted file

`Fig 4 BJCP.pptx` available at https://authorea.com/users/312614/articles/443169-advances-and-roadblocks-in-the-treatment-of-malaria

Hosted file

`Fig 5 BJCP.pptx` available at https://authorea.com/users/312614/articles/443169-advances-and-roadblocks-in-the-treatment-of-malaria