

**TERG**



# Artemisinin Resistant Malaria: Options for the Global Fund

December 2012

## **TERG Thematic Review: One Page Summary**

### **Artemisinin Resistant Malaria: options for the Global Fund**

#### **Summary**

Highly effective artemisinin-based combination therapies (ACTs) are the global standard treatment for uncomplicated *P. falciparum* malaria. Currently there are no alternative treatments which are practical for wide-spread use. The recent scale-up in improving access to ACTs has contributed to the much heralded progress in reducing malaria illness and deaths.

However, the development and spread of malaria parasites resistant to artemisinin is already a looming threat and would be disastrous to ongoing efforts to control and eventually eliminate malaria. The emergence of artemisinin resistance in the Greater Mekong Sub-region<sup>1</sup> (GMS) is therefore a matter of grave concern. Resistance to earlier antimalarial drugs was also detected in the same region and eventually spread worldwide. Loss of effective drugs has been one of the greatest challenges hindering earlier global malaria control efforts.

The Global Fund and its investments are implicated as:

- artemisinin resistance is a serious global risk. Without viable treatment alternatives, the current impact on malaria incidence and mortality of activities funded by the Global Fund would be seriously reduced;
- artemisinin resistance could erode not only the value of future investments but also the gains made to date;
- the Global Fund is the largest funder of malaria activities and is the primary international funder of malaria control in many countries. The new funding model and ongoing grants have a unique potential to promote intervention activities that could detect and track artemisinin resistance, ensure the establishment of mechanisms for quick response and containment thereby lessening the risk of artemisinin resistance spreading further;
- the artemisinin resistance case which underscores an urgent situation requiring rapid actions to protect gains achieved to date is an example of strategic investment needs that should be considered and incorporated into the Global Fund business model.

This paper assesses recent reviews on the status of malaria parasite resistance to artemisinin and ongoing efforts to contain the problem. The paper then assesses the contribution and challenges posed by the Global Fund's current model, including an honest assessment of where current strictures have actually hindered the response to artemisinin resistance and potentially jeopardizing the success of containment efforts.

Options for the Global Fund are also presented to facilitate efforts to support monitoring and containment of artemisinin resistance through ongoing efforts and also in the future. This "case study" is also used as an example to examine a more generic question: How can the Global Fund best respond to serious risks with the potential to substantially undermine, or even negate, past and future investments in one of the three diseases? In addition to individual grant investments, options include:

1. Integrate preemptive strategic investments in key activities to control regional and global risks in high-risk areas in early 2013 (i.e. certain key countries where artemisinin resistance has already been detected or at risk have on-going grants where detection, containment and prevention activities could be added);
2. Ensure continuous funding to strategic interventions in key countries through current and future funding modalities e.g. with continuity of services, safeguards and streamlining of existing procurement procedures, including after audit findings;
3. Require systematic investment in resistance monitoring in key countries to address global risks;
4. Develop regional responses and grants coordination together with partners, in some key areas of global risk, i.e. cross-border initiatives may be required as multiple countries are implicated and will require a more direct role of technical agencies such as the WHO and CDC. The response could include regional-level grants through these agencies to ensure the most effective measures are put in place rapidly.
5. Develop greater flexibility in procurement requirements in these situations, especially regarding the drug regime used to ensure most effective drugs are used in a rapidly evolving context.
6. Consider special dispensation of certain activities directly related to artemisinin containment activities in key areas, including during and after audit procedures.

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<sup>1</sup> The Greater Mekong Sub-region includes Cambodia, Lao PDR, Myanmar, Thailand, Vietnam and Yunnan Province of China

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11. Develop greater flexibility in procurement requirements in these situations, especially regarding the drug regime used to ensure most effective drugs are used in a rapidly evolving context.
12. Consider special dispensation of certain activities directly related to artemisinin containment activities in key areas, including during and after audit procedures.

