

# Drug-Resistant Malaria



*A Generation of Progress in Jeopardy*

AUTHOR  
J. Christopher Daniel

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*Author*  
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Center for Strategic & International Studies  
1616 Rhode Island Avenue, NW  
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# Contents

Acknowledgments	iv
Drug-Resistant Malaria: A Generation of Progress in Jeopardy	1
What Is Artemisinin Resistance?	2
Why Should We Care?	3
What Is Driving Resistance?	6
What Is Being Done?	7
What Challenges Remain?	11
Conclusion	14
Glossary	16

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The author believes that his report reflects a broad consensus, but it is the author, and the author alone, who is accountable for the final conclusions.

# Drug-Resistant Malaria

## A Generation of Progress in Jeopardy

J. Christopher Daniel<sup>1</sup>

*The damage this disease [malaria] does is quite incredible.... The parasite has been killing children and sapping the strength of whole populations for tens of thousands of years.... Now we can chart a course to end it.*—Bill Gates, 2011<sup>2</sup>

In recent years, there has been impressive progress in controlling malaria, an ancient and deadly parasitic disease. It has become possible to imagine a future in which malaria-related deaths end. Powerful antimalarial drugs have been vital to this effort; making these drugs available and accessible around the world is the key to sustaining progress.

At the same time, resistance to artemisinin—the frontline drug used to combat malaria—has emerged in the Greater Mekong Subregion (hereafter referred to as “the Mekong”).<sup>3</sup> Resistance threatens to reverse the impressive progress achieved in recent years, with grave consequences for global health.

This report aims to inform interested, nontechnical readers. What is artemisinin resistance? Why should we care? What is driving it? What is being done to address it? And what challenges remain?

There is a window of opportunity to overcome the threat of resistance. Additional resources, high-level political leadership, smart partnerships that span sectors as well as borders: all are required. Resistance poses an enormous challenge that requires a concerted and sustained effort by the world community.

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<sup>1</sup> J. Christopher Daniel, M.D., is a senior associate with the CSIS Global Health Policy Center. A retired U.S. Navy captain with extensive interagency and international senior leadership experience, he was the first naval officer to serve as deputy commander of the Army Medical Research and Materiel Command, which conducts innovative and lifesaving research, development and acquisition to deliver, distribute and maintain medical information, products, supplies and equipment to the U.S. military community, most of which also benefits citizens throughout the world. While commanding the Naval Medical Research Center, Dr. Daniel led Navy Medicine’s global enterprise of laboratories in Egypt, Peru, Indonesia, Ghana, Cambodia, and throughout the United States, to enhance the health, safety, readiness and performance of Navy and Marine Corps personnel. Earlier assignments included command of the Naval Submarine Medical Research Laboratory and 10 years of overseas tours in the Philippines, Sicily, and Indonesia. A graduate of Princeton University and Jefferson Medical College, Dr. Daniel also earned an M.B.A. from Yale University as a charter member of its Leadership in Healthcare Program. He is a fellow of the American Academy of Family Physicians.

<sup>2</sup> World Health Organization (WHO), “World Malaria Day 2013: Invest in the Future: Defeat Malaria,” <http://www.rbm.who.int/worldmaliaday/support.html>.

<sup>3</sup> The Greater Mekong Subregion consists of Cambodia, parts of southern China, Laos PDR, Myanmar, Thailand, and Vietnam.

# What Is Artemisinin Resistance?

Parasites, like all living organisms, undergo genetic mutations. Resistance occurs when mutations result in a significant proportion of parasites becoming invincible to (or at least much less affected by) a drug that would otherwise kill them.

Artemisinin is an extract of *qing hao*, a traditional Chinese herbal medicine first recommended for use against “intermittent fevers” in 340 AD; its effectiveness as an antimalarial was confirmed in 1971. Since the mid-1990s, Thailand and Cambodia, and eventually almost all countries where malaria is a threat, have taken advantage of that “discovery,” adapting national drug policies to recommend artemisinin combination therapy (ACT), which pairs artemisinin with a longer-acting drug, as first-line treatment for uncomplicated malaria. The intent is for artemisinin to quickly clear most parasites from the bloodstream, leaving the partner drug to kill those that remain.<sup>4, 5</sup>

Around 2003, ACT failures began occurring among patients along the Thailand-Cambodia border.<sup>6</sup> Since then, resistance to artemisinin by *Plasmodium falciparum*, the parasite that most frequently causes malaria,<sup>7</sup> has been officially confirmed in Cambodia, Myanmar, Thailand, and Vietnam (see Figure 1). Though not yet recognized by the World Health Organization (WHO), it has also been detected in the southwestern provinces of China along the Myanmar/China border, and is suspected as far away as Guyana and Suriname.<sup>8</sup>

This is not the first time the parasite has developed resistance to a drug. Resistance to chloroquine—the world’s first mass-administered antimalarial drug, which helped eliminate malaria from Europe, North America, the Caribbean, and parts of Asia and South-Central America during the 1950s—began appearing on the Thailand-Cambodia border later that decade. By 1978, resistance was detected in Africa; by the early 1990s, resistance made chloroquine virtually useless as an antimalarial in much of the world. This pattern of emerging antimalarial drug resistance, first on the Thailand-Cambodia border and eventually in Africa and elsewhere, repeated itself with sulfadoxine-pyrimethamine in the late 1960s.<sup>9</sup>

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<sup>4</sup> References to malaria’s intermittent fevers go back to 2700 BC in China. However, with no knowledge of *qing hao* until recently, pharmacological treatment in the West dates only to the seventeenth century, when quinine, obtained from the bark of the cinchona tree and used by the Quechua in Peru to control fever, was found to be effective. Quinine’s use was limited until the nineteenth century, when botanical improvements and increased cinchona cultivation, particularly on the Indonesian island of Java, greatly increased its availability.

