

# The Danger of Untreatable Malaria Is Real and Present



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*A Report of the CSIS Global Health Policy Center*

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# The Danger of Untreatable Malaria Is Real and Present

Christopher V. Plowe<sup>1</sup>

The malaria parasite is thought to have killed more people throughout human history than any other single cause.<sup>2</sup> Over the last decade, a large increase in resources for combating malaria—with the lion's share coming from U.S. taxpayers—has resulted in dramatic reductions in malaria cases and deaths in many countries.<sup>3</sup> These successes spurred the Bill & Melinda Gates Foundation and the World Health Organization (WHO) to call for global eradication of malaria in 2007.<sup>4</sup>

The massive global investment in malaria control and elimination, and prospects for global eradication, are threatened by the emergence in the Greater Mekong Subregion<sup>5</sup> of malaria parasites that have become resistant to artemisinins, the first line drug for treating malaria worldwide.

A CSIS report published just over one year ago provides a good overview of drug-resistant malaria and efforts to address it.<sup>6</sup> The current report is an update for the nontechnical reader on drug-resistant malaria, summarizing new developments, threats, and opportunities that have emerged over the last year.

## Multidrug-Resistant Malaria Has Arrived in Cambodia

The recent emergence of artemisinin-based combination therapy (ACT)-resistant parasites in Cambodia raises the specter of untreatable malaria. When first detected in western Cambodia about seven years ago, artemisinin resistance was manifested by a delay in the time it took to clear *Plasmodium falciparum* malaria parasites from

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<sup>2</sup> P. C. C. Garnham, *Malaria Parasites and Other Haemosporidia* (Oxford, UK: Blackwell, 1966).

<sup>3</sup> World Health Organization, *World Malaria Report 2013*, Geneva: 2014, [http://www.who.int/malaria/publications/world\\_malaria\\_report\\_2013/en/](http://www.who.int/malaria/publications/world_malaria_report_2013/en/).

<sup>4</sup> L. Roberts and M. Enserink, "Malaria. Did They Really Say . . . Eradication?," *Science*, December 7, 2007, 318(5856): 1544–45.

<sup>5</sup> Greater Mekong Subregion countries include Cambodia, Thailand, Vietnam, Laos, Myanmar (formerly Burma), and the Yunnan Province of the People's Republic of China.

<sup>6</sup> J. Christopher Daniel, *Drug-Resistant Malaria: A Generation of Progress in Jeopardy* (Washington, DC: CSIS, November 2013), [http://csis.org/files/publication/131107\\_Daniel\\_DrugResistantMalaria\\_Web.pdf](http://csis.org/files/publication/131107_Daniel_DrugResistantMalaria_Web.pdf).

the blood following treatment with ACTs.<sup>7,8</sup> Because these early cases were eventually cured by standard doses of ACTs—just more slowly than usual—some experts questioned whether alarm bells were being rung prematurely.<sup>9</sup>

More than 40 percent of ACT treatments of falciparum malaria at some sites in western Cambodia now either fail to clear the parasites from the blood of patients or are followed by a recurrence soon after treatment, signaling the arrival of bona fide ACT treatment failure.<sup>10</sup> This ominous development is likely to result from the emergence of resistance to piperazine, the partner drug in the ACT dihydroartemisinin-piperazine. As long as at least one of the two drugs in an ACT remains effective, ACTs can eventually clear most infections. But when parasites become resistant to both drugs, the parasites continue to cause illness as well as to transmit malaria to others by blood-feeding mosquitoes.

Switching to another ACT, artesunate-mefloquine, may provide a temporary solution for malaria treatment in Cambodia. But mefloquine resistance—now low after several years of using other drugs—is likely to resurge if artesunate-mefloquine returns to widespread use. Another short-term tactic for overcoming resistance may be to extend the duration of treatment with standard ACTs. Triple combination therapies with existing drugs are also being considered. But either of these interim strategies would be hard to implement because of their impact on supply chain and clinical practice. With very few other treatment options, and with new, non-artemisinin-based treatments still years away, the danger of untreatable malaria—now in Cambodia, but potentially throughout the region and eventually worldwide—is real and present.