## **Part 1: Brief overview of artemisinin resistance and its containment**

### **What is artemisinin resistance and what is the evidence for its presence in the Greater Mekong Sub-region (GMS)?**

Emergence of malaria parasites resistant to any certain drug is driven by their exposure to that same drug – especially sub-therapeutic doses. While parasites are sensitive to a drug, widespread treatment at an adequate dosing level (i.e. sufficiently high level of active ingredient and taking the full recommended course) does result in a reduction in the number of cases. Exposure to sub-therapeutic doses of a drug (i.e. low levels of active ingredient or not taking all the recommended pills) allows parasites to adapt to the drug without being killed off – favouring the emergence of resistance. Once parasites have become resistant, the proportion of cases due to them will rise as it takes longer to cure the illness and there is more time to pass the parasite on to others.

Using two drugs in combination, as in ACT, aims to increase treatment efficacy and slow the emergence of resistance. ACT combines a fast-acting high impact drug, an artemisinin derivative, to knock down the parasite numbers, with a longer-acting drug to clear any remaining parasitaemia. If the efficacy of one drug in an ACT is diminished, this increases pressure on the other drug, increasing the likelihood that resistance to this drug will also develop. Increasing resistance to artemisinin derivatives will accelerate resistance to ACT partner drugs, and vice versa.

### **Box 1: Working definitions of artemisinin resistance**

Working definitions of artemisinin resistance are based on clinical and parasitological outcomes observed during routine therapeutic efficacy surveillance (TES) of ACTs and clinical trials of artesunate monotherapy.

**Suspected resistance** is defined by an increase in parasite clearance time, as evidenced by  $\geq 10\%$  of cases with parasites detectable 72 hours after treatment with an ACT (also referred to as Day 3 parasitaemia).

**Confirmed resistance** is defined by 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.

**Day 3 parasitaemia is the best available proxy indicator for artemisinin resistance at the time of writing.**

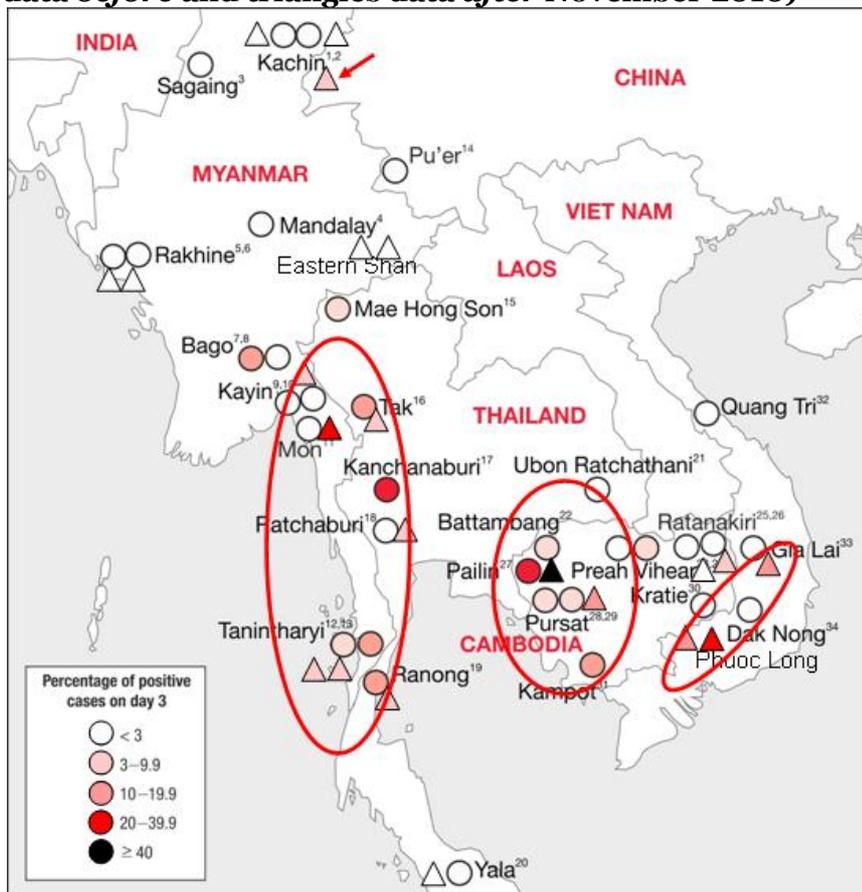
The history of resistance to anti-malarial drugs in the GMS is long and has stimulated an active network for therapeutic efficacy surveillance complemented by laboratory testing and research. Data from these sources has allowed mapping of the emergence of artemisinin resistance; signs of its presence have now been detected in at least 13 sites in Cambodia, Myanmar, Thailand and Vietnam. Figure 1 summarizes data on Day 3 parasitaemia (a marker for artemisinin resistance, see Box 1) detected across the GMS. There is no evidence yet of artemisinin resistance beyond the GMS.