<sup>5</sup> E. Hsu, “Reflections on the ‘Discovery’ of the Antimalarial *Qinghao*,” *British Journal of Clinical Pharmacology* 61, no. 6 (2006): 666–70; M. Willcox, “Artemisia Species: From Traditional Medicines to Modern Antimalarials—and Back Again,” *Journal of Alternative and Complementary Medicine* 15, no. 2 (2009): 101–109. See also Malaria Site, “History of Malaria Treatment,” [http://www.malariasite.com/malaria/history\\_treatment.htm](http://www.malariasite.com/malaria/history_treatment.htm).

<sup>6</sup> S. Vijaykadga et al., “In Vivo Sensitivity Monitoring of Mefloquine Monotherapy and Artesunate-Mefloquine Combinations for the Treatment of Uncomplicated Falciparum Malaria in Thailand in 2003,” *Tropical Medicine and International Health* 11, no. 2 (2006): 211–19.

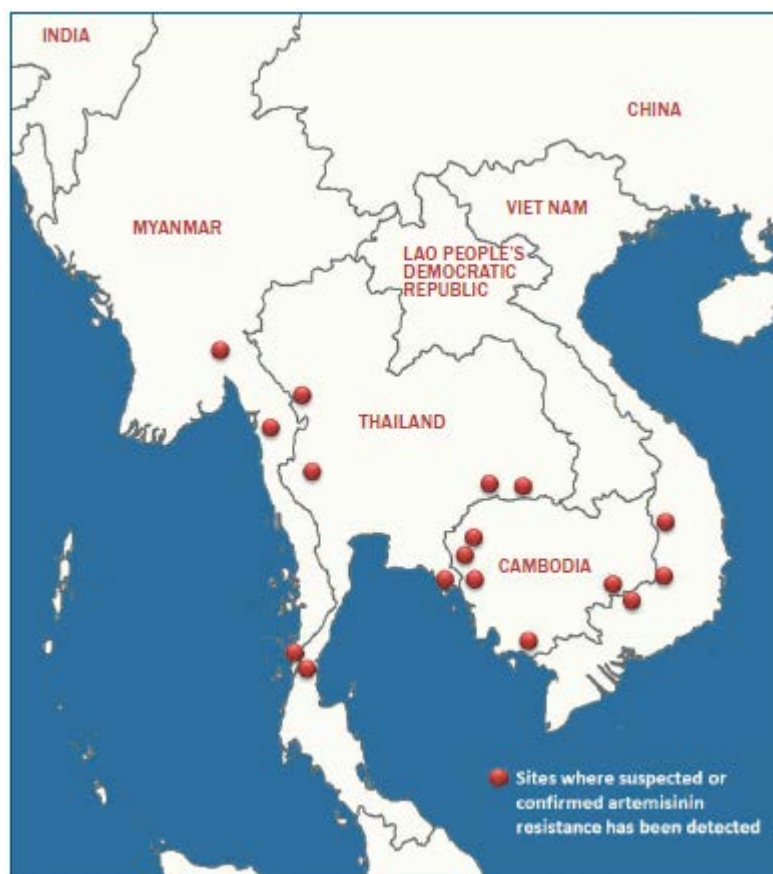
<sup>7</sup> Malaria results from an infection by one or more of the *Plasmodia* family of parasites, most commonly *Plasmodium falciparum*. In 2010, 91 percent of reported cases of malaria were due to *P. falciparum*. It is also the main cause of severe clinical disease and death.

<sup>8</sup> WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion: Regional Framework for Action 2013–2015* (Geneva: WHO, 2013), [http://apps.who.int/iris/bitstream/10665/79940/1/9789241505321\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/79940/1/9789241505321_eng.pdf); U.S. Global Malaria Coordinator, *President’s Malaria Initiative Greater Mekong Sub-Region Malaria Operational Plan FY 2013 (2013)*, [http://pmi.gov/countries/mops/fy13/mekong\\_mop\\_fy13.pdf](http://pmi.gov/countries/mops/fy13/mekong_mop_fy13.pdf); “PAHO/WHO to support Guyana and Suriname in studies of resistance to artemisinin-based combination therapy (ACT),” United Nations, <http://sr.one.un.org/pahowho-to-support-guyana-and-suriname-in-studies-of-resistance-to-artemisinin-based-combination-therapy-act-3/>.

<sup>9</sup> Resistance by the parasite to mefloquine, another widely used antimalarial (though not extensively used in Africa), also first emerged along the Thailand-Cambodia border in the 1980s.



**Figure 1. Sites of Suspected or Confirmed Artemisinin Resistance as of 2012**



Source: WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion: Regional Framework for Action 2013–2015* (Geneva: WHO, 2013), [http://apps.who.int/iris/bitstream/10665/79940/1/9789241505321\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/79940/1/9789241505321_eng.pdf).

