GLOBAL MALARIA PROGRAMME

World Health Organization

Status report on artemisinin resistance

January 2014

Key messages

1. **artemisinin resistance and delayed parasite clearance**

The term artemisinin resistance[1] is used to describe delayed parasite clearance observed after treatment with an artesunate monotherapy, or after treatment with an artemisinin-based combination therapy (ACT). Delayed parasite clearance, observed following treatment with either artesunate monotherapy or an ACT, will not necessarily lead to treatment failure. In the Greater Mekong Subregion, failure following treatment with an ACT has only been observed where resistance to the partner drug exists regardless of the presence of artemisinin resistance:

- in Thailand and Cambodia following treatment with artesunate-mefloquine, due to the high prevalence of mefloquine resistance;
- in Cambodia following treatment with dihydroartemisinin-piperaquine, due to the likely emergence of resistance to piperaquine.

2. **a molecular marker for artemisinin resistance has recently been identified**

A molecular marker associated with delayed parasite clearance in patients treated with artemisinin has been identified, and will help improve the global surveillance of artemisinin resistance.

Background on artemisinin resistance

Monitoring therapeutic efficacy

Routine monitoring of the therapeutic efficacy of ACTs is essential for timely changes to treatment policy and can help to detect early changes in *P. falciparum* sensitivity to antimalarial drugs. WHO currently recommends monitoring the efficacy of first-line and second-line ACTs every two years in all endemic countries. The results of the therapeutic efficacy studies allow researchers to determine:

- the **proportion of patients who are parasitemic on day 3**, which is currently the indicator of choice for routine monitoring to identify suspected artemisinin resistance in *P. falciparum*;
- the **proportion of treatment failure** after 28- or 42-day follow-up (depending on the specific ACT). A treatment failure rate exceeding 10% should prompt a change in the national antimalarial treatment policy.

[1] Artemisinin refers to artemisinin and its derivatives.

Current definition of artemisinin resistance

The working definition of artemisinin resistance is based on observations from routine therapeutic efficacy studies of ACTs and clinical trials of artesunate monotherapy:

- an increase in parasite clearance time, as evidenced by ≥ 10% of cases with parasites detectable on day 3 after treatment with an ACT (suspected resistance);

or

- treatment failure after treatment with an oral artemisinin-based monotherapy with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for 7 days, or the presence of parasites at day 3 and recrudescence within 28/42 days (confirmed resistance).

The current definition remains subject to potential confounding factors (i.e. splenectomy, haemoglobin abnormalities and reduced immunity), which can also delay parasite clearance. The definition of artemisinin resistance is likely to be revised in the near future, because of the recent identification of a molecular marker, and improvement of in vitro and ex vivo laboratory sensitivity tests to identify artemisinin resistance.

Possible implications of delayed clearance

Delayed clearance after treatment with an ACT is of paramount concern to WHO. Failure to rapidly clear parasites will compromise the use of artemisinin both for the treatment of severe malaria and for the treatment of uncomplicated falciparum malaria with ACTs.

Slow parasite clearance in patients treated with an ACT causes more parasites to be exposed to the partner medicine alone, increasing the risk of resistance developing to the partner medicine. If this occurs, treatment failures are likely to increase. Currently the majority of patients with a delayed parasite clearance response are still cured by ACTs, provided that the partner drug remains effective.

Recent progress in monitoring artemisinin resistance

Recently, a molecular marker of artemisinin resistance was identified. Mutations in the Kelch 13 (K13)-propeller domain were shown to be associated with delayed parasite clearance in vitro and in vivo. This new tool will help to improve the global surveillance of artemisinin resistance.

Containing and eliminating artemisinin resistance

Global plan for artemisinin resistance containment (GPARC) [2]

The GPARC was developed in response to the identification of artemisinin resistance in the border region between Cambodia and Thailand and the concern that it could spread and/or emerge spontaneously elsewhere. The primary objective of GPARC is to protect ACTs as an effective treatment for *P. falciparum* malaria. The GPARC identifies three tier-levels in order to stratify containment activities:

TIER I – areas for which there is credible evidence of artemisinin resistance, where an immediate, multifaceted response is recommended to contain or eliminate resistant parasites as quickly as possible;

[2] WHO (2011). *Global plan for artemisinin resistance containment*. http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf

TIER II – areas with significant inflows of mobile and migrant populations from tier I areas or shared borders with tier I areas, with intensified malaria control to reduce transmission and/or limit the risk of emergence or spread of resistant parasites;

TIER III – *P. falciparum* endemic areas which have no evidence of artemisinin resistance and have limited contact with tier I areas, where prevention and preparedness should focus on increasing coverage with parasitological diagnostic testing, quality-assured ACTs and vector control.