## Genetic Testing Offers a New Tool for Tracking Artemisinin Resistance

Like drug resistance in bacteria, viruses, or cancer cells, resistance arises in malaria when genetic mutations occur that allow the parasites to survive the presence of a drug that would normally kill it. A gene in *P. falciparum* that causes artemisinin resistance was recently identified.<sup>11</sup> Parasites carrying mutations in this gene have become prevalent in Cambodia,<sup>12</sup> as well as in Vietnam and Myanmar.<sup>13, 14</sup> This new “molecular marker” makes it possible to rapidly map the prevalence and distribution

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<sup>7</sup> H. Noedl, Y. Se, K. Schaefer, B. L. Smith, et al., “Evidence of artemisinin-resistant malaria in western Cambodia,” *New England Journal of Medicine*, December 11, 2008, 359(24): 2619–20.

<sup>8</sup> A. M. Dondorp, F. Nosten, P. Yi, D. Das, et al., “Artemisinin resistance in Plasmodium falciparum malaria,” *New England Journal of Medicine*, July 30, 2009, 361(5): 455–67.

<sup>9</sup> S. Meshnick, “Perspective: artemisinin-resistant malaria and the wolf,” *American Journal of Tropical Medicine and Hygiene*, November 2012, 87(5): 783–84.

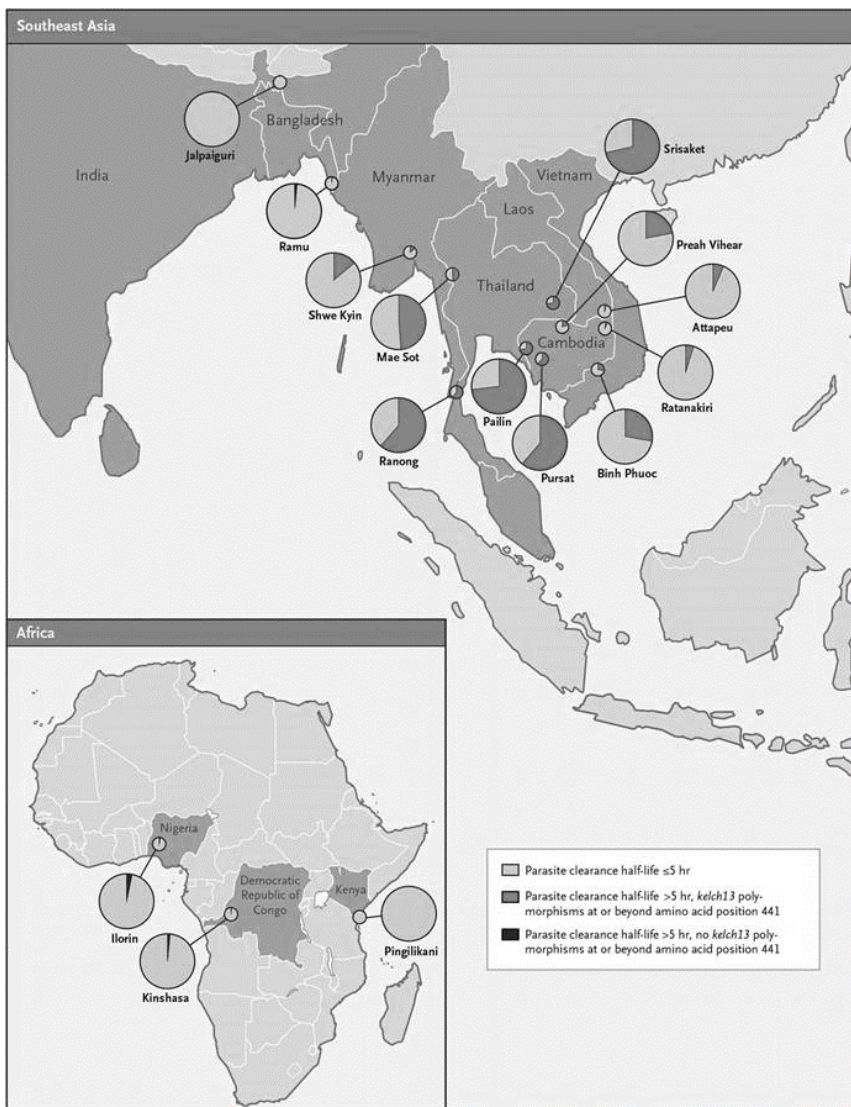
<sup>10</sup> Rick Fairhurst, “Artemisinin-Resistant Plasmodium falciparum Malaria: Latest findings from in vitro, genomic, epidemiological, and clinical studies” (presentation at *Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC]*, 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, September 9, 2014).