### **Why are we concerned by artemisinin resistance?**

Between the 1980s and the 1990s malaria mortality in children in Africa, where most malaria deaths occur, increased by 80%, associated, at least in part, with growing resistance to the antimalarial drugs used at the time. ACT has been a key component of the subsequent scale-up of malaria control globally that has improved the situation dramatically; global malaria-specific mortality fell by a quarter from 2000 to 2010 – driven in large part by ACT scale-up in African countries. ACT is now the mainstay of treatment for uncomplicated *P. falciparum* malaria worldwide. Meeting the Global Malaria Action Plan goal of near-zero malaria deaths globally by 2015 depends on the continued efficacy of ACT. The corollary is that loss of ACT as an antimalarial would bring huge loss of life, probably in the tens of thousands of lives, before a new anti-malarial drug would become available. Such a set-back would greatly hinder control efforts and severely derail the push for malaria elimination, as well as represent a huge loss on the investments already made.

No other drug regimen is currently available that could replace ACT. Atovaquone-proguanil, an effective non-ACT combination mostly used for prophylaxis in travellers, is expensive and it is expected that resistance to it would develop rapidly. Its use would require directly observed treatment, which is practically difficult. Another alternative, quinine and tetracycline (or doxycycline), requires many doses over a 7-day period and is not recommended for children under 8 years or pregnant women. However, it's worth noting that artemisinin compounds are also not recommended in the 1st trimester of pregnancy due to concerns about early fetal loss, unless there are no other life-saving drugs available.

**Figure 1. Percentage of cases with Day 3 parasitaemia after ACT (Circles represent data *before* and triangles data *after* November 2010)**



Source: WHO Global Malaria Programme, 2012

New non-ACT drugs are in the research and development pipeline but would not be available for wide-scale use for another 5 years in the best case scenario. Even if an alternative treatment were available there are huge costs associated with changing first-line treatment in terms of increasing manufacturing capacity, producing guidelines, retraining staff and educating the public.

Estimation of the economic costs of not responding to artemisinin resistance is difficult but they are likely to far out-weigh the costs of intensified malaria control in what are still a limited number of geographic foci of resistance. The projected devastating losses in terms of lives and economic investment could be limited and/or even averted by investing today in a major effort to respond to artemisinin resistance. Responding to artemisinin resistance represents a sensible and foresightful investment in good malaria control; it will strengthen systems, improve the quality of operations and stimulate and inform progress towards elimination of the disease while existing affordable tools remain effective.

### **What has been done to respond to the threat of artemisinin resistance?**

Four countries in the GMS region have initiated special efforts specifically designed for artemisinin resistance containment: Cambodia and Thailand, in 2009 and Myanmar and Vietnam in 2011. In 2011, after an extensive consultation with stakeholders WHO released the Global Plan for Artemisinin Resistance Containment (GPARC). The containment strategy involves the rapid implementation of proven malaria control interventions with a very high level of coverage and quality, especially in the geographic areas closest to the detected cases of resistance, known as containment Tiers 1 and 2. These interventions include parasitological diagnosis for all patients with

suspected malaria; treatment of confirmed cases of *P. falciparum* malaria with a full course of quality-assured ACTs; and personal protection and vector control, as locally appropriate.

In late 2011 and early 2012, an assessment of the response to artemisinin resistance in the GMS was carried out with the collaboration of WHO, DFID and USAID/PMI and sponsored by AusAID and the Bill and Melinda Gates Foundation. The joint assessment conducted an extensive review of available documentation and visited areas where artemisinin resistance has been detected in Cambodia, China (Yunnan province), Myanmar and Vietnam. The full report of this activity is available from AusAID and the draft report is available online at <http://malaria2012conference.com/cms/wp-content/uploads/2012/10/Joint-Assessment-of-the-Response-to-Artemisinin-Resistance.pdf>.

