World Health Organization

Tackling antimalarial drug resistance

Launch of the WHO Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010–2019)

Antimalarial drug resistance has emerged as a threat to global malaria control efforts, particularly in the Greater Mekong subregion. The WHO *Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010–2019)*, published on 19 November 2020, presents a decade's worth of data on drug efficacy and surveillance, as well as recommendations to monitor and protect the efficacy of malaria treatment in the decades to come. The report will be launched through a WHO webinar during World Antimicrobial Awareness Week (18–24 November).

Key definitions

Artemisinin-based combination therapies

Isolated from the plant *Artemisia annua*, or sweet wormwood, artemisinin and its derivatives are powerful medicines known for their ability to rapidly reduce the number of *Plasmodium* parasites in the blood of patients with malaria.

Artemisinin-based combination therapies (ACTs) combine an artemisinin derivative (artesunate, artemether or dihydroartemisinin) with a partner drug. The role of the artemisinin compound is to reduce the number of parasites during the first three days of treatment. The role of the partner drug is to eliminate the remaining parasites and cure the infection. Over the last 15 years, expanded access to ACTs in malaria-endemic countries has played an important role in lowering the global the burden of this disease.

WHO currently recommends six artemisinin-based combination therapies (ACTs) as first- and second-line treatment for uncomplicated *P. falciparum*[1] malaria:

- artemether-lumefantrine (AL)
- artesunate-amodiaquine (AS-AQ)
- artesunate-mefloquine (AS-MQ)
- artesunate-pyronaridine (AS-PY)
- artesunate+sulfadoxine-pyrimethamine (AS+SP)
- dihydroartemisinin-piperaquine (DHA-PPQ)

For the treatment of uncomplicated *P. vivax* malaria, WHO recommends either chloroquine (CQ) or an ACT in areas with CQ-resistant *P. vivax*.

1 The *P. falciparum* (Pf) malaria parasite is responsible for some 97% of malaria deaths globally.

Artemisinin resistance

Artemisinin resistance typically refers to a delay in the clearance of malaria parasites from the bloodstream following treatment with an ACT. As a result, the artemisinin compound is less effective in clearing all parasites within a three-day period among patients infected with artemisinin-resistant strains of malaria.

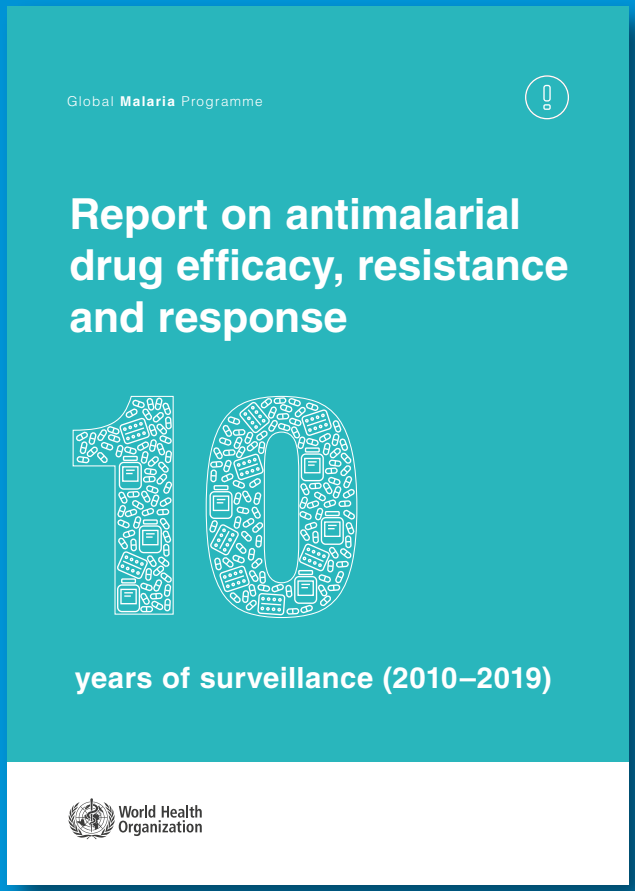
Recent studies have shown that the mechanisms of resistance developed by the parasites against artemisinin compounds affect only one stage of the malaria parasite cycle in humans: the ring stage. As such, it is more appropriate to refer to the delayed clearance of malaria parasites as "partial resistance" to highlight this time-limited and cycle-specific feature.