<sup>11</sup> F. Ariey, B. Witkowski, C. Amaratunga, J. Beghain, et al., “A molecular marker of artemisinin-resistant Plasmodium falciparum malaria,” *Nature*, January 2, 2014, 505(7481): 50–55.

<sup>12</sup> *Ibid.*

<sup>13</sup> E. A. Ashley, M. Dhorda, R. M. Fairhurst, C. Amaratunga, et al., “Spread of artemisinin resistance in Plasmodium falciparum malaria,” *New England Journal of Medicine*, July 31, 2014, 371(5): 411–23.

**Figure 1. Map of artemisinin resistance**



Note: Based on clinical trials of artemisinin efficacy for treating falciparum malaria, and on testing for a genetic mutation associated with resistance, artemisinin resistance is widespread in western Cambodia, and along the Thailand-Myanmar border. Resistance is present at lower levels in southern Vietnam and southern Laos, and in central Myanmar. Resistance does not yet appear present in Bangladesh or in East or West Africa.

Source: E. Ashley et al., “Spread of Artemisinin Resistance in *Plasmodium falciparum* Malaria,” *New England Journal of Medicine* 371 (2014): 411–423, <http://www.nejm.org/doi/full/10.1056/NEJMoa1314981>.

of artemisinin resistance. Earlier this year, a large multicenter study found a pattern of resistance that seems consistent with the spread outward from its original focus in western Cambodia to Vietnam, Laos, and Myanmar (see Figure 1).

Knowing the resistance gene also makes it possible to do “paternity testing” of artemisinin-resistant parasites to find out whether new resistance foci represent a spread from elsewhere, or independent emergences of resistant parasites. Despite the appearance of spreading from Cambodia—based on proportionally more resistant parasites in Cambodia than in surrounding countries—this parasite genetic testing clearly shows both a spread and a new, independent emergence of resistance. The most common resistance

<sup>14</sup> S. Takala-Harrison, C. G. Jacob, C. Arze, M. P. Cummings, et al., “Independent emergence of artemisinin resistance mutations among *Plasmodium falciparum* in Southeast Asia,” *Journal of Infectious Diseases*, September 1, 2014.

mutation appears to have spread from Cambodia to Vietnam, but this same mutation arose on a completely different genetic background in Myanmar.<sup>15</sup>

This evidence supports a concerning and challenging new scenario—rather than a wave of resistance spreading outward from Cambodia through the Greater Mekong Subregion and then to the rest of the world, as has happened with resistance to at least three earlier antimalarial drugs<sup>16,17,18</sup> and as was assumed likely to occur with artemisinin resistance—artemisinin resistance appears to be both “popping” and “jumping,” as the Myanmar minister of health has put it.

