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Stephen P Kachur, John R MacArthur & Laurence Slutsker

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A call to action: addressing the challenge of artemisinin-resistant malaria

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Stephen P Kachur
Malaria Branch, US Centers for Disease Control and Prevention, Mailstop F-22, 4770 Buford Highway, NE, Atlanta, GA 30341, USA

John R MacArthur
Malaria Branch, US Centers for Disease Control and Prevention, Mailstop F-22, 4770 Buford Highway, NE, Atlanta, GA 30341, USA

Laurence Slutsker, MD, MPH
Author for correspondence
Malaria Branch, Division of Parasitic Diseases, Center for Global Health, Centers for Disease Control and Prevention, Mailstop F-22, 1600 Clifton Road, Atlanta, GA 30333, USA
Tel.: +1 770 488 7789
Fax: +1 770 488 4206
lms5@cdc.gov

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Malaria continues to exert an enormous toll globally. In 2008, there were an estimated 243 million clinical cases and 863,000 deaths [101]. More than 80% of these cases and approximately 90% of the deaths occur in sub-Saharan Africa, mainly among children less than 5 years of age.

Despite these staggering figures, the past decade has seen a resurgence of optimism regarding progress in malaria control. Although much remains to be done, there are now well-documented examples of success achieved through scale-up of key interventions. Reduced malaria infection and associated reductions in child morbidity and mortality have been reported in Equatorial Guinea [1], Zanzibar [2], São Tomé and Principe [3], Rwanda and Ethiopia [4]. As scale-up and coverage continue to progress in other countries, especially those with a very high malaria burden, it is expected that similar gains will be achieved.

The strategy to reduce malaria morbidity and mortality in sub-Saharan Africa is predicated on achieving rapid, high-level population coverage with four key interventions: long-lasting insecticide-treated nets (ITNs), indoor residual spraying (where appropriate), intermittent preventive treatment in pregnancy, and prompt and effective treatment with artemisinin-containing combination therapies (ACTs) [102]. ACTs have been shown to be highly effective in the treatment of uncomplicated malaria [5].

All 42 countries in Africa with endemic *Plasmodium falciparum* transmission have adopted ACTs as a first-line treatment, replacing older, less effective choices such as chloroquine or sulfadoxine–pyrimethamine [101]. These older regimens were greatly compromised by high levels of parasite drug resistance and were associated with an alarming deterioration in child survival [6]. While programmatic roll out of ACTs has lagged somewhat behind that seen with ITNs [101], major efforts are underway to increase access to these antimalarials through the public and private sectors, and through facility and community-based delivery systems. High ACT coverage is expected to substantially contribute to further reductions in child mortality in Africa over the next 5–10 years. To date, in Africa there has been no evidence of a decreased response of *P. falciparum* to artemisinin.

Recent reports from Southeast Asia suggest that falciparum parasites now show early signs of resistance to ACTs and artemisinin monotherapies [7]. These reports sparked a call for containment of the resistant parasite and/or elimination of malaria transmission from the subregion [103]. Scientists have yet to uncover the biological basis for this development. Southeast Asia has been, historically, the crucible in which biological, pharmacological, cultural, political and economic factors have catalyzed the emergence of parasites resistant to one antimalarial compound after another. If artemisinin-resistant parasites make their way from the forests and swidden farms in the Mekong Basin to the East African Coast – just as chloroquine- and sulfonamide-resistant parasites have done [8,9] – many fear the remarkable achievements just getting underway in many African countries will be short-lived.

The immediate call to contain or eliminate ACT-resistant malaria in Southeast Asia has implications for the rest of the

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malaria-endemic world. It is unclear how well transmission reduction efforts, such as indoor spraying and ITNs or insecticide-treated hammocks, will be able to affect mosquito vectors in this region that typically bite or rest outside. Other challenges will include reaching migrant and ethnic minority populations, and finding the tools to detect and characterize potentially resistant parasites. On top of these, additional concerns exist about enhancing poorly regulated private sector access to ACTs, and the expansion of poor-quality or deliberately fake drugs entering widespread use. The efforts to contain or eliminate resistant parasites in Southeast Asia would undoubtedly benefit from advances in identifying and measuring the evolution of drug-resistant parasites. In the absence of a biological or molecular marker, researchers are forced to rely on clinical outcomes, such as parasite clearance times, to track this emerging crisis. The global community urgently needs to develop more nimble tools. Yet even in the absence of these, it is possible to track genetic drift and other dynamics that can document the movement of parasite populations from areas where resistance has been established to higher transmission zones in Africa and beyond. In addition, more systematic reliance on laboratoryconfirmed diagnosis as a precondition for ACT treatment could help limit the exposure of these drugs at subtherapeutic levels to future infections. Encouraging these as basic first steps toward confronting the challenge of multidrug resistance should be a global priority.

The current crisis demands that we reinvest in tracking drug resistance outside the areas of immediate concern in the Mekong basin. After adopting highly efficacious ACTs, many endemic countries and their donor partners have de-emphasized, interrupted or abandoned previously strong programs for tracking drug resistance through *in vivo* clinical studies. Control programs and their donor partners must urgently reinvigorate these, not only in Southeast Asia but also in high-burden countries in Africa. While the search for molecular markers of resistance and tracking the mobility of parasite populations must continue, we also need to heighten our vigilance for early indicators of deteriorating ACT efficacy, such as slowed parasitological clearance.

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For now, debate over whether or not containment and elimination efforts can succeed in ACT-resistant hot zones like Southeast Asia has been somewhat hushed. The consensus is clear. They had better suceed. At the same time, malaria control programs and their donor partners across the endemic world should urgently revitalize efforts to characterize and track potentially resistant parasites, especially where they are investing heavily in rolling out access to ACTs. Research and development must prioritize identifying and approving the next generation of malaria treatment drugs. Global research consortia, such as those funded by the Bill and Melinda Gates Foundation, are an important first step toward these goals. In addition, understanding the progressive interplay between malaria prevention and treatment interventions across varying levels of transmission now demands the greatest possible global attention.

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