Currently, nearly all patients infected with artemisinin-resistant parasites who are treated with an ACT are fully cured, provided the partner drug is highly efficacious. In the absence of partner drug resistance, artemisinin partial resistance rarely leads to treatment failure. Furthermore, there is no evidence that artemisinin partial resistance alone has resulted in an increase in malaria cases and deaths.

Partial artemisinin resistance has occurred as a result of several factors, including poor treatment practices, inadequate patient adherence to prescribed antimalarial regimens, and the widespread availability of oral artemisinin-based monotherapies and substandard forms of the drug.

The efficacy of WHO-recommended ACTs is assessed through therapeutic efficacy studies. Such studies at regular intervals at the same sites allow for the early detection of declines in drug efficacy, providing evidence to guide national malaria treatment policies. Molecular markers allow for a precise mapping and monitoring of the geographical distribution of resistance.

Key findings



The new report draws on data collected through more than 1000 therapeutic efficacy studies as well as molecular marker studies of *P. falciparum* drug resistance over a 10-year period (2000–2019). For *P. falciparum*, WHO's global database contains data from approximately 66 000 patients worldwide.

- Overall, first- and second-line ACTs remain effective in curing *P. falciparum* malaria. Where high treatment failure rates were reported, policy changes have been made or are ongoing.[2]

- In four countries in the Greater Mekong subregion – Cambodia, Lao People's Democratic Republic, Thailand and Viet Nam – high treatment failure rates were detected after patients were treated with some ACTs. However, in all of these countries, there were at least two other ACT options that could effectively treat *P. falciparum* malaria.

[2] Since 2006, WHO has recommended a policy change if treatment efficacy falls below 90%.

- In Africa, the continent that carries the world's heaviest malaria burden, the two most commonly-used ACTs are artemether-lumefantrine (AL) and artesunate-amodiaquine (AS-AQ), with some countries adding dihydroartemisinin-piperaquine (DHA-PPQ). Between 2010 and 2019, the overall average efficacy rates for these three medicines were consistently high: AL (98.0%), AS-AQ (98.4%) and DHA-PPQ (99.4%).

- Outside of the Greater Mekong, the findings from two countries – Rwanda and Guyana – are a cause for concern. In 2010 and 2017, Guyana reported a validated molecular marker (C580Y) associated with partial artemisinin resistance. In Rwanda, studies from 2018 also showed an increase in the prevalence of a validated marker (R561H) of artemisinin partial resistance. However, to date, ACTs remain effective in both countries. The drug-resistant malaria strains detected in Rwanda and Guyana have not spread directly from the Greater Mekong subregion, but have emerged independently.

- While *P. vivax* resistance to chloroquine has been reported from all WHO regions, chloroquine remains effective in most parts of the world. *P. vivax* resistance to artemisinin has not be identified.

- WHO continues to work with countries and partners monitor the efficacy of ACTs on an ongoing basis. The latest information and data can be found in the Malaria Threats Map (http://apps.who.int/malaria/maps/threats/).

Global context

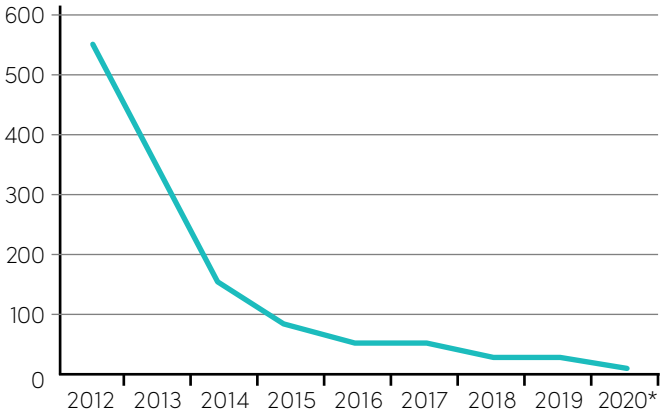
Although drug resistance remains a cause for concern, all strains of *P. falciparum* malaria worldwide can currently be treated with at least two ACTs.