New, unpublished data from the Chinese Center for Disease Control and Prevention and the University of Maryland support this scenario. A completely different artemisinin resistance mutation, unrelated to those reported in Cambodia, is highly prevalent along the China-Myanmar border and in Kachin and Shan States in Myanmar.<sup>19</sup>

This new evidence of both multiple independent emergences and international spread of artemisinin resistance calls into question the strategy of erecting a “firewall” against a wave of artemisinin resistance moving westward from Cambodia through Myanmar toward Bangladesh and India, and then to the rest of the world. Instead, consensus is moving toward the need to eliminate falciparum malaria from all of the Greater Mekong Subregion.<sup>20</sup>

## Committing to Malaria Elimination in the Greater Mekong Subregion

As the 2013 CSIS report on drug-resistant malaria describes, international efforts are underway in the Greater Mekong Subregion to contain artemisinin-resistant malaria in—or, in current thinking, eliminate falciparum malaria entirely from—the region. In 2013 the World Health Organization launched the Emergency Response to Artemisinin Resistance (ERAR)<sup>21</sup> with support from the Australian government and the Bill & Melinda Gates Foundation, and the Global Fund to Fight AIDS, Tuberculosis and Malaria committed \$100 million for the Regional Artemisinin Resistance

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<sup>15</sup> Ibid.

<sup>16</sup> J. C. Wootton, X. Feng, M. T. Ferdig, R. A. Cooper, et al., “Genetic diversity and chloroquine selective sweeps in *Plasmodium falciparum*,” *Nature*, July 18, 2002, 418(6895): 320–23.

<sup>17</sup> C. Roper, R. Pearce, S. Nair, B. Sharp, et al., “Intercontinental spread of pyrimethamine-resistant malaria,” *Science*, August 20, 2004, 305(5687): 1124.

<sup>18</sup> T. Mita, M. Venkatesan, J. Ohashi, R. Culleton, et al., “Limited geographical origin and global spread of sulfadoxine-resistant dhps alleles in *Plasmodium falciparum* populations,” *Journal of Infectious Diseases*, December 15, 2011, 204(12): 1980–88.

<sup>19</sup> F. Huang et al., “Therapeutic efficacy of dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria and K13-propeller polymorphisms along the China-Myanmar border” (presentation at 63rd Annual Meeting of the American Society of Tropical Medicine and Hygiene, New Orleans, LA, November 4, 2014).

<sup>20</sup> G. C. Smith, G. Newby, J. Hwang, A. A. Phillips, et al., “The challenge of artemisinin resistance can only be met by eliminating *Plasmodium falciparum* malaria across the Greater Mekong subregion,” *Malaria Journal* (2014)13: 286.

<sup>21</sup> World Health Organization (WHO), “Emergency response to artemisinin resistance in the Greater Mekong subregion,” [http://www.who.int/malaria/areas/greater\\_mekong/en/](http://www.who.int/malaria/areas/greater_mekong/en/).



Initiative.<sup>22</sup> Also in 2013, the U.S. President’s Malaria Initiative (PMI) began directly funding activities in Myanmar and Cambodia in addition to continuing funding for the Mekong Regional Program, initiated in 2011, spending a total of \$14 million a year in the region. The Asian Development Bank is working with regional governments and international development agencies on a regional funding mechanism for long-term control and prevention of malaria and other communicable diseases in Asia and the Pacific region.<sup>23</sup> The Bill & Melinda Gates Foundation is funding numerous academic groups and nongovernmental organizations to conduct research and build capacity for malaria elimination in the Greater Mekong Subregion. In November 2014, Bill Gates announced that the Gates Foundation would increase its malaria spending by 30 percent to more than \$200 million per year.<sup>24</sup>

This surge in resources is both needed and welcomed. However, it is bewildering for those on the front lines—dollars and ideas are flowing in from all directions, without a unified, coherent plan. The various development partners are communicating with each other, but no one organization or individual is in charge, and most of the present commitments are for just one to three years. Coordinating these national, international, bilateral, multilateral, public, and private funding streams and activities is critical for success and efficiency and is extremely challenging. Longer-term commitments are likewise essential for eliminating *falciparum* malaria from the Greater Mekong Subregion.