The joint assessment concluded that the strategy laid out in the GPARC was still appropriate but may need modification as new evidence on the nature of artemisinin resistance is produced. Implementation of such a strategy along the Thai-Cambodia border had significantly reduced the incidence of malaria, especially that caused by *P. falciparum*, and the number of malaria deaths. The joint assessment concluded, however, that “**not enough is yet being done, with enough intensity, coverage and quality, to respond to a problem that could not only slow future progress but also undo the gains already made in malaria control worldwide.**”

The initial model of containment was aimed at eliminating resistant *P. falciparum* malaria in the areas where evidence of resistance had been detected to stop its spread to other areas. With evidence of artemisinin resistance now detected also on the Thai-Myanmar border and in Vietnam, it appears likely that containment of artemisinin resistance in a limited area may not be possible or, at least, is no longer possible. Nevertheless, the components of the containment strategy are appropriate to reducing the circulation of resistant parasites wherever they are detected and limiting spread to other areas is certainly beneficial. Achieving this may require the trialing, and if successful, implementation of more aggressive efforts to detect and/or treat every case of malaria in areas of containment.

## **Part 2: Artemisinin resistance and the Global Fund**

### **Has Global Fund financing contributed to monitoring of artemisinin resistance?**

The Global Fund has financed the procurement of many millions of courses of ACT treatment. It has, therefore, a strong interest, even responsibility, to ensure that the drugs that it provides are efficacious against malaria.

In almost 40 countries Global Fund grants have included funding for monitoring of resistance to antimalarial drugs with \$18.7 million allocated to (and \$ 13.2 million spent on) such activities up to 2011. From the perspective of their contribution to global monitoring of drug resistance, the outcome of this expenditure has been mixed. Analysis of the budget structure of Global Fund grants in six countries with the highest reported expenditure on antimalarial drug resistance shows that the resources were used in the following areas:

- Development of study protocols and Standard operating procedures;
- Developing and distributing reporting materials and systems;
- Training of national teams (as trainer), clinicians and information officers;
- Procurement of laboratory consumables;
- Patient recruitment, follow-up and data collection;
- Data analysis and dissemination of results;
- Collaboration with research institutions;
- Transport and logistics; and
- Technical assistance

For this surveillance to be useful, it needs to be done according to a standardized protocol by teams that have been trained in its use. WHO promotes and coordinates the use of such a protocol and provides funding and technical assistance to countries to conduct therapeutic efficacy surveillance (TES). Such assistance and coordination is essential for detecting and tracking the emergence of drug resistance. WHO also supports a series of regional networks which links neighbouring countries conducting TES to share experience and findings; the GMS has a well-developed network, and the primary funding for the TES in the region has been from the US government.

In some countries the combination of Global Fund financial support and WHO technical input has worked well. In Cambodia TES has been supported by Global Fund and WHO funding. Global Fund also supports TES in Thailand, Viet Nam, and Myanmar. WHO is involved in the surveillance studies and has access to the data generated. The Global Fund support for artemisinin resistance monitoring goes beyond the GMS. In the Gambia the TES has been supported by the Global Fund and at the request of the national malaria control program WHO reviewed the protocol (which was based on the standard WHO template) and provided quality assured drugs; WHO will have access to the data.