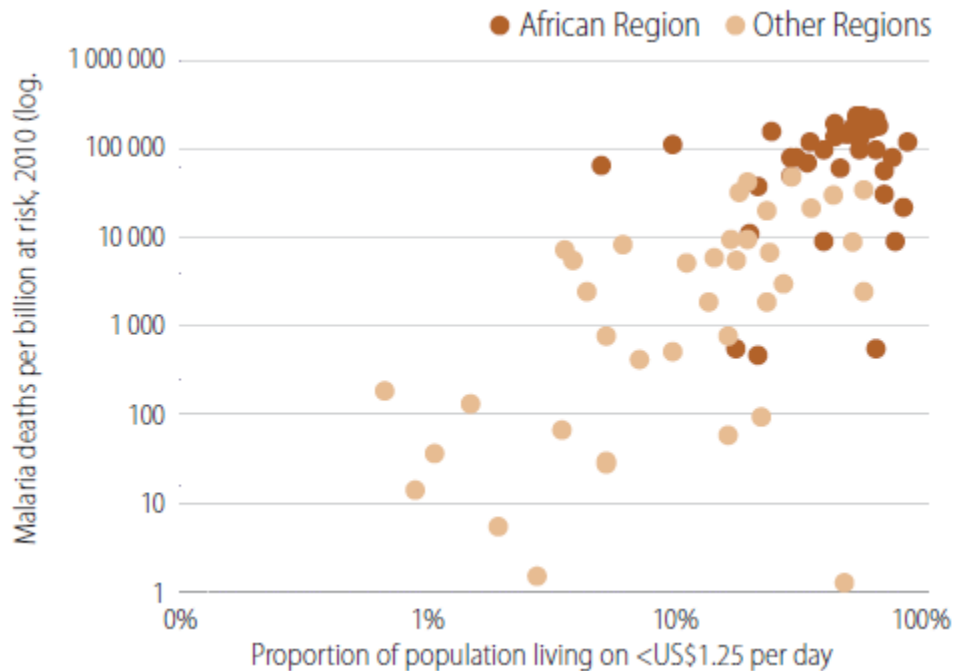
## Why Should We Care?

Since much of the recent progress in controlling malaria was due to the availability and expanded access of a safe and effective drug as first-line therapy, and since this time no next-generation drug is on the horizon, artemisinin resistance represents a substantial threat.<sup>10, 11</sup> In the words of Dr. Robert Newman, director of WHO's Global Malaria Programme, "we are at a tipping point."

<sup>10</sup> The lack of a next-generation drug is not due to a lack of effort. The Medicines for Malaria Venture (MMV) partners with public and private entities to bring new malaria drugs to the market, including new ACTs and non-artemisinin alternatives. The current global portfolio of antimalarial drugs in research and development can be downloaded at the MMV website.

<sup>11</sup> Medicines for Malaria Venture, "Interactive R&D Portfolio," <http://www.mmv.org/research-development/rd-portfolio>; M.P. Anthony et al., "The Global Pipeline of New Medicines for the Control and Elimination of Malaria," *Malaria Journal* 11 (2012): 316.

**Figure 2. Relation between Proportion of Country's Population Living in Poverty and Malaria Mortality Rates**



Source: WHO, *World Malaria Report 2012* (Geneva: WHO, 2012), [http://www.who.int/malaria/publications/world\\_malaria\\_report\\_2012/wmr2012\\_no\\_profiles.pdf](http://www.who.int/malaria/publications/world_malaria_report_2012/wmr2012_no_profiles.pdf).

What seems to be a localized threat could easily get out of control and have serious implications for global health.”<sup>12</sup>

Malaria is caused by a single-celled parasite that commonly infects a certain type of mosquito. When these mosquitoes, known as *Anopheles*, feed on humans, they transmit the parasite and disease.

Across the centuries, malaria has taken a terrible toll on human lives and economic development.<sup>13, 14, 15</sup> Reflecting malaria’s tremendous impact on U.S. forces during the Spanish American War and almost every war since then, U.S. military medical researchers—Walter Reed, William Gorgas, and their successors—have long been at the forefront of efforts to control the disease. During World War II, about 500,000 U.S. soldiers were infected with malaria in the

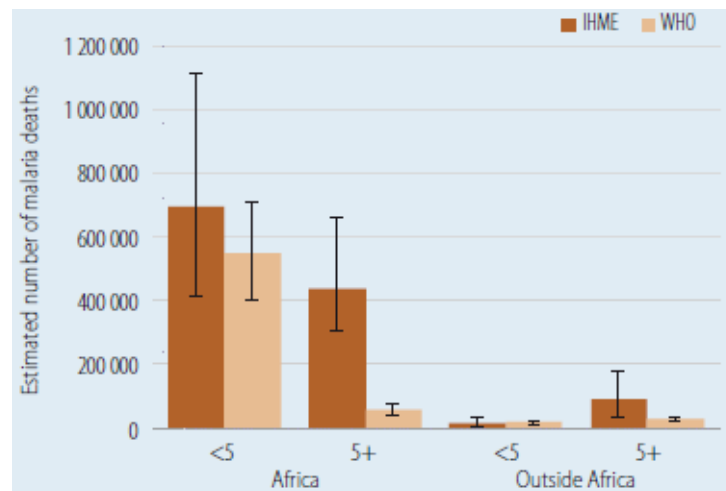
<sup>12</sup> Glenn Thomas, “WHO Launches Emergency Response to Antimalarial Drug Resistance,” WHO, April 24, 2013, [http://www.who.int/mediacentre/news/releases/2013/world\\_malaria\\_day\\_20130424/en/](http://www.who.int/mediacentre/news/releases/2013/world_malaria_day_20130424/en/).

<sup>13</sup> Alexander the Great, St. Augustine, Lord Byron, Oliver Cromwell, Dante, Genghis Khan, and Amerigo Vespucci are among those who have succumbed to malaria.

<sup>14</sup> Including health care costs, days lost in education, lost work days, decreased productivity from brain damage due to cerebral malaria, and loss of investment and tourism, the annual economic burden of malaria on Africa has been estimated to exceed \$12 billion.

