Artemisinin resistance and artemisinin-based combination therapy efficacy

DECEMBER 2019

STATUS REPORT

STATUS OF ANTIMALARIAL DRUG EFFICACY (2010–2018)

Plasmodium resistance to antimalarial medicines is one of the key recurring challenges in the fight against malaria. Monitoring antimalarial drug efficacy supports early detection of changes in how well the recommended treatments work; this enables rapid action to mitigate any impact of resistance and prevent its spread. Therapeutic efficacy studies (TESs) provide a measure of clinical and parasitological patient outcomes, and are the main source of data on which the NMPs base their decisions regarding which treatment to recommend (1). In areas implementing malaria elimination activities, the routine surveillance system can track treatment and follow-up of all malaria cases, and use the data generated for integrated drug efficacy surveillance (iDES) (2). Information from TESs and iDES is supplemented by information on the prevalence and read of molecular markers – genetic changes in the parasite – that are found to be associated with resistance. PfKelch13 mutations have been identified as molecular markers of partial artemisinin resistance. PfKelch13 mutations associated with artemisinin resistance are widespread in the Greater Mekong subregion GMS in South-East Asia, and have also been detected at a significant prevalence (over 5%) in Guyana, Papua New Guinea and Rwanda.

The WHO global database on antimalarial drug efficacy and resistance contains data from TESs conducted on Plasmodium falciparum, P. vivax, P. knowlesi, P. malaria and P. ovale, as well as molecular marker studies of P. falciparum drug resistance (PfKelch13, PfPlasmepsin 2–3, Pfmdr1 and Pfcrtr in Mesoamerica). Summary reports are regularly updated and are available on the WHO website (3). In addition, the Malaria Threats Maps provide a geographical representation of drug efficacy and resistance data (4).
WHO AFRICA REGION

The first-line treatments used in most African countries for *P. falciparum* are artemether-lumefantrine (AL) and artesunate-amodiaquine (AS-AQ), with some countries’ treatment policies also allowing for the use of dihydroartemisinin-piperazine (DHA-PPQ). Between 2010 and 2018, treatment efficacy data for AL were available from 28 countries, for AS-AQ from 26 and for DHA-PPQ from 14. The overall average efficacy rates of AL, AS-AQ and DHA-PPQ for *P. falciparum* were 98.0%, 98.5% and 99.3%, respectively. When the failure rates of all three treatments were analysed separately by year, it was found that their high efficacy has remained constant over time. Treatment failure rates above 10% detected in Gambia and Malawi in 2010 are likely to be statistical outliers; recent studies show that most treatment failure rates remain low. The high reported failure rate from two studies in Angola was probably due to methodological issues. For all other medicines, treatment failure rates remain below 10%.

In Africa, artemisinin partial resistance has not yet been confirmed. Surveys are detecting a number of different validated and unvalidated *PfKelch13* mutations at low prevalence, except in Rwanda, where clearance and efficacy of the first-line treatment AL does not seem to be affected. There have been unconvincing case reports of travellers returning from Africa with malaria and not responding as expected to treatment. These include a Vietnamese male returning in 2013 to Viet Nam from Angola, who developed malaria that did not respond to intravenous artesunate, clindamycin or DHA-PPQ (5). Another case was reported in a Chinese male, who developed malaria 8 weeks after returning from Equatorial Guinea in 2013. The patient responded to treatment with DHA-PPQ but had low-level parasitaemia on day 3 after the start of treatment, and the infection was identified as carrying the *PfKelch13* mutation M579I, previously only reported once in Myanmar (6, 7). Three recent surveys conducted in Equatorial Guinea did not identify M579 among a total of 721 samples.

Eleven cases of treatment failure were reported in European travellers returning from different locations in Africa and treated with DHA-PPQ or AL (8–10). The patients were infected with parasites not carrying *PfKelch13* mutations, and molecular markers or blood levels of the partner medicines could not confirm resistance. Combined, these cases do not provide convincing evidence for the presence of resistance to artemisinin or artemisinin-based combination therapy (ACT) partner drugs in Africa. Nevertheless, reporting on these cases is important because resistance or treatment failures in travellers could be an early warning signal, supplementing the information collected in the endemic countries.

The *P. vivax* species is only endemic in a few countries in the WHO African Region. TESs with chloroquine (CQ) were conducted in Ethiopia, Madagascar and Mauritania. Ethiopia confirmed high rates of treatment failure for both CQ and AL. The high failure rate of AL without primaquine (PQ) is probably caused by the short half-life of artemisinin, which fails to prevent the first relapse. Madagascar monitored the efficacy of AS-AQ in 2012 and 2013, and Mauritania monitored CQ in 2012. The efficacy in these studies was found to be 100%.