In other countries it is less apparent how the Global Fund financing has contributed to the global knowledge on drug resistance. It remains yet to be established how exactly the Global Fund funding contributed to antimalaria drug resistance monitoring and surveillance in countries outside GMS. It is possible that it has strengthened some institutions or covered core costs, which has allowed them to participate in the network activities with only modest funding from WHO. In some countries Global Fund support for drug resistance monitoring has been substantial compared with the known drug surveillance output of the country. For example, Papua New Guinea (PNG) has spent around \$2.4 million of Global Funding support for drug resistance testing but has only been able to finance two surveillance sites. (WHO usually provides \$50,000-70,000 per site per year, which is adequate for most institutions to conduct good quality studies.) In addition, the researchers who conducted the studies in PNG have not shared the results with WHO. In nine countries the amount of funding was less than \$50,000, probably insufficient to conduct a single study. It should be mentioned that this is an area that is sufficiently specialized that the average TRP member would be unlikely to be able to adequately assess the appropriateness of proposed actions and funding. Although in most countries the amounts of money were not large, cumulatively the amount spent could have gone a long way to maintaining and strengthening the WHO coordination and technical support to therapeutic efficacy surveillance thus contributing more concretely to the global surveillance database.

## **Has the Global Fund contributed to containing artemisinin resistance?**

As noted above, Cambodia and Thailand initiated artemisinin resistance containment in 2009 and Myanmar and Vietnam in 2011. The Global Fund has funded malaria control in all of these countries and thus contributed very significantly to the base on which artemisinin resistance containment efforts have been built. Considerable quantities of commodities for malaria control, for example, have been bought with Global Fund financing and used in areas of artemisinin resistance containment.

In Cambodia the funded Round 9 proposal for malaria was specifically designed for continuing artemisinin resistance containment activities carried out with Bill and Melinda Gates Foundation support from 2008-2011. In Thailand, Round 10 funding was also significantly targeted to activities on the Thai-Cambodia border to respond to artemisinin resistance, including establishment of screening posts along the Thai-Myanmar border. Global Fund proposals for Myanmar and Vietnam were developed before evidence of resistance was detected. Global Fund financing to China has enabled activity in Yunnan province, which while not designated as artemisinin resistance containment has helped to reduce the malaria burden in an area where there is judged to be a risk of importation of resistant malaria from Myanmar. Importantly, the Global Fund funding to China has also supported NGO activity across the border in remote areas of Myanmar not served by the Government of Myanmar. This support is not only important for the financing it brings but also because the external source of the funding facilitates funding of cross-border activity that might otherwise be more difficult.

Global Fund financing has supported operational research and pilot studies in countries with artemisinin resistance of innovative interventions in support of containment. The funding has not necessarily been available to take these to scale.

## **Have Global Fund procedures impeded progress on artemisinin resistance containment?**

During the joint assessment of the response to artemisinin resistance the rigidity in Global Fund procurement procedures and the unwillingness to look beyond the immediate issue to the bigger picture were frequently raised as issues. The assessment did not go into detail on each issue but there are clear examples of slowness in procurement decisions significantly impeding the implementation of activities aimed at artemisinin resistance containment.

The most significant example is the unwillingness of the Global Fund, in the light of increasing treatment failures with artesunate-mefloquine in Cambodia, to finance the procurement of the recommended alternative, dihydroartemisinin-piperaquine, because there was no prequalified supplier of the latter combination. The recommendation to use dihydroartemisinin-piperaquine was made by an international expert group and fully endorsed, but not prequalified, by WHO. Supplies were available and were eventually financed by DFID and Bill and Melinda Gates Foundation but only after a long delay caused by extended and ultimately fruitless negotiation with the Global Fund due to the lack of prequalification. However, it is worth noting that the pressure from the Global Fund was instrumental in expediting the WHO pre-qualification of the supplier. A program to supply the private sector with ACT was severely disrupted for the same reason with stock-outs over nine months undermining credibility and nascent public acceptance of ACTs. RDTs were also affected. This episode may have resulted in deaths that would not have otherwise occurred and had a negative impact on attempts to eliminate resistant parasites through use of an effective ACT.

There is a general perception that Global Fund Portfolio Managers, and the Global Fund more generally, can be quite rigid in its decision making even when there are compelling reasons to be more flexible.