<sup>15</sup> Ranker, “Famous People Who Died of Malaria,” <http://www.ranker.com/list/famous-people-who-died-of-malaria/reference>; Malaria Site, “History of Malaria: Famous Victims,” [http://www.malariasite.com/malaria/history\\_victims.htm](http://www.malariasite.com/malaria/history_victims.htm); B.M. Greenwood et al., “Malaria,” *The Lancet* 365, issue 9469 (2005): 1487–98.

**Figure 3. Estimates of Malaria Deaths in 2010, by Age Group and Geographic Region**



Source: WHO, *World Malaria Report 2012* (Geneva: WHO, 2012), [http://www.who.int/malaria/publications/world\\_malaria\\_report\\_2012/wmr2012\\_no\\_profiles.pdf](http://www.who.int/malaria/publications/world_malaria_report_2012/wmr2012_no_profiles.pdf).

Pacific, leading to the Malaria Control in War Areas initiative, the forerunner of the present-day U.S. Centers for Disease Control and Prevention.<sup>16</sup>

Although malaria remains a significant threat to deploying U.S. military personnel, its staggering burden is today most felt among pregnant women and children in the developing world. In 2010, 80 percent of malaria cases and over 90 percent of malaria deaths occurred in Africa; 86 percent of deaths were children under five years of age. Malaria's burden is also heaviest among those in poverty, whose vulnerability is much greater, in part because they are frequently undernourished and too poor to prevent or treat the disease.<sup>17</sup>

In 2010, WHO estimated that 219 million cases of malaria and 660,000 deaths occurred in 99 endemic countries. However, underdiagnosis, along with incomplete or inconsistent reporting in over 40 countries—some of which bear the greatest disease burden—mean that these figures are subject to considerable error. Indeed, 1.17 million deaths were attributed to malaria by the Institute of Health Metrics and Evaluation's (IHME) Global Burden of Disease and Risk Factors Study 2010, which also cited malaria as the world's fifth-leading cause of years of life lost due to premature mortality.<sup>18</sup> Perhaps most tragically, malaria is today the third-leading cause of death for children under the age of five. Every hour, the disease claims more than 50 children's lives.<sup>19</sup>

<sup>16</sup> R.S. Bray, *Armies of Pestilence: The Effects of Pandemics on History* (Cambridge: James Clarke, 2004).

<sup>17</sup> WHO, *World Malaria Report 2012* (Geneva: WHO, 2012), [http://www.who.int/malaria/publications/world\\_malaria\\_report\\_2012/wmr2012\\_no\\_profiles.pdf](http://www.who.int/malaria/publications/world_malaria_report_2012/wmr2012_no_profiles.pdf); L. Tusting et al., "Socioeconomic Development as an Intervention against Malaria: A Systematic Review and Meta-Analysis," *The Lancet* 382, issue 9896 (2013): 963–72.

<sup>18</sup> Coordinated by IHME, the GBD 2010 was an unprecedented international collaborative effort involving 488 researchers from 303 institutions in 50 countries. It produced a comprehensive set of population health metrics, including mortality statistics, published in a special edition of *The Lancet* in December 2012.

<sup>19</sup> "Global Burden of Disease Study 2010," *The Lancet*, December 13, 2012, <http://www.thelancet.com/themed/global-burden-of-disease>; UN Children's Fund (UNICEF), *Committing to Child Survival: A Promise*

Despite these staggering numbers, the last few years have seen remarkable improvement. Global efforts to eliminate the disease accelerated with WHO's establishment of the "Roll Back Malaria" program in 1998. Malaria targets were included in the UN's trailblazing Millennium Development Goals (MDGs). Investments have increased exponentially, led by the Global Fund to Fight AIDS, Tuberculosis and Malaria and the President's Malaria Initiative (PMI), launched in 2002 and 2005, respectively.<sup>20, 21</sup>

These efforts have paid off. WHO's 2010 estimates represent a decrease of six million cases and over 120,000 deaths from a year earlier, and a drop of roughly 85 percent and 26 percent in incidence and mortality over a decade, resulting in a cumulative total of 1.1 million malaria deaths averted. IHME's 2010 estimates of malaria mortality, though much larger than WHO's, are themselves down 25 percent from its 2005 estimates. Roll Back Malaria and MDG goals for 2015, of reducing malaria case incidence by 75 percent, which many once thought overly ambitious, now seem within reach.

The pace of recent progress has been so swift that in 2011, Malaria No More, an NGO formed in 2006 with a mission of ending malaria deaths in Africa, announced that it was tentatively planning to close by 2015,<sup>22</sup> and UN secretary-general Ban Ki-moon declared a new goal of ending *all* malaria deaths by 2015. At the time of this writing, these targets are not going to be met; one among many important factors is that less than half of the funding needed to ensure universal access to malaria interventions has been made available. Still, WHO's *World Malaria Report 2012* noted that among the 104 countries still considered endemic, 50 were on track to meet the original 2015 targets, with particularly impressive progress occurring in 34 countries that have embarked on national elimination plans.<sup>23, 24</sup>

## What Is Driving Resistance?

The most important factors driving resistance are the numerous ways antimalarial drugs have been misused in the Mekong. These include:

- Treatment of feverish patients without confirmation by appropriate diagnostic tests;
- Misdiagnosis due to poor laboratory technique or interpretation;
- Underdosing;

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*Renewed: Progress Report 2013* (New York: UNICEF, 2013), [http://www.unicef.org/publications/files/APR\\_Progress\\_Report\\_2013\\_9\\_Sept\\_2013.pdf](http://www.unicef.org/publications/files/APR_Progress_Report_2013_9_Sept_2013.pdf).