WHO REGION OF THE AMERICAS

The first-line treatments for *P. falciparum* in the Amazon region are AL and artesunate-mefloquine (AS-MQ). Treatment efficacy was high for both medicines. One treatment failure was detected in a TES of AL, conducted in Suriname, among 11 patients. In
Guatemala, Haiti, Honduras and Nicaragua, where the first-line treatment is CQ, molecular marker studies of Pfcrts are conducted to supplement TESs. Between 2010 and 2018, a low prevalence of Pfcrt mutation was observed in Haiti, Honduras and Nicaragua. TESs almost always confirmed the high efficacy of CQ in these countries.

A retrospective study of Guyanese samples collected in 2010 identified the PfKelch13 mutation C580Y in five out of 98 samples (5.1%). A larger survey done in 2016–2017 found C580Y in 14 out of 877 samples (1.6%). Genetic studies have confirmed that these parasites were not imported from South-East Asia; rather, the mutation emerged in parasites of South American origin.

The first-line treatment policy for *P. vivax* in all endemic countries in this region is CQ. Between 2010 and 2018, TESs of *P. vivax* were conducted in Bolivia (Plurinational State of), Brazil, Colombia, Peru and Venezuela (Bolivarian Republic of). All countries conducted studies for *P. vivax* with CQ alone or with CQ and PQ. One study conducted in the Plurinational State of Bolivia confirmed CQ resistance. Additionally, Brazil conducted studies of AS-AQ, AL+PQ and AS-MQ+PQ. None of these resulted in treatment failures above 10%.

**WHO SOUTH-EAST ASIA REGION**

In Bhutan, Nepal and Timor-Leste, the first-line treatment policy for *P. falciparum* is AL. TESs conducted in these countries between 2010 and 2013 found high treatment efficacy, with less than 10% treatment failure.

Indonesia monitored DHA-PPQ efficacy between 2010 and 2017. All studies resulted in less than 10% treatment failures.

In Bangladesh, the first-line treatment policy includes AL, AS-AQ, AS-MQ and DHA-PPQ. Bangladesh monitored AL treatment failure between 2010 and 2018, and found rates above 10% in two studies, each with a small number of patients.

India’s first-line treatment policy includes AL and artemunate + sulfadoxine-pyrimethamine (AS+SP). India has extensively monitored the efficacy of AS+SP and found treatment failure rates ranging from 0% to 21.4%. Failure rates above 10% in north-eastern parts of India led to the treatment policy in this region changing to AL. All studies conducted for AL in India between 2011 and 2017 found treatment failure rates to be less than 10%.

Thailand’s first-line treatment policy was AS-MQ until treatment failure rates began to progressively increase. The first-line treatment was changed to DHA-PPQ in 2015. Treatment failure for DHA-PPQ was monitored between 2014 and 2017, and treatment failure rates as high as 92.9% (13/14) were detected in 2017 in the north-eastern part of the country, probably from importation of malaria from Cambodia. As a result, the first-line treatment has since been changed to artemunate-pyronaridine (AS-PY) in eastern Thailand.

Myanmar’s first-line treatment policy includes AL, AS-MQ and DHA-PPQ. Treatment failure rates were less than 10% despite the high prevalence of artemisinin partial resistance. In addition, Myanmar monitored AS-PY efficacy in four studies in 2017 and 2018, and found the treatment to be 100% efficacious.
The presence of molecular markers of artemisinin resistance has been reported in Bangladesh, India, Myanmar and Thailand. In Myanmar, seven different validated mutations have been reported, and the most frequently identified since 2010 is F446I. In Thailand, eight different validated mutations have been reported. In western Thailand, it is still possible to identify a range of different PfKelch13 mutations, whereas C580Y is becoming dominant in eastern Thailand. In Bangladesh, one C580Y mutation has been identified in a sample collected in 2018. Recently, two articles reported the emergence of artemisinin resistance in West Bengal, India based on the results from a TES with AS+SP done in the period 2014–2016 (11, 12). Among the 226 patients in the study, 10.6% (24/226) were found to have parasite clearance half-lives of more than 5 hours, 5.8% (13/226) were found to carry the PfKelch13 mutation G625R, and 0.9% (2/226) carried R539T. The treatment failure rate was 8% (18/226). These results should be interpreted with caution (13). The data contrast with other available data on drug efficacy from India, including from West Bengal. PfKelch13 mutations are rare in India, and the G625R mutation has not yet been validated as an artemisinin resistance marker; further investigation is needed to examine the role of G625R in delayed parasite clearance. TESs are now being conducted in West Bengal, with an evaluation of parasite clearance times and analysis of PfKelch13 mutations. Until appropriate validation and external quality control is completed, it is premature to claim that artemisinin resistance has emerged in India.

For *P. vivax*, CQ is the first-line treatment in Bangladesh, Bhutan, the Democratic People’s Republic of Korea, India, Myanmar, Nepal, Sri Lanka and Thailand. DHA-PPQ is the first-line treatment in Indonesia, and AL in Timor-Leste. Although most studies demonstrated high efficacy of CQ, high failure rates of treatment with CQ were confirmed in Myanmar and Timor-Leste.

