



Artemisinin resistance and artemisinin-based combination therapy efficacy

DECEMBER 2018

STATUS REPORT

WHO recommends artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria caused by *Plasmodium falciparum*. ACTs have been an integral part of the recent success in global malaria control. There is a broad consensus that protecting the efficacy of ACTs for the treatment of malaria is a global health priority. The primary advantage of the combination is that the artemisinin quickly and drastically reduces the majority of malaria parasites, and the partner drug clears the small number of parasites that remain. However, the future efficacy of ACTs is endangered by the emergence of resistance to both artemisinin and the partner drugs.

Artemisinin resistance is defined as delayed parasite clearance following treatment with an artesunate monotherapy or ACT. This represents partial resistance. Artemisinin resistance alone does not necessarily lead to treatment failure. However, reduced efficacy of the artemisinin component places greater demands on the partner drug to clear a larger parasite mass, jeopardizing the future efficacy of the partner drug. It is also possible for partner drug resistance to emerge independently from artemisinin resistance. Unlike artemisinin resistance, the presence of partner drug resistance brings a high risk of treatment failure.

Artemisinin and the partner drug have different roles; hence, the efficacy of both drugs must be monitored independently. Monitoring has been central to tracking the evolution of resistance in the Greater Mekong subregion (GMS), where there is now multidrug *P. falciparum* resistance (i.e. resistance to both artemisinin and partner drugs), leading to treatment failure with several ACTs.

Chloroquine (CQ) remains a first-line treatment for *P. falciparum* malaria in the Dominican Republic, Guatemala, Haiti, Honduras and Nicaragua. Central America and the Caribbean (Mesoamerica) remain the last regions where the presence of resistance has not yet been confirmed.

For *Plasmodium vivax*, CQ remains an effective first-line treatment in many countries. Countries endemic for vivax malaria recommend either CQ or an ACT for the treatment of uncomplicated *P. vivax*. Most treatment policies also include primaquine (PQ), to eliminate latent liver stage infections and prevent relapse, because it improves the activity of CQ against CQ-resistant blood stage parasites. Where there is a high treatment failure rate with CQ (>10%), countries are encouraged to change their first-line treatment to an ACT. To date, *P. vivax* resistance to artemisinin has not been detected.

NETWORKS FOR MONITORING ANTIMALARIAL DRUG EFFICACY

WHO supports several subregional networks for monitoring antimalarial resistance. Through these networks, WHO offers updates on the global situation of antimalarial drug resistance; it also advises on protocol implementation, microscopy, data analysis and validation, and reporting and publication. The information on therapeutic efficacy generated by the networks is shared among countries, to provide the best possible advice to ministries of health. Network meetings facilitate discussions on changes to the national malaria treatment policy, if needed. The creation of networks facilitates effective management of problems in border areas. Recent network meeting reports provide a summary of the results of drug efficacy and resistance monitoring in the subregions. All meeting reports are available on the WHO Global Malaria Programme (GMP) website (1).

STATUS OF ANTIMALARIAL DRUG EFFICACY (2010–2017): TREATMENT OF *P. FALCIPARUM*

The WHO global database on antimalarial drug efficacy and resistance contains data on therapeutic efficacy studies for *P. falciparum* and *P. vivax* and, more recently, data from studies of molecular markers. Up-to-date summary reports of the global database are available on the GMP website (2).

Artemether-lumefantrine

The analysis of artemether-lumefantrine (AL) included 289 studies conducted in 47 countries. The overall efficacy of AL was 98.2%. In the WHO African Region, where more than half of the studies were conducted, the overall efficacy of AL was 98.1%. Treatment failure rates greater than 10% occurred in four of the 159 studies conducted: Malawi (19.5% in 2010), Angola (11.7% in 2013 and 13.6% in 2015) and Gambia (11.9% in 2010). The results of these studies can be considered as outliers, because similar failure rates were not reported afterwards in any of the three countries. In addition, lumefantrine resistance could not be confirmed by molecular marker studies, in vitro tests or blood dosage levels in any of the failures reported. In the WHO Region of the Americas, the overall efficacy of AL was 98.2%. No treatment failures were observed in four of the five studies conducted. A study in Suriname in 2011 detected a 9% treatment failure rate; however, the study had a limited sample size. In the WHO Eastern Mediterranean Region, the overall efficacy of AL in all 28 studies conducted was 99.1%. In the WHO South-East Asia Region, the overall efficacy of AL was 98.5%. Among the 68 studies conducted, three studies observed treatment failures of greater than 10%. One study in

Thailand's Ranong Province detected a treatment failure rate of 11.3% in 2012 (n=44). Two studies conducted in Bangladesh observed treatment failure rates of 11.1% in 2013 and 14.3% in 2017, but both studies had sample sizes of fewer than 10 patients. In the WHO Western Pacific Region, the overall efficacy of AL was 96.4%. Among the 25 studies conducted, three studies had treatment failure rates of at least 10%. High treatment failure rates were observed in the southern Lao People's Democratic Republic, with treatment failure rates of 10% (n=20), 14.3% (n=49) and 17.2% (n=29) observed in 2013, 2014 and 2017, respectively.