<sup>20</sup> According to the Kaiser Family Foundation, as of March 2013, the Global Fund had committed over \$8.2 billion to 80 countries for malaria-related initiatives, while U.S. bilateral funding for malaria, including PMI and other malaria efforts, exceeded \$5 billion during the 10 fiscal years from 2004 to 2013. A separate review of Organization for Economic Cooperation and Development (OECD) data found that the Global Fund provided 57 percent and the United States 26 percent of the approximately \$1.5 billion per year of public-sector malaria assistance from 2009 to 2011. Other major public donors include the United Kingdom, World Bank, Canada, and others. The Bill and Melinda Gates Foundation has also committed billions of dollars, leading all private-sector donors.

<sup>21</sup> Kaiser Family Foundation, "The Global Malaria Epidemic," March 7, 2013, <http://kff.org/global-health-policy/fact-sheet/the-global-malaria-epidemic-4/>; Kaiser Family Foundation, "Mapping the Donor Landscape in Global Health: Malaria," August 29, 2013, <http://kff.org/global-health-policy/report/mapping-the-donor-landscape-in-global-health-malaria/>.

<sup>22</sup> Stephanie Strom, "Mission Accomplished, Nonprofits Go Out of Business," *New York Times*, April 1, 2011, [http://www.nytimes.com/2011/04/02/business/02charity.html?\\_r=0](http://www.nytimes.com/2011/04/02/business/02charity.html?_r=0).

<sup>23</sup> Four countries were certified as malaria-free between 2007 and 2011, more than had been declared malaria-free in the prior quarter century.

<sup>24</sup> C. Cotter et al., "The Changing Epidemiology of Malaria Elimination: New Strategies for New Challenges," *The Lancet* 382, issue 9895 (2013): 900–11.

- Drugs used in incomplete dosages even when correct dosages have been prescribed;
- Artemisinin used alone instead of in combination therapy (or, even worse, not taken for the full seven days required for it to be effective);
- Delay in access to treatment; and
- Treatment with counterfeit and substandard antimalarial drugs.

The Mekong countries are working to address these varied issues. Nonetheless, many patients still have poor access to public health facilities, which is exacerbated by limited financial resources and poor transportation networks. The quality of the facilities is often unreliable, particularly in more remote areas. Many patients turn to the private sector to obtain drugs, with or without an intermediate stop to visit a private health care provider, further increasing the likelihood that drugs of poor quality will be used and/or that they will be used incorrectly.<sup>25, 26</sup>

Two mobile and vulnerable Mekong populations with occupational exposure to infected mosquitoes merit special attention. Military troops with limited immunity frequently deploy to remote border areas with limited health care access. Migrant workers frequently cross borders to seek temporary or seasonal work, and as many are both impoverished and undocumented, tend to avoid accessing public health systems. In both populations, it is common for patients with low-level infections to go undiagnosed and untreated; or they self-treat, often with substandard drugs. Either way, they can fuel the development and spread of resistant parasites.<sup>27</sup>

## What Is Being Done?

WHO initiated a response to artemisinin resistance in November 2008, supported by additional funding from the Bill and Melinda Gates Foundation. Initial goals were to contain the resistant parasites within the “hotspot” area of the Thailand-Cambodian border, and ultimately to eliminate malaria from the region by enhancing surveillance and ensuring the diagnosis and full treatment of all confirmed malaria cases.

These efforts expanded in 2011 with the initiation of the Global Plan for Artemisinin Resistance Containment, “a high-level plan of attack to protect ACTs as an effective treatment for *P. falciparum* malaria,” with two primary goals: containing or eliminating artemisinin resistance where it already exists, and preventing it where it has not yet appeared. The Global Plan laid out five priorities:

1. Stop the spread of resistant parasites;

<sup>25</sup> A 2005 study in Cambodia noted that over 80 percent of patients seeking treatment for malaria initially did so from private providers or pharmacies. Similarly, only a small percentage of patients are able to access and utilize the public health system in Myanmar, and a 2001 Lao PDR survey indicated that over half of respondents self-treated for malaria.

<sup>26</sup> S. Duong et al., “Piloting of a Strategy for Collection of Malaria Information from the Private Sector, Cambodia, Final Report, March 2005,” National Centre for Parasitology, Entomology and Malaria Control GTZ BACKUP Initiative (2005). J. Stephen Morrison et al., *Rehabilitating Health in the Myanmar Transition: “This is the time we have been dreaming of for decades.”* (Washington DC: CSIS, November 2013). Laos PDR National Health Survey, 2001.

<sup>27</sup> Cotter et al., “The Changing Epidemiology of Malaria Elimination,” 900–911. P.K. Rathod et al., “Variations in Frequency of Drug Resistance in *Plasmodium falciparum*,” *Proceedings of the National Academy of Sciences USA* 94 (1997): 9389–93; C. Wongsrichanalai and C.H. Sibley, “Fighting Drug-Resistant *Plasmodium falciparum*: The Challenge of Artemisinin Resistance,” *Clinical Microbiology and Infection* 19, no. 10 (2013): 908–16; C. Wongsrichanalai and S.R. Meshnick, “Declining Artesunate-Mefloquine Efficacy against *Falciparum* Malaria on the Cambodia-Thailand border,” *Emerging Infectious Diseases* 14, no. 5 (2008): 716–18.