**WHO EASTERN MEDITERRANEAN REGION**

Studies conducted in Somalia and Sudan between 2011 and 2015 detected high failure rates of treatment with AS+SP, ranging from 12.3% to 22.2%. The evidence prompted a decision to change the new first-line treatment policy to AL. Therefore, the first-line treatment for *P. falciparum* in Afghanistan, Djibouti, Pakistan, Somalia and Sudan is AL. The efficacy of AL has been monitored in each of these countries, except in Djibouti. All TESs show low rates of AL treatment failure (<5%).

For infection with *P. vivax*, the first-line treatment policy is AL in Somalia and Sudan, and CQ in Afghanistan, Djibouti, Iran (Islamic Republic of), Pakistan, Saudi Arabia and Yemen. TESs of AL were conducted in Afghanistan and Sudan, and TESs of CQ were conducted in Iran (Islamic Republic of) and Pakistan. All studies showed high treatment efficacy. A study conducted in Pakistan in 2013 for DHA-PPQ detected one treatment failure among 103 cases (1%).

**WHO WESTERN PACIFIC REGION**

For *P. falciparum*, AL is the first-line treatment policy in countries outside the GMS as well as in Lao People’s Democratic Republic. All studies conducted outside of the GMS resulted in failure rates of less than 10% for treatment with AL. In Lao People’s Democratic Republic, treatment failure rates above 10% were found in three of nine studies between 2011 and 2017. However, the recommended samples sizes were not achieved.
In Cambodia, AS-MQ is the current first-line treatment. AS-MQ replaced DHA-PPQ after high rates of treatment failure were observed. Of the 17 studies conducted with AS-MQ since 2014, the treatment failure rate has been less than 2%. One study of AL found a treatment failure rate of 5% (3/60). The most recent studies with AS-PY in 2017 and 2018 showed efficacy of more than 95%. Treatment failure rates for AS-AQ ranged between 13.8% and 22.6%.

In Viet Nam, the first-line treatment policy is DHA-PPQ. Of the 42 TESs of DHA-PPQ conducted between 2010 and 2017, five studies detected treatment failure rates between 14.3% and 46.3%, all from 2015 to 2017. These studies were concentrated in the south, in the neighbouring provinces of Dak Nong and Binh Phuoc. Most recently, high failure rates for treatment with DHA-PPQ were observed in a third province, Dak Lak. Viet Nam has also monitored the efficacy of AL and AS-PY, with overall efficacies of 100% and 95.5%, respectively. Papua New Guinea monitored the efficacy of DHA-PPQ, and Malaysia monitored that of AS-MQ; both countries found 100% treatment efficacy for these medicines.

Artemisinin resistance has been confirmed in Cambodia, Lao People’s Democratic Republic and Viet Nam through several studies conducted between 2001 and 2018. Between 2010 and 2018, eight \textit{PfKelch13} mutations were identified in Cambodia and Lao People’s Democratic Republic. C580Y was the most frequent, with about 71.7% of the genotypes carrying this mutation. In Viet Nam, six \textit{PfKelch13} mutations were identified, and C580Y was also the most predominant, appearing on an average of 33.3% of the genotypes. The \textit{PfKelch13} mutation C580Y has been identified twice in Papua New Guinea: in a survey in 2017 where 2.3% (3/132) of the samples carried the mutation (the percentage was higher in 2018) and in one traveller. No validated molecular markers of artemisinin resistance were found in studies conducted in Malaysia, the Philippines, Solomon Islands or Vanuatu.

The first-line treatment for \textit{P. vivax} in Lao People’s Democratic Republic, Malaysia, Papua New Guinea, Solomon Islands and Vanuatu is AL. High failure rates of treatment with AL were observed in Papua New Guinea (35% in 2011), Solomon Islands (31.6% in 2011), and Vanuatu (12.1% in 2013). These high rates in areas where early relapses occur are possibly explained by the short half-life of lumefantrine. In China, the Republic of Korea and Viet Nam, the first-line treatment for \textit{P. vivax} is CQ. China and Viet Nam conducted TESs of CQ; only Viet Nam detected a treatment failure rate above 10% in 2015. In the Philippines, the recommended first-line treatments for \textit{P. vivax} are AL and CQ. The nine studies in the Philippines conducted on CQ between 2010 and 2016 all showed treatment failure rates below 10%. In Cambodia, the first-line treatment for \textit{P. vivax} is AS-MQ. Three recent TESs conducted in Cambodia showed 100% efficacy for AS-MQ. The efficacy of AS-MQ was also monitored in Lao People’s Democratic Republic and Malaysia between 2012 and 2018. Both studies showed 100% efficacy. The efficacy of DHA-PPQ was monitored in Cambodia, Papua New Guinea and Viet Nam between 2010 and 2015. All studies found treatment failure rates below 10%.

\textbf{Note}

This content of this document was first published in the \textit{World malaria report 2019}. Data covers the period 2010–2018.
REFERENCES


4. https://apps.who.int/malaria/maps/threats/