Artesunate+sulfadoxine-pyrimethamine

The analysis of artesunate+sulfadoxine-pyrimethamine (AS+SP) included 101 studies in eight countries: Afghanistan (3), India (55), Iran (Islamic Republic of) (7), Mali (3), Pakistan (6), Somalia (4), Sudan (18) and Yemen (5). Studies of AS+SP demonstrated an overall efficacy of 97.7%. Treatment failure rates greater than 10% occurred in eight of the 101 studies, in India (12.1%, 17.3% and 21.4% in 2012), Somalia (22.2% in 2011 and 12.3% in 2015), and Sudan (10.8% and 18.1% in 2014, and 16.4% in 2015). India has since changed its treatment policy to AL in the north-eastern part of the country, and Somalia and Sudan have since both changed their treatment policies to AL and dihydroartemisinin- piperazine (DHA-PPQ).

Artesunate-amodiaquine

The analysis of artesunate-amodiaquine (AS-AQ) included 99 studies in 27 countries. Studies of AS-AQ demonstrated an overall efficacy of 98%. In the WHO African Region, where 96 studies were conducted, the efficacy was 98.5%. Among the 99 studies, only two studies, both of which were conducted in Cambodia in 2016, detected high treatment failures (13.8% and 22.6%).

Artesunate-mefloquine

The analysis of artesunate-mefloquine (AS-MQ) included 42 studies in six countries. Studies of AS-MQ demonstrated an overall efficacy of 94.9%. In the WHO African Region, two studies were conducted in Senegal in 2010, both with a high treatment efficacy of 99.5%. In the WHO Region of the Americas, two studies were conducted in Brazil (2010, 2012) and one in Suriname (2013); all three studies observed an overall efficacy of 100%. Among the 23 studies conducted in the WHO South-East Asia Region (Myanmar and Thailand only), the overall efficacy was 91.4%. Although treatment remained 100% effective in Myanmar in 2011 and 2012, high treatment failure rates were observed in seven studies conducted in Thailand between 2010 and 2013 (range: 12.5–49.1%). Thailand changed its treatment policy from AS-MQ to DHA-PPQ in 2015. In the WHO Western Pacific Region, 14 studies were conducted in Cambodia; one study in 2010 observed a treatment failure rate of 11.1%, but all subsequent studies conducted during 2011–2017 showed high treatment efficacy (98.3–100%).

Artesunate-pyronaridine

The analysis of artesunate-pyronaridine (AS-PY) included 11 studies conducted in four countries (Burkina Faso, Cambodia, Mali and Myanmar). Studies of AS-PY demonstrated an overall efficacy of 96.9%. Treatment failure rates exceeded 10% in two studies conducted in western Cambodia in 2014 (10.2% and 18%), while treatment success remained high in eastern Cambodia in 2017 (96.7% and 98.3%).

Dihydroartemisinin-piperaquine

The analysis of DHA-PPQ included 130 studies conducted in 21 countries. Studies of DHA-PPQ demonstrated an overall efficacy of 94.5%. In the WHO African Region, 21 studies conducted in Angola, Democratic Republic of the Congo, Gambia, Guinea-Bissau, Kenya, Malawi, Nigeria, Senegal, Sierra Leone and Zambia demonstrated an overall efficacy of 99.3%. In the WHO Eastern Mediterranean Region, eight studies conducted in Pakistan, Somalia and Sudan showed a treatment efficacy of 99.3%. In the WHO South-East Asia Region, 28 studies conducted in Indonesia, Myanmar and Thailand showed a treatment efficacy of 99%. In the WHO Western Pacific Region, 74 studies were conducted in Cambodia, China, Lao People's Democratic Republic, Papua New Guinea and Viet Nam. The overall treatment efficacy was 90.7%. Treatment failure rates greater than 10% were observed in 19 studies from Cambodia, Lao People's Democratic Republic and Viet Nam. In Cambodia, treatment failure rates exceeded 10% in 13 of the 27 studies conducted; the maximum treatment failure rate was 62.5% in 2014. In 2016, Cambodia changed the first-line treatment policy of DHA-PPQ to AS-MQ. In Lao People's Democratic Republic, two studies with treatment failure rates of 13.3% (n=15) and 47.4% (n=19) were observed in 2016. In Viet Nam, treatment failure rates exceeded 10% in four of the 34 studies conducted (range: 25.9–46.3% in 2015–2016). This evidence has prompted discussions of a change in Viet Nam's current treatment policy in areas where DHA-PPQ is failing.