Emergency response to artemisinin resistance in the Greater Mekong subregion

In April 2013, WHO launched the Emergency response to artemisinin resistance (ERAR) [3] in the Greater Mekong subregion, Regional framework for action 2013-15. The framework urges malaria partners to work in a coordinated manner to provide malaria interventions to all at-risk risk groups; to achieve tighter coordination and management of field operations; to obtain better information for artemisinin resistance containment; and to strengthen regional oversight and support.

WHO has received support from the Australian Department of Foreign Affairs and Trade and the Bill & Melinda Gates Foundation to strengthen the coordination and technical support for containment activities in the Greater Mekong subregion. The project is implemented by the WHO Global Malaria Programme, the WHO Regional office for South-East Asia, the WHO Regional office for the Western Pacific and WHO country offices. A regional hub has been established in Phnom Penh, Cambodia to support countries and help coordination of activities.

In line with the call to action and recommendations contained in the ERAR, the Global Fund to Fight AIDS, Tuberculosis and Malaria has allocated US$ 100 million to a regional artemisinin initiative, funding activities to contain and eliminate artemisinin resistance in Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. The regional artemisinin initiative includes a regional component to support cross-border activities.

Country updates[4]

South-East Asia

Cambodia

Background

- Retrospective analysis of molecular markers indicates that artemisinin resistance likely emerged in 2001, before the widespread deployment of ACTs in Cambodia; significant clinical artemisinin resistance was only identified in 2006;
- Due to high failure rates with artesunate-mefloquine, the first-line treatment for the treatment of uncomplicated falciparum malaria was changed from co-blistered artesunate-mefloquine to fixed-dose dihydroartemisinin-piperaquine in Pailin in 2008 and then nationwide in 2010;
- After the implementation of the containment project in 2009, the number of falciparum malaria patients has declined, but in the presence of continued artemisinin drug pressure, the proportion of patients treated with dihydroartemisinin-piperaquine who were still parasitemic on day 3 increased from 26% to 45%, between 2008 and 2010;

[3] WHO (2013). *Emergency response to artemisinin resistance in the Greater Mekong Subregion*. http://apps.who.int/iris/bitstream/10665/79940/1/9789241505321_eng.pdf

[4] WHO (2011). *Global report on antimalarial efficacy and drug resistance: 2000-2010*. http://whqlibdoc.who.int/publications/2010/9789241500470_eng.pdf

- In parallel, an increase in treatment failures with dihydroartemisinin-piperaquine was reported between 2008 and 2013 in four provinces: Battambang, Oddar Meanchey, Pailin and Pursat; the high treatment failures observed with dihydroartemisinin-piperaquine could be related to the emergence of piperaquine resistance, a drug related to chloroquine;
- A consensus meeting held in November 2011 recommended the use of atovaquone-proguanil delivered as directly-observed therapy for Pailin province as a short-term interim solution, with stringent follow-up for monitoring resistance.

Update

- Stringent follow-up of the patients treated with atovaquone-proguanil led to the detection of atovaquone resistance (mutations of cytochrome b) in Pailin in September 2012;
- The use of atovaquone-proguanil was extended to one health centre in Battambang and four health centre in Oddar Meanchey in 2013;
- A consensus meeting will be held in January 2014 to decide on a new treatment policy in provinces with high treatment failure rates with dihydroartemisinin-piperaquine.

Laos

Update

- In 2013, a trial conducted in Champasack province reported that 22.2% of the patients treated with artemether-lumefantrine were still parasitemic on day 3 after treatment;
- The emergence of artemisinin resistance in southern Laos is supported by the recent (2013) identification of the presence of K13 mutants in the circulating parasite populations;
- The therapeutic efficacy of artemether-lumefantrine is not affected and cure rates have remained high since 2005.
- Containment activities will start in 2014.

Myanmar

Background

- Artemisinin resistance likely emerged at the border between Thailand and Myanmar in 2001, but clear identification of the problem was recognized only in 2008;
- Since 2009, available data show consistently delayed parasite clearance times in part of the patients treated with ACTs, suggesting the emergence of artemisinin resistance in five regions and states in south-eastern Myanmar, and in relation with all the three first-line ACTs used in the country (artemether-lumefantrine, artesunate-mefloquine and dihydroartemisinin-piperaquine);
- The results showing delayed parasite clearance rates in several parts of the country led to the initiation of the Myanmar Artemisinin Resistance Containment (MARC) framework, based on the action points designed for tier I and tier II areas described in the GPARC. This containment project started in September 2011, funded by the donor consortium Three Diseases Fund. Funding for the project was granted until June 2012.
- The three first-line ACTs used in the country are still effective as treatment for uncomplicated falciparum malaria, with high cure rates.

