Malaria

Q&A on artemisinin resistance

July 2016

1. What is artemisinin?

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-line treatment for uncomplicated *P. falciparum* malaria. Expanding access to ACTs in malaria-endemic countries has been integral to the remarkable recent success in reducing the global malaria burden. The number of ACT treatment courses procured from manufacturers increased globally from 11 million in 2005 to 337 million in 2014.

ACTs combine artemisinin derivatives with a partner drug. The role of the artemisinin compound is to reduce the main parasite load during the first 3 days of treatment, while the role of the partner drug is to eliminate the remaining parasites. In patients who are infected with artemisinin-resistant strains of malaria, the artemisinin compound does not clear all parasites by the third day of treatment. However, patients are still cured as part of a longer treatment regimen, provided that they are treated with an ACT containing a partner drug that is effective in that geographical area. WHO currently recommends 5 different ACTs.

2. What is the state of artemisinin resistance around the world?

As of July 2016, artemisinin resistance has been confirmed in 5 countries of the Greater Mekong subregion (GMS): Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. In the large majority of sites, patients with artemisinin-resistant parasites still recover after treatment, provided that they are treated with an ACT containing an effective partner drug. However, along the Cambodia-Thailand border, *P. falciparum* has become resistant to almost all available antimalarial medicines. There is a real risk that multidrug resistance will soon emerge in other parts of the subregion as well.

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. The geographic scope of the problem could widen quickly and have dire public health consequences: the spread or independent emergence of

artemisinin resistance in other parts of the world could pose a major health security risk as no alternative antimalarial medicine is available at present with the same level of efficacy and tolerability as ACTs.

In late 2013, researchers identified a 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 could allow for a more precise mapping and monitoring of the geographical distribution of resistance. It could also enable a retrospective mapping of possible resistance in a large number of settings. WHO is working with researchers, national malaria programmes and other partners – within and outside of the GMS – to map the presence of artemisinin resistance. Meanwhile, therapeutic efficacy studies remain a central tool for monitoring the efficacy of nationally recommended antimalarial treatments in all countries.

3. What does WHO recommend to tackle artemisinin resistance?

In May 2007, the World Health Assembly called on malaria-endemic countries to progressively cease the provision of artemisinin-based monotherapies (resolution WHA60.18), and in January 2011, WHO released the *Global plan for artemisinin resistance containment*, calling on all stakeholders to maximize efforts to protect the efficacy of ACTs. The global plan contains a comprehensive set of technical recommendations on how to contain existing resistance and prevent it from emerging elsewhere.

In April 2013, WHO launched an emergency response to artemisinin resistance (ERAR) in the GMS and set up a regional hub in Phnom Penh, Cambodia. Though the ERAR programme, WHO is working with affected countries and partners to ensure a rapid and comprehensive scale up of malaria interventions and containment efforts. The emergency response has received funding from the Bill & Melinda Gates Foundation and the Government of Australia.

In May 2015, GMS Ministers of Health adopted the WHO *Strategy for malaria elimination in the Greater Mekong Subregion*. The plan aims to eliminate *P. falciparum* malaria from the subregion by 2025 and all species of human malaria by 2030. The *Global Technical Strategy for Malaria 2016-2030*, endorsed by the World Health Assembly in May 2015, also deals with this issue explicitly, urging countries to eliminate *P. falciparum* malaria in the subregion while current tools remain effective.

Global Technical Strategy for Malaria 2016–2030

Strategy for malaria elimination in the Greater Mekong Subregion (2015–2030

Implementation of the regional elimination strategy will require robust and predictable financing. According to a feasibility study produced for WHO in September 2014, malaria elimination in the GMS would cost over US$ 3 billion between 2015 and 2030.

In recent years, new financial and political commitments have helped to move the GMS malaria agenda forward. In 2013, the Global Fund to Fight AIDS, Tuberculosis and Malaria committed US$ 100 million for 3 years to help affected GMS countries to intensify malaria efforts. In the same year, countries of the Asia and the Pacific, with leadership from Australia and Viet Nam, launched the Asia Pacific Leaders Malaria Alliance at the East Asia Summit in Brunei Darussalam in October 2013. In November 2014, leaders of the East Asia Summit committed to an Asia-Pacific free of malaria by 2030.

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

4. 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. Governments of endemic countries also need to take targeted regulatory measures to remove oral artemisinin-based monotherapies from markets, along with antimalarials that do not meet international quality standards.

Endemic countries outside this region – and in particular on the African continent, where malaria took an estimated 438 000 lives in 2015 – also need to identify additional resources to fully implement WHO recommendations to prevent the emergence of artemisinin resistance. One of the most urgent challenges is to strengthen pharmaceutical market regulation, and remove oral artemisinin-based monotherapies from markets around the world once and for all.

This Q&A was originally issued in April 2013 and was last updated in July 2016.

Note

To learn more about which countries still allow the marketing of oral artemisinin-based monotherapies, and which companies still produce and market these products, please visit:

Withdrawal of oral artemisinin-based monotherapies