2. Increase monitoring and surveillance to evaluate the threat;
3. Improve access to diagnostics and rational treatment with ACTs;
4. Invest in research;
5. Mobilize resources.<sup>28</sup>

Numerous international donors and organizations have made substantial contributions to these efforts. After receiving a considerable boost in funding by the 2008 Lantos-Hyde Act, the President's Malaria Initiative expanded from its traditional Africa focus countries to include the Mekong.<sup>29</sup> In early 2013, as part of its new funding model, the Global Fund announced that it would contribute \$100 million for a new Regional Artemisinin Resistance Initiative.<sup>30, 31</sup>

On World Malaria Day 2012, WHO Director-General Margaret Chan launched the "T3: Test, Treat, Track" initiative. T3's goal is for all countries to ensure that every suspected malaria case is tested, that every confirmed case is treated appropriately with good-quality ACT antimalarial drugs,<sup>32, 33</sup> and that the disease is tracked through timely and accurate surveillance systems. Scaling up these elements, along with measures to control the *Anopheles* mosquito, are the cornerstones of malaria elimination, and are essential to an effective response to artemisinin resistance.

*Test:* In 2009, WHO estimated that only 35 percent of suspected malaria cases were tested by microscopy or rapid diagnostic test, while a 2010 study estimated that 78 percent of patients treated with ACTs for malaria in Africa did not have malaria. While the Mekong has seen progress, particularly in the public sector, in the demand for and use of parasitological diagnosis before treatment, it is still far from the norm.<sup>34</sup>

Microscopy requires a skilled, trained technician and is therefore subject to human error. Rapid diagnostic tests have been a boon in endemic countries, but would be better if they could detect infections when only a small number of parasites are present in the blood sample. Being able to reliably diagnose and treat patients with small numbers of parasites in their bloodstream and

<sup>28</sup> W. Satimai et al., "Artemisinin Resistance Containment Project in Thailand.II: Responses to Mefloquine-Artesunate Combination Therapy among Falciparum Malaria Patients in Provinces Bordering Cambodia," *Malaria Journal* 11 (2012): 300; WHO, *Global plan for artemisinin resistance containment* (Geneva: WHO, 2011).

<sup>29</sup> The President's Malaria Initiative goals for the Mekong, as stated in its Fiscal Year 2013 Malaria Operational Plan, are to: 1) strengthen malaria prevention and control interventions in focus areas with existing or emerging artemisinin-resistant malaria; 2) ensure effective drug efficacy surveillance networks to monitor artemisinin resistance; and 3) monitor the quality of antimalarial drugs and build country capacity to prevent the availability of substandard or counterfeit drugs.

<sup>30</sup> A list of key international partners and donors can be found in WHO, *Malaria in the Greater Mekong Subregion: Regional and Country Profiles* (Geneva: WHO, 2010), <http://www.searo.who.int/myanmar/documents/malariainthegreatermekongsubregion.pdf>. The Gates Foundation has been by far the largest private-sector sponsor; a review of OECD data from 2009–2011 (when the President's Malaria Initiative was just beginning its efforts in the Mekong) found that the Global Fund provided 95 percent of public-sector malaria assistance to countries in Far East Asia.

<sup>31</sup> WHO, *Malaria in the Greater Mekong Subregion*; J. Kate's et al., "Mapping the Donor Landscape in Global Health: Malaria," Kaiser Family Foundation, August 29, 2013, <http://kff.org/global-health-policy/report/mapping-the-donor-landscape-in-global-health-malaria/>.

<sup>32</sup> In some cases, WHO has endorsed using another drug, primaquine, to supplement ACT.

<sup>33</sup> WHO, *Updated WHO Policy Recommendation (October 2012): Single Dose Primaquine as a Gametocytocide in Plasmodium falciparum Malaria* (Geneva: WHO, 2012), [http://www.who.int/malaria/pq\\_updated\\_policy\\_recommendation\\_en\\_102012.pdf](http://www.who.int/malaria/pq_updated_policy_recommendation_en_102012.pdf).

<sup>34</sup> WHO, *Global Plan for Artemisinin Resistance Containment*; V. d'Acremont et al., "Reduction in the Proportion of Fevers Associated with *Plasmodium falciparum* Parasitaemia in Africa: A Systematic Review," *Malaria Journal* 9 (2010): 240.

minimal or no symptoms, but who can still transmit parasites, would also greatly facilitate the interruption of transmission required for elimination.<sup>35</sup>

*Treat:* The number of ACT treatments procured by the public and private sectors increased from 11 million in 2005 to 278 million in 2011. WHO has “prequalified” several ACT combinations, including one in a single, fixed dose combination tablet. Eliminating oral artemisinin-based monotherapies from circulation is a priority goal of WHO’s Emergency Response to Artemisinin Resistance in the Mekong (ERAR), launched in April 2013. Although 44 countries have withdrawn marketing authorization for monotherapies, WHO noted that 14 still allowed it; at least 31 companies around the world are still marketing them.

Malaria monotherapy predominantly occurs in the private sector, with the exception of Myanmar, where ACT had been considered unaffordable. Encouragingly, the Myanmar military announced in June 2013 that it would cease production of monotherapy and convert to ACT. Conversion is projected to be completed in early 2014.<sup>36</sup>

Another ERAR priority is addressing counterfeit and substandard drugs in the Mekong.<sup>37, 38</sup> This problem is particularly vexing along border areas, where many unofficial ports of entry make control extremely difficult. A drug quality monitoring network involving WHO, US Pharmacopeia (USP), the German Pharma Health Fund, and the Thai Bureau of Drug and Narcotics has been in place in the Mekong since 2002, sampling antimalarial drugs in varying locations<sup>39</sup> within all six countries two to three times per year. The USP and others have also focused efforts on training national quality-control laboratory personnel and manufacturers in good manufacturing practices, supporting public education campaigns, providing technical guidance, and working with national and international authorities to enforce drug-manufacturing policies. Within the areas where antimalarial sampling is ongoing, and consistent with other reports, there has been a steady downward trend in counterfeit and substandard drugs; USP data showed overall failure rates of 22 percent in 2003, declining to 4.7 percent in 2005 and to 1.4 percent in 2010.<sup>40</sup>

