Q&A on artemisinin resistance

March 2018, Geneva, Switzerland

The Q&A on artemisinin resistance is also available online at: http://www.who.int/malaria/media/artemisinin_resistance_qa/en/

1. What is artemisinin and how is it used for the treatment of malaria?

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

Artemisinin-based combination therapies (ACTs) are recommended by WHO as the first- and second-line treatment for uncomplicated P. falciparum malaria as well as for chloroquine-resistant P. vivax malaria. ACTs combine an artemisinin derivative1 with a partner drug. The role of the artemisinin compound is to reduce the number of parasites during the first 3 days of treatment (reduction of parasite biomass), while the role of the partner drug is to eliminate the remaining parasites (cure).

WHO currently recommends 5 different ACTs.2 Artesunate-pyronaridine, a new ACT which has received a positive scientific opinion from the European Medicines Agency,3 is recommended by WHO in areas where other ACTs are failing. Two injectable treatments, artesunate or artemether, are recommended for the treatment of severe malaria and should be followed by an ACT when the patient can tolerate oral therapy.

Increased access to ACTs in malaria-endemic countries has been integral to the remarkable success in reducing the global malaria burden over the last 15 years. The number of ACT treatment courses procured from manufacturers increased globally from 187 million in 2010 to 409 million in 2016.

2. What is the definition of “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 3-day period among patients who are infected with artemisinin-resistant strains of malaria.

Recent studies have demonstrated 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. It is, thus, more appropriate to call the delayed clearance “partial resistance”, to highlight this time-limited and cycle-specific feature. It is unknown whether partial artemisinin resistance could further evolve to affect other stages of the parasites, developing into complete resistance.

Currently, even if patients are infected with artemisinin-resistant parasites, nearly all patients treated with an ACT are fully cured provided that the partner drug is highly efficacious in that geographical area. 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 morbidity and mortality in the GMS. Nevertheless, the proportion of treatment failures increase when both resistance to artemisinin and to ACT partner drugs are present, compared to resistance to the partner drug alone.

3. What is the state of partial artemisinin resistance around the world?

Artemisinin partial resistance likely emerged prior to 2001, and prior to the widespread deployment of ACTs in the GMS. To date, it has been confirmed in 5 countries of the GMS: Cambodia, the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam.

In late 2013, researchers identified a new molecular marker: mutations in the Kelch 13 (K13) propeller domain were shown to be associated with delayed parasite clearance in vitro and in vivo. The molecular marker allows for a more precise mapping and monitoring of the geographical distribution of resistance. It could also be a mechanism for retrospective mapping of resistance in a large number of settings.

Parasites carrying mutations in the K13 propeller domain have been reported in all 5 GMS countries listed above as well as in Guyana, where studies are ongoing to evaluate impact of this mutation on delayed clearance and ACT efficacy and its potential spread within and outside South America.

Molecular studies have shown that partial artemisinin resistance has emerged independently in several locations in the GMS and spread within the subregion. The K13 mutation identified in South America has also emerged independently. Artemisinin partial resistance has not been confirmed in Africa.

Partial artemisinin resistance has occurred as a consequence of several factors: 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.

4. What is the current state of ACT failures around the world?

Artémisinin resistance alone rarely leads to treatment failure. However, resistance of malaria parasites to ACT partner drugs can lead to treatment failure (regardless of the presence of artemisinin partial resistance). As a consequence, several ACTs are failing in the Greater Mekong an area where both artemisinin and ACT partner drug resistance have been identified.

The geographic scope of the problem could widen quickly and have important public health consequences: the spread or independent emergence of partner drug resistance or multidrug resistance globally could pose a public health threat, as no alternative antimalarial medicine is available at present with the same level of efficacy and tolerability as ACTs.

The efficacy of WHO-recommended ACTs is assessed through therapeutic efficacy studies (TES). Such studies at regular intervals at the same sites allow for the early detection of declines in drug efficacy, providing evidence for guiding national malaria treatment policies.
5. How is WHO supporting countries in their efforts to tackle multidrug resistance including partial artemisinin resistance and ACT partner drug resistance?

WHO is working with national malaria programmes, research institutions, and other partners – within and outside of the GMS – to map the presence of artemisinin partial resistance and partner drug resistance; the latter is equally important in view of the consequences seen in terms of ACT treatment failures.

TES 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 ACT treatment failures were to the result of resistance. To improve the response to multidrug resistance in the GMS, countries, with the support of WHO and partners, continually collect and analyse quality data at sentinel sites across the subregion.

Reducing the prevalence of malaria in the GMS – with the ultimate goal of elimination – will mitigate the risk of the spread of multidrug resistant parasites outside the GMS. 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 GMS by 2030, with priority action targeted to areas where multidrug-resistant malaria parasites have been identified.


With technical guidance from WHO, all GMS countries have developed national malaria elimination plans. As countries implement these plans, WHO is providing ongoing technical support through its 5 GMS country offices, regional offices in New Delhi and Manila, and the Organization’s Geneva headquarters.

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

Urgent action now will deliver significant savings in the long run, improving the sustainability and public health impact of malaria interventions around the world.

6. Who is funding these efforts?

The fight to eliminate malaria in the GMS is supported through generous contributions from a number of donors, including: the Australian Department of Foreign Affairs and Trade, the Bill & Melinda Gates Foundation, the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), the UK Department for International Development and the US Agency for International Development.

In response to the emergence of partial artemisinin resistance in the GMS, the Global Fund launched the Regional Artemisinin-resistance Initiative (RAI) in 2013. Funding provided through this initiative has enabled countries to purchase and distribute commodities such as long-lasting insecticidal nets (LLINs), rapid diagnostic tests and quality-assured drugs. In 2017, the Global Fund announced an expansion of the RAI (RAI2E), committing an additional US$ 242 million for the period 2018 to 2020. WHO is working with GMS countries and the Global Fund to optimize the use of this funding in the subregion.
7. What more needs to be done to address this threat?

Scaling up prevention and control interventions and implementing all of WHO’s recommendations require considerable financial resources, long-term political commitment, and strong cross-border cooperation. Endemic countries outside the GMS – and, in particular, in the WHO African Region, where malaria took an estimated 407,000 lives in 2016 – need to also identify additional resources to prevent the emergence and spread of partial artemisinin and partner drug resistance.

One of the most urgent challenges is to strengthen pharmaceutical market regulation, and remove oral artemisinin-based monotherapies and substandard medicines from markets around the world once and for all.

This Q&A was originally issued in April 2013 and was last updated in March 2018.

Notes

1. Artemisinin derivatives include artesunate, artemether and dihydroartemisinin.
2. Artesunate-amodiaquine; artesunate-mefloquine; artesunate+sulfadoxine-pyrimethamine; artemether-lumefantrine; dihydroartemisinin-piperaquine.
3. Through a regulatory procedure known as Article 58, the European Medicines Agency (EMA) assesses the quality, safety and efficacy of medicines that are intended exclusively for use outside the European Union.