Summary of antimalarial drug efficacy for treatment of *P. falciparum*

In summary, most studies show that the ACTs currently recommended in national malaria treatment policies remain effective, with overall efficacy rates of greater than 95%. Of particular concern, however, are studies that show treatment failure rates of greater than 10% associated with treatments currently recommended in the national treatment policy. Specifically, in Lao People's Democratic Republic, AL remains the first-line treatment; however, high treatment failure rates have been observed, increasing since 2013. In addition, high treatment failure rates have been observed with Viet Nam's first-line treatment, DHA-PPQ. Studies are underway in both countries to review the efficacy of alternative treatments. Consensus meetings will be needed once evidence is available, to decide on and implement new treatment options. Several countries that detected high treatment failure rates have responded by changing their treatment policies, including Cambodia, India (in north-eastern states), Somalia, Sudan and Thailand.

STATUS OF ANTIMALARIAL DRUG EFFICACY (2010–2017): TREATMENT OF *P. VIVAX*

Chloroquine

The analysis included 105 studies of CQ and 20 studies of CQ+PQ. No differences were observed in treatment outcomes; therefore, results were combined for this analysis. The 125 studies were conducted in 21 countries. The overall treatment efficacy was 97.4%. In the WHO African Region, 11 studies were conducted, for an overall treatment efficacy of 94.6%. One study in Ethiopia observed a treatment failure rate of 22% in 2010. In the WHO Region of the Americas, 13 studies were conducted, with an overall treatment

efficacy of 97.1%. Studies conducted in Bolivia (Plurinational State of) and Brazil observed treatment failure rates of 10.4% in 2011 and 18.3% in 2012. In three studies from the WHO Eastern Mediterranean Region conducted in Iran (Islamic Republic of) (2) and Pakistan (1), each showed 100% treatment efficacy. In the WHO South-East Asia Region, 71 studies observed an overall efficacy of 98.2%. Among these, two studies from Myanmar showed a high treatment failure rate of 11.9% in 2010, and 21.7% in 2012. One study in Timor-Leste showed a treatment failure rate of 17.5% in 2011. In the WHO Western Pacific Region, 26 studies were conducted, with an overall efficacy of 96.3%. One study from Malaysia observed a treatment failure rate of 61.9% in 2012.

ACTs

The analysis included studies of AL (16), AS+SP (4), AS-AQ (3), AS-MQ (2), AS-PY (2) and DHA-PPQ (12). Studies of AL demonstrated an overall efficacy of 93.4%. Treatment failure rates greater than 10% were observed in four studies: Ethiopia (11.9% in 2012), Papua New Guinea (35% in 2011), Solomon Islands (31.6% in 2011) and Vanuatu (12.1% in 2013). High treatment failure rates with AL may be explained by the short half-life of lumefantrine, which fails to cover the first relapse. In Sudan, two studies of AS+SP and two studies of AS+SP+PQ were conducted. The recurrent risk of failure was 9.9% for AS+SP alone; however, when PQ was added to the treatment, efficacy rose to 100%. In this case, the failures may be attributed to *P. vivax* resistance to SP. Studies of AS-AQ, AS-MQ, AS-PY and DHA-PPQ all demonstrated high treatment efficacy (99–100%).