## **Is Global Fund action jeopardizing current artemisinin resistance containment efforts?**

Cuts in Global Fund financing are having a negative impact on the fight to limit artemisinin resistance. In Cambodia for example, funding for some areas of work under Round 9 are being cut by 35% at a time when artemisinin resistance containment activities have already been affected by the end of the Bill and Melinda Gates Foundation interim support. On a positive note, given the recent malaria program review in Cambodia the Global Fund is making an effort to keep funds flowing to the country rather than suspending the grant, which would have happened in the past. China's ineligibility for further Global Fund support is also likely to result in a reduction in support for artemisinin resistance containment related activities, including across the border into Myanmar. Thailand Round 10 funding has also been affected. Perhaps most problematic is the suspension of Round 11. With newly initiated artemisinin resistance containment activities in Myanmar and Viet Nam both countries were planning to submit Round 11 proposals specifically focused on this area of work. Following the suspension of Round 11 this was not possible and funding in both countries was thrown into a crisis. Representation to the Global Fund around the possibility of obtaining Transitional Funding were ultimately abandoned because the criteria for such funding were not sufficiently flexible to make it possible despite the urgency and importance of the issue.

## Part 3: Implications for the Global Fund

### Are there lessons for the Global Fund funding model?

Considering the example of artemisinin resistance it would seem reasonable to set aside a certain amount of funding that could be allocated for similar risks through a process that does not depend on countries submitting proposals. This might include:

- Initiate strategic investment systematically across countries and regions to fill programmatic gaps in key interventions, e.g., resistance surveillance, ensuring impact and managing global risks;
- Ensure no gaps in funding in key interventions and strategic activities in key countries. This should be taken into consideration in grant management and OIG recommendations in key countries;
- Investigate regional grants, coordinated by partners, e.g., WHO in these areas of global risk. Risks such as artemisinin resistance require urgent coordinated multi-country actions to address and manage effectively.

With respect to country proposals that are already funded the artemisinin resistance example suggests that some situations require decisions that cannot be taken only from the perspective of Global Fund procurement guidelines, or as a consequence of audit outcomes. There is little benefit in respecting procurement integrity at the expense of the entire investment. Similarly, abrupt action on the basis of audit findings may also jeopardize the entire Global Fund investment. These situations may need to be managed more cautiously and through special measures.

### How could the Global Fund better support field operations for artemisinin resistance containment?

There are a number of actions that could be taken in this regard, for example:

- **avoiding abrupt suspension of funding in countries where artemisinin resistance containment activities depend on Global Fund financing, as the consequences could be disastrous, and not just for the country concerned;**
- through performance monitoring encouraging 100% intervention coverage in containment Tiers 1 and 2;
- encouraging operational research in artemisinin resistance containment with population groups at highest risk;
- requiring parasitological diagnosis of malaria cases before treatment where the drugs used are procured with Global Fund financing;

### How could Global Fund better support artemisinin resistance monitoring?

There are a number of ways that the Global Fund could better support the **therapeutic efficacy surveillance**<sup>3</sup> that allows the detection and tracking of resistance to artemisinin and other antimalarial drugs; these include:

- ensuring that all countries receiving Global Fund support for malaria control have the capacity and funding to monitor drug resistance;
- ensuring the TRP consults with WHO on any proposals involving drug resistance surveillance requiring that all therapeutic efficacy studies conducted with Global Fund financing are carried out according to the WHO protocol and results communicated as soon as available. One possible

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<sup>3</sup> Note that in addition to the Global Fund there are others who are supporting the TES—e.g., PMI, NIH, DFID, Wellcome Trust.

approach to this will be to ensure TRP briefing and additional guidance by WHO prior to review of proposals;

- coordinating with WHO to ensure that any funding to countries for drug resistance monitoring is complementary (not duplicative) and value-for-money in terms of the proposed output. This is in line with the new funding model that facilitates dialogue with CCMs;
- working with WHO to ensure that it is adequately funded to play its standard setting, capacity building, technical support and coordination roles, without which drug resistance surveillance in individual countries is of limited value.

**Are there other issues in malaria control that raise similar questions?**

One area that is arguably in the same class as drug resistance is resistance to insecticides, evidence of which is occurring sporadically in Africa. Given the great importance of LLINs, and to a lesser extent indoor residual spraying of insecticide, in the control of malaria, increasing resistance to insecticides could have a devastating effect. High quality surveillance and the trialing of appropriate containment activities are critical to ensure the continued success of the malaria control programs.