Current approaches to eliminating malaria range from ramping up support for delivering standard interventions such as insecticide-treated nets, rapid diagnostic tests, and ACTs, as PMI is doing, to funding from the Gates Foundation and the Global Fund to evaluate new interventions like “targeted mass treatment” of infected human populations. Early results of studies of targeted mass treatment suggest that low-level *P. falciparum* infection may be much more common in relatively low malaria transmission areas than previously expected, providing a reservoir of parasites that may still be a source of transmission even though they are not causing symptoms of illness in the majority of infected individuals. These “subclinical” infections can apparently be cured by effective drug treatment, but they can only be detected by ultrasensitive molecular tests that are presently too cumbersome and expensive for routine screening.<sup>25</sup>

Targeted mass treatment is a high-risk strategy, in that if it is unsuccessful it will select for the most drug-resistant parasites, which could then resurge and spread across the region in a new wave of highly resistant parasites. The drugs used for mass treatment must be very safe and well tolerated, since people who have no symptoms—or who are not infected at all—will be asked to take pills in order to ensure that all parasites

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<sup>22</sup> The Global Fund, “Grant Portfolio: Multicountry East Asia and Pacific (RAI), <http://portfolio.theglobalfund.org/en/Country/Index/MER>.

<sup>23</sup> Asian Development Bank, “Regional Strategic Response to Malaria and Other Communicable Diseases in Asia and the Pacific,” August 25, 2013, [http://adb.org/projects/details?page=details&proj\\_id=47272-001](http://adb.org/projects/details?page=details&proj_id=47272-001).

<sup>24</sup> Associated Press, “Amid Ebola outbreak, Bill Gates pledges more money to fight malaria,” CBS News, November 2, 2014, <http://www.cbsnews.com/news/amid-ebola-outbreak-gates-foundation-boosts-aid-to-stamp-out-malaria/>.

<sup>25</sup> Arjen Dondorp, “Spread and elimination of artemisinin-resistant malaria in Southeast Asia” (presentation at Symposium 132, Artemisinin-Resistant Malaria in a “Post-Marker” World: Latest Findings from in vitro, genomic, epidemiological, and clinical studies, 63rd Annual Meeting of the American Society of Tropical Medicine and Hygiene, New Orleans, LA, November 5, 2014).

are eliminated from all infected and potentially infected people in a targeted area. Operational research to evaluate and improve this and other interventions and then scale them up for elimination is a top priority. This research should aim to quickly result in a minimum standard kit of scalable surveillance tools, elimination interventions, and health systems strengthening strategies.

Malaria parasites, mosquitoes, and people have a wide range of behaviors, and a one-size-fits-all approach to elimination does not work.<sup>26</sup> Interventions that work well in one setting—for example, bed nets to protect African children against indoor-biting mosquitoes—may have little value elsewhere—for example, where malaria is transmitted to adult men by forest-biting mosquitoes, as is common in the Greater Mekong Subregion.

Malaria elimination in the Greater Mekong Subregion, where malaria is already relatively rare compared to sub-Saharan Africa, will require strengthening health systems, including health surveillance systems. As clinical illness due to malaria becomes even rarer, health workers who are testing, treating, and tracking malaria will increasingly need to be able to diagnose, treat, and prevent other common diseases in order to be seen as providing value to communities.