GLOBAL PUBLIC HEALTH IMPLICATIONS OF ANTIMALARIAL DRUG RESISTANCE

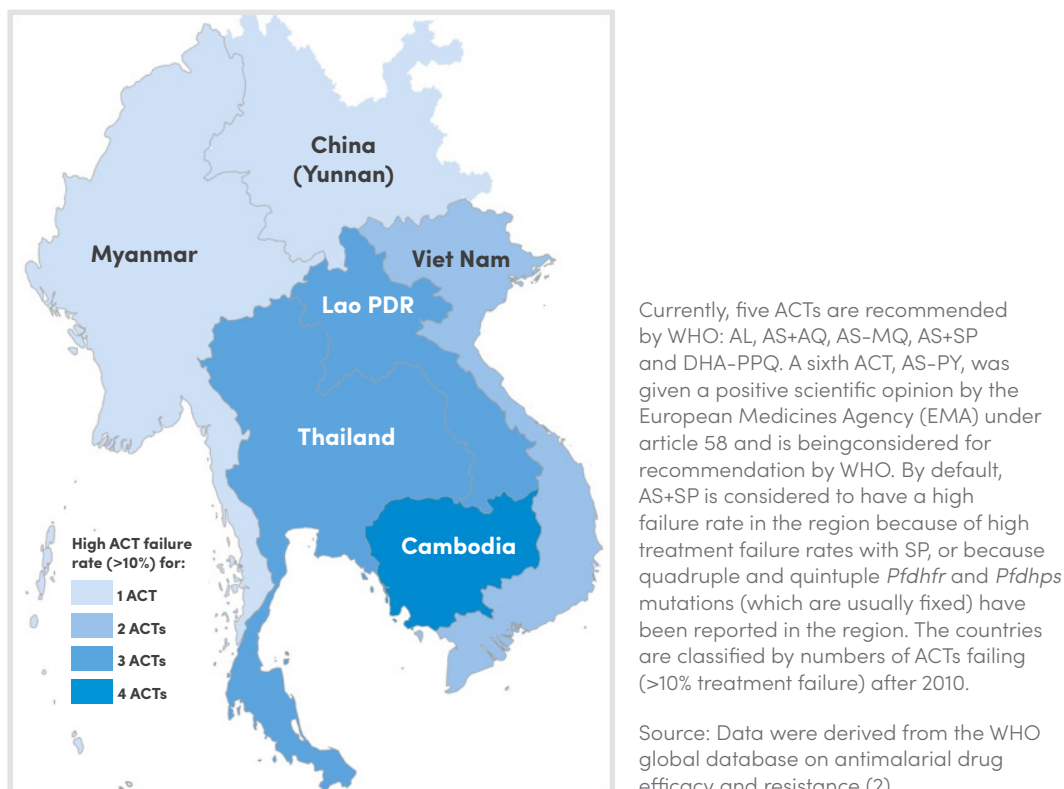
Antimalarial drug resistance is a major threat to malaria control and has important implications for global public health. For example, when CQ resistance emerged in Africa in the 1980s, there were documented increases in hospital admissions and mortality rates, mainly due to severe malaria and increased transmission. Resistance to antimalarial drugs has had a significant impact on the cost of global malaria control, as new drugs have had to be developed to replace those that have become ineffective. In addition, patients whose treatment fails because of infection with a resistant strain require repeated consultations at health facilities for further diagnosis and treatment, resulting in lost work-days, school absence and increased health care costs.

With the implementation of combination therapy, improvements to health systems and surveillance systems to monitor first- and second-line treatment, and the availability of guidelines on policy change, the consequences of the development of resistance to antimalarial medicines may be less severe today than those that were observed with CQ in the 1980s. In the event that parasites develop reduced sensitivity to artemisinin, ACTs will continue to cure patients, provided that the partner drug remains effective. Further, by regularly monitoring the national malaria treatment, and by making prompt changes to national malaria treatment policies following the detection and confirmation of resistance, ministries of health can be actively involved in maintaining the effectiveness of their national treatment policy.

The GMS has long been the epicentre of antimalarial drug resistance, and currently *P. falciparum* resistance to artemisinin is present in five countries of the subregion: Cambodia, Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.

During the early 2010s, while containment efforts to stop the spread of resistant parasites were underway, it was discovered that artemisinin resistance had emerged independently in multiple areas, and that resistance to ACT partner drugs had also emerged, threatening the progress achieved in the region to date. In 2014, an assessment of the feasibility of *P. falciparum* elimination in the subregion concluded that elimination was technically and operationally feasible at a reasonable cost. These developments, together with the subregion's impressive reduction in malaria burden in the past decade, led to a shift in strategy focusing on malaria elimination. A strategy for eliminating malaria in the GMS has been developed and is targeting malaria elimination in the GMS by 2030 (3).

Number of ACTs with high failure rates in the treatment of *P. falciparum* infections



Note

This content of this document was first published in the *World malaria report 2018*. Data covers the period 2010–2017.

REFERENCES

1. Antimalarial drug efficacy and drug resistance (updated 27 April 2018). Geneva: World Health Organization; 2018 (http://www.who.int/malaria/areas/treatment/drug_efficiency/en/, accessed 15 October 2018).
2. Global database on antimalarial drug efficacy and resistance (updated 26 October 2018). Geneva: World Health Organization; 2018 (http://www.who.int/malaria/areas/drug_resistance/drug_efficiency_database/en/, accessed 30 October 2018).
3. Eliminating malaria in the Greater Mekong subregion: united to end a deadly disease. Geneva: World Health Organization; 2016 (<http://www.who.int/malaria/publications/atoz/eliminating-malaria-greater-mekong/en/>, accessed 24 October 2018).