A potential tool in malaria elimination campaigns is mass drug administration, in which everyone within a defined geographical area receives treatment, regardless of whether they have

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<sup>35</sup> Australian Agency for International Development (AusAID) and Bill & Melinda Gates Foundation (BMGF), *Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Sub-Region* (AusAID/BMGF, 2011–2012); S. Hoyer et al., “Focused Screening and Treatment (FSAT): A PCR-Based Strategy to Detect Malaria Parasite Carriers and Contain Drug Resistant *P. falciparum*, Pailin, Cambodia,” *PLOS ONE* 7, no. 10 (October 2012), <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0045797>.

<sup>36</sup> Thomas, “WHO Launches Emergency Response to Antimalarial Drug Resistance,” WHO, *World Malaria Report 2012*; Wongsrichanalai and Sibley, “Fighting Drug-Resistant *Plasmodium falciparum*,” 908–16; Morrison et al., *Rehabilitating Health in the Myanmar Transition*.

<sup>37</sup> A multicountry survey of 188 artemisinin packages in 2002–2003 found 53 percent were counterfeit. A meta-analysis of seven surveys published since 2001 revealed that 43 percent of almost 1,500 samples failed chemical assay analysis and 42 percent failed packaging tests. Of those failing chemical analysis, 34 percent had no active ingredient, 4 percent low active ingredient.

<sup>38</sup> A.M. Dondorp et al., “Fake Antimalarials in Southeast Asia Are a Major Impediment to Malaria Control: Multinational Cross-sectional Survey on the Prevalence of Fake Antimalarials,” *Tropical Medicine and International Health* 9, no. 12 (2004): 1241–46; G.M.L. Nayyar et al., “Poor-quality Antimalarial Drugs in Southeast Asia and Sub-Saharan Africa,” *The Lancet Infectious Diseases* 12, no. 6 (2012): 488–96; WHO, *Malaria in the Greater Mekong Subregion*.

<sup>39</sup> Sampling is done in varying locations within large geographic areas to reduce the risk that counterfeiters would simply avoid or target their sales to specific vendors or specific villages to avoid detection.

<sup>40</sup> U.S. Global Malaria Coordinator, *President’s Malaria Initiative Greater Mekong Sub-Region Malaria Operational Plan FY 2013*; WHO, *Malaria in the Greater Mekong Subregion*; Australian Agency for International Development (AusAID) and BMGF, *Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Sub-Region*.

symptoms and without being diagnosed. Large-scale pilot studies are currently being considered to assess the safety, effectiveness, and feasibility of this tool in the face of resistance.<sup>41</sup>

*Track:* The therapeutic efficacy studies that are routinely conducted by national malaria-control programs in the Mekong are the basis of antimalarial drug-resistance monitoring and play a major role in informing national treatment policies. It is critical that such monitoring continue (even in areas where resistance has not yet been detected), that studies incorporate advances in research and technology and remain compliant with the latest WHO protocols, and that the data obtained be of reliable quality.<sup>42, 43</sup>

Surveillance across borders requires enhanced cooperation between governments. All six Mekong countries participate in WHO's Mekong Malaria Program and its drug-efficacy network, which has been operational for over a decade and now includes almost 40 sentinel sites. On a rotating basis, these sites routinely collect surveillance data, which has become increasingly reliable as a result of the network's microscopy and other quality-assurance efforts. WHO convenes regular network meetings and publishes reviews to share and disseminate the data.<sup>44</sup>

Cambodia, China, Thailand, and Vietnam also participate in the Asia Pacific Malaria Elimination Network, a 14-nation grouping established in 2009 to advance capacity, research, and surveillance in the wider region. An important global surveillance network called the Worldwide Artemisinin Resistance Network provides training and technical assistance to laboratories in Mekong countries, and brings together study groups to analyze dosing, parasite clearance, molecular markers, and other research issues. The chairman of the board of the network is also the principal investigator for the Tracking Resistance to Artemisinin Collaboration, which conducts clinical research into factors of resistance and vector control, as well as efficacy studies in Asia and Africa.

*Prevent:* The ERAR's top priority is to scale up the "key interventions" required to successfully eliminate malaria. Many of these primary interventions are preventive: the use of long-lasting insecticide-treated bednets, additional personal protective measures for those not adequately protected by nets, and indoor residual spraying of insecticides in some situations.<sup>45, 46</sup>

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<sup>41</sup> WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion*; WHO, *Consideration of Mass Drug Administration for the Containment of Artemisinin-Resistant Malaria in the Greater Mekong Subregion: Report of a Consensus Meeting, 27–28 September 2010* (Geneva: WHO, 2010), <http://www.who.int/malaria/publications/atoz/9789241501644/en/>; Wongsrichanalai and Sibley, "Fighting Drug-resistant *Plasmodium falciparum*," 908–16.

<sup>42</sup> One urgent focus of current research is molecular surveillance. A genetic marker indicating artemisinin resistance has yet to be found (unlike with chloroquine and sulfadoxine-pyrimethamine).

<sup>43</sup> WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion*.

<sup>44</sup> U.S. Global Malaria Coordinator, *President's Malaria Initiative Greater Mekong Sub-Region Malaria Operational Plan FY 2013*.