## Politics: An Essential Tool in Malaria Elimination

Drug-resistant malaria is particularly cruel. It arises and takes hold precisely in areas where it is most difficult to fight it—in remote, rural border and conflict areas with limited health infrastructure, populated by migrant workers, refugees, and soldiers. This makes malaria elimination a tough job—but it can be done. China has virtually stopped all malaria transmission within its borders, and is now working with a variety of partners along the China-Myanmar border, where malaria outbreaks continue to occur. The Chinese CDC works closely with both with the Myanmar Ministry of Health and with health officials of the Kachin Independence Organization and other ethnic groups in areas not under the control of the central government of Myanmar.<sup>27</sup> As demonstrated during the smallpox eradication campaign, political adversaries have proven willing to cooperate on, or at least not interfere with, malaria control and elimination activities.

As the country in the Greater Mekong Subregion with by far the most malaria, and as the current frontier of artemisinin-resistant malaria, Myanmar presents both a great challenge but perhaps a greater opportunity for malaria elimination. The notion of “malaria as a catalyst for social change” has been advocated as a multisectoral approach for achieving a common goal.<sup>28</sup>

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<sup>26</sup> J. A. Najera, M. Gonzalez-Silva, and P. L. Alonso, “Some lessons for the future from the Global Malaria Eradication Programme (1955–1969),” *PLoS Medicine* (2011)8(1): e1000412.

<sup>27</sup> F. Huang, H. Liu, M. Nyunt, and C. Plowe, observations during field visits to China-Myanmar border, Yunnan Province, People’s Republic of China, June 2014.

<sup>28</sup> “Malaria as a Catalyst for Social Change” is the title of a grant from the Open Society Foundations to Myaing Myaing Nyunt, M.D., Ph.D., M.P.H., a former student activist and member of the “88 Generation,” who fomented revolution against the military regime in Myanmar 25 years ago and who is now an internationally recognized malariologist based at the University of Maryland School of Medicine in Baltimore and working on malaria surveillance and elimination in Myanmar.

At the request of the Myanmar minister of health, and with support from the Open Society Foundations, a meeting was organized in early 2014 in Yangon, Myanmar, for all malaria partners working in Myanmar to discuss malaria elimination, including the potential role of targeted mass treatment in Myanmar. Holding all discussions in the Myanmar language, this meeting included civilian and military health officials and scientists, representatives of border groups with a long adversarial history with the Myanmar government, and Myanmar nationals working for a variety of international nongovernment organizations and development partners. This meeting was an early step in the process toward building and sustaining the essential political will for malaria elimination in Myanmar. As a result, we have a strategic opportunity to explore the formation of a national unity campaign around malaria elimination.

Now is the time to prevent the global health catastrophe that will result if artemisinin-resistant malaria becomes widespread in Africa. This collaboration in Myanmar—across political lines for a shared global health agenda—must be emulated elsewhere in the region, as well as in the donor countries, including the United States.

If the United States, in response to concerns about the pace of movement toward democracy or other political issues, decides to reduce aid to countries targeted for malaria elimination, an exception should be made for aid directed at malaria elimination. Just as would have been the case for the now much heralded smallpox eradication campaign, reducing funding or political will for malaria elimination, or erecting barriers to efficient mobilization of resources for this urgent work, would be foolishly self-injurious to the United States and to the world.

Because so much malaria occurs among military troops and in areas that cannot safely be accessed by civilian workers, it is also essential to directly engage militaries in the Greater Mekong Subregion in malaria elimination, even when this is politically unpalatable. Where direct military-to-military collaboration remains unfeasible, civilian-to-military engagement, information sharing, and capacity building needs to be encouraged and supported.

If we are to conquer artemisinin-resistant malaria, we must be equipped for the long-term win rather than the next short-term funding cycle. There is no doubt that this is challenging in today's world with economic downturns and international conflicts on multiple fronts. In fact, it can be said that it is precisely for these reasons that a multigovernment commitment to ending malaria once and for all make sense. Aside from the humanitarian rationale for ending the suffering caused by malaria, we will all benefit from supporting the desires of malaria endemic countries to focus on building their local and national economies, redirecting their limited resources to the growing toll of chronic diseases, and participating in the global arena as strong and vibrant nations.



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