Since 2008, when artemisinin resistance was first reported in the Greater Mekong subregion (GMS), there has been a major decline in the rate of malaria cases and deaths. In the six countries of the subregion – Cambodia, China (Yunnan Province), Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam – the reported number of malaria cases fell by 83% from 2012 to 2019. *P. falciparum* malaria cases fell by 93% in the same time period.

Last year, there were approximately 27 malaria deaths and just over 10 000 cases reported in these six countries. Insufficient access to prompt diagnosis and treatment – and not drug resistance – remains the main risk factor for malaria-related deaths in this subregion.

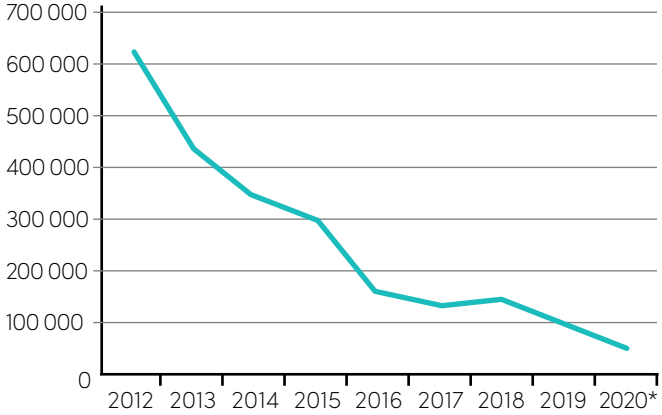
While the risk of drug-resistant malaria spreading directly from the Greater Mekong to Africa cannot be discounted, drug-resistant

Figure 1: Malaria deaths in the six GMS countries (2012–2020)



*The year 2020 covers January to October.

Figure 2: Malaria cases in the six GMS countries (2012–2020)



parasite strains are more likely to emerge independently – as seen in Rwanda – than to spread directly from the GMS.

The consequences of drug-resistant malaria in Africa are likely to be less severe today than those observed with chloroquine in the 1980s. When chloroquine resistance emerged in Africa in the 1980s, malaria control across the continent was very limited; as an example, less than 1% of the population slept under an insecticide-treated mosquito net (ITN).

Since that time, the malaria landscape has changed dramatically. With the massive roll-out of effective vector control (particularly ITNs), chemoprevention to protect the most vulnerable, strengthened case management through diagnostics and combination therapies, improvements to health systems, and increased monitoring of drug efficacy, countries across Africa are in a much better position today to fight antimalarial drug resistance, should they be confronted with it.

> "Countries in the Greater Mekong are winning the battle against *P. falciparum* malaria. The massive reductions in disease and death reported across the subregion in recent years are a testament to the sustained progress that has been achieved along the path toward elimination. The threat of antimalarial drug resistance expanding from the Greater Mekong to other malaria-affected areas has been significantly reduced. What was once seen as the greatest challenge to malaria control globally has been brought under control. Countries still need to walk the last mile, but there is room for optimism."
>
> **Dr Pedro Alonso, Director, WHO Global Malaria Programme**

WHO response to drug resistance in the GMS

WHO is working with national malaria programmes, research institutions, and other partners – within and outside of the Greater Mekong subregion – to map the presence of antimalarial drug resistance, monitor drug efficacy and ensure that patients have access to effective treatment.

Therapeutic efficacy studies remain the primary tool for monitoring the efficacy of nationally recommended antimalarial treatments in all countries. Molecular markers are an asset for early warning signals, or to investigate whether an ACT treatment failure was the result of resistance.

In collaboration with national malaria programmes and partners, WHO led the development of the *Strategy for malaria elimination in the Greater Mekong subregion (2015–2030).* Urging immediate action, the strategy calls for the elimination of all species of human malaria across the subregion by 2030, with priority action targeted to areas where multidrug-resistant malaria parasites have been identified.

In 2017, WHO launched the Mekong Malaria Elimination (MME) programme. The MME subregional team in Phnom Penh, Cambodia, supports the malaria elimination strategy by facilitating coordination and dialogue among partners, communicating with external stakeholders, and coordinating cross-border initiatives.

World Health Organization

Photos © WHO/V. Sokhin