Update

- Studies evaluating the presence of K13 mutants are currently on-going with filter papers collected in Myanmar during the 2012-2013 therapeutic efficacy study to better map the extent of artemisinin resistance and to adapt containment activities accordingly.

Thailand

Background

- Containment activities on the Thailand side of the Cambodian-Thai border began simultaneously with Cambodia in 2008;
- Until 2008, Thailand used a regimen of 2-day artesunate-mefloquine as first-line treatment. Despite the change to a 3-day regimen, treatment failures with artesunate-mefloquine increased in Kanchanaburi, Ranong, Tak and Ubonratchathani reaching treatment failure ≥ 10%;
- Higher treatment failures observed in Thailand with artesunate-mefloquine could be explained by the presence of mefloquine resistance (which has been confirmed countrywide) on top of reduced artesunate susceptibility. Mefloquine drug pressure has been considerable over the last decades, since Thailand has been using different regimens of mefloquine (15 to 25 mg/kg) as monotherapy or in combination with artesunate;

Update

- The first line treatment for Thailand is currently using a loose combination of artesunate and mefloquine. Consensus is urgently needed on optimal treatment scenarios for Thailand;
- Artemether-lumefantrine was evaluated in two provinces in 2012 but the failure rate was close to or exceeded 10%;

Viet Nam

Background

- Delayed parasite clearance was first detected after treatment with dihydroartemisinin-piperaquine in Bu Dang district of Binh Phuoc province in 2009;
- Routine monitoring in 2011 with dihydroartemisinin-piperaquine also detected other foci of reduced susceptibility to artemisinins in Gia Lai province (2010), in Dak Nong and Quang Nam (2012);
- In mid-2011, Viet Nam began containment activities based on the GPARC document with support from WHO Western Pacific Regional Office and country office.

Summary of the status of artemisinin resistance in the Greater Mekong Subregion

	artemisinin resistance		containment activities started	AL		AS-MQ		DHA-PPQ	
	suspected year of emergence	detected		D3+	TF	D3+	TF	D3+	TF
Cambodia	2001*	2006	2009	♦	♦	♦	♦	♦	♦
Laos	2013	2013	2014	♦	–				
Myanmar	2001*	2008	2011	♦	–	♦	–	♦	–
Thailand	2001*	2008	2009	♦	♦	♦	♦		
Viet Nam	2009	2009	2011					♦	–

Legend: first-line treatment; * detected retrospectively using molecular markers or retrospective data;
♦ observed to be > 10%; – observed to be < 10%; blank = undetermined

Africa

Efficacy of ACTs is being monitored in most malaria endemic countries. There have been no reports of consistent delayed parasite clearance during routine therapeutic efficacy studies conducted in Africa.

South America

Suriname

In 2011, the efficacy of artemether-lumefantrine was monitored in gold miners: 28% of patients were parasitemic on day 3 (compared with 2% in 2005-2006). Despite this high day 3 positivity rate, the therapeutic efficacy was 100% at day 28. A confirmatory study using artesunate and mefloquine is ongoing.

Guyana

The last study with artemether-lumefantrine was conducted from May 2011 to July 2012: a total of 92 patients were enrolled, with 68 completing the 28 day follow-up. 70.8% of day 3 slides were found positive, but after quality control review, the study was considered flawed, and a new study with 7-day artesunate is planned to start soon.

French Guyana

In the Cayenne hospital, between 2009 and 2013, the day 3 positivity rate among patients treated with artemether-lumefantrine was 7.5%, but the treatment was not systematically supervised. An additional study is planned for 2014.

Conclusion

Despite the delayed response to artemisinin in some areas of the Greater Mekong Subregion, ACTs remain the most effective treatment for uncomplicated falciparum malaria. Most patients with delayed response are cured if the partner drug remains effective. Routine monitoring must be continued to ensure that the recommended first-line ACTs are effective, for timely changes in national treatment policies, and for the early detection of artemisinin resistance. The discovery of a molecular marker will greatly facilitate the tracking of artemisinin resistance as it emerges.

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Please also visit the following WHO website for additional information and data:
http://www.who.int/malaria/areas/drug_resistance/en/index.html

Tier maps of the Greater Mekong subregion (January 2014)