<sup>45</sup> Other potential preventive modalities include intermittent preventive treatment in pregnancy (IPTp) and vaccination, though IPTp coverage is not generally used in the Mekong and vaccines are not yet available. In 1999, the Malaria Vaccine Initiative (MVI) was established with a mission "to accelerate the development of malaria vaccines and catalyze timely access in endemic countries." In October, phase 3 clinical trial results for the RTS,S malaria vaccine showed almost 50 percent reduction in clinical malaria in young children (5–17 months) and a 27 percent reduction in infants at 18 months of follow-up. The reductions were far less than optimal, and reductions in hospitalizations, severe malaria, and death even less, but enough to potentially augment existing preventive measures. MVI and GlaxoSmithKline jointly announced they would apply to the European Medicines Agency (EMA) for regulatory approval in 2014; if the vaccine is approved by EMA, WHO may recommend its use as early as 2015. Much earlier in the pipeline, though also figuring prominently in global health news this year, is the PfSPZ Vaccine, derived from radiation-attenuated malaria parasites. The results of a recent phase 1 clinical trial demonstrated safety and full protection in patients receiving the highest dosages, and impressive results in lower dosages. However, at this stage of development the vaccine must be administered in several doses and intravenously—conditions that will be difficult to meet for large



Implementation of interventions to control mosquitoes has been quite impressive in several parts of the Mekong. For example, high levels of net ownership have been achieved in several high-resistance areas. However, sustaining such high levels of coverage is more challenging, and ownership does not equal use. Many people—including those who sleep or work outside during the *Anopheles* mosquitos' biting hours<sup>47</sup>—are not well protected by existing preventive methods.<sup>48</sup> Worryingly, insecticide resistance has recently emerged in the Mekong and elsewhere.<sup>49</sup>

## What Challenges Remain?

*The clock is ticking.... The spread of artemisinin resistance is a global threat—it is serious, it is urgent, but it might still be preventable.... A speedy, scientifically sound, and coordinated response from affected countries, donors, and international organisations is essential.... Tough decisions might well be needed, and if extraordinary measures are required, there needs to be high-level political backing.*—Professor Nicholas White, 2010<sup>50</sup>

**Mobilizing more resources:** There has been a surge in financial support for the emergency response to artemisinin resistance and for eliminating malaria in the Mekong. Yet WHO estimates that \$300-350 million more is needed between 2013 and 2015; the Asian Development Bank believes that at least \$400 million will be required.<sup>51</sup>

Even though securing the required resources will be tremendously difficult, it will ultimately be much less expensive than not doing so. Malaria elimination, once achieved, is relatively affordable to maintain, while continued control places an ongoing, likely unsustainable burden on donor support and national health infrastructures and can be threatened by climate change,<sup>52</sup> economic downturns, social upheaval, or declining effectiveness of existing control measures.

Resources are needed across the board: more manpower; increased training and development for existing and new members of the health workforce; more ACTs; more insecticide-treated bednets (particularly for migrants and other highly mobile populations); continued strengthening of drug-efficacy monitoring (including in Africa and other malaria-endemic countries); continued development of new drugs and vaccines. Holding the line—perhaps even making continued slow progress—might be possible at current levels of investment. Yet, absent elimination of the malaria parasite in the Mekong, it is only a matter of time before artemisinin resistance becomes the global norm, reversing the recent gains.

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numbers of people in many countries. For a current snapshot of the vaccine pipeline, see WHO, “Global malaria vaccine pipeline,” [http://www.who.int/vaccine\\_research/links/Global\\_malaria\\_vaccine\\_portfolio.pdf](http://www.who.int/vaccine_research/links/Global_malaria_vaccine_portfolio.pdf).

<sup>46</sup> P. Bejon et al., “Efficacy of RTS,S Malaria Vaccines: Individual-Participant Pooled Analysis of Phase 2 Data,” *Lancet Infectious Diseases* 13, no. 4 (2013): 319–27; R.A. Seder et al., “Protection against Malaria by Intravenous Immunization with a Nonreplicating Sporozoite Vaccine,” *Science* 341, issue 6152 (2013): 1359–65.

<sup>47</sup> Typically from nightfall to sunrise, though evidence has recently been found for daytime biting by some species.

<sup>48</sup> Some insecticide-treated nets are specifically designed for use with hammocks, useful for certain populations including forest workers.

<sup>49</sup> WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion*.

<sup>50</sup> N.J. White, “Artemisinin Resistance—the Clock is Ticking,” *The Lancet* 376, issue 9758 (2010): 2051–52.

<sup>51</sup> Thomas, “WHO Launches Emergency Response to Antimalarial Drug Resistance”; Cris Larano, “Asia-Pacific Leaders Ally to Fight Malaria,” *Wall Street Journal*, October 11, 2013, <http://blogs.wsj.com/searealtime/2013/10/11/asia-pacific-leaders-back-alliance-to-fight-malaria/?cb=logged0.8997861291281879&cb=logged0.752900741994381>.

<sup>52</sup> D.L. Smith et al., “A Sticky Situation: The Unexpected Stability of Malaria Elimination,” *Philosophical Transactions of the Royal Society B* 368, no. 1623 (2013), <http://rstb.royalsocietypublishing.org/content/368/1623/20120145.long>.

*Improving supply-chain management:* Ensuring adequate supplies of essential commodities for testing and treating malaria is critical to building credibility and trust in the public health sector. Seeking care at a public facility only to find that no tests or treatments are available discourages patients from returning and encourages self-treatment and/or use of the private sector. Unfortunately, this is currently an all-too-common occurrence. Addressing this issue will require significant attention to improving supply-chain management from procurement through transportation, storage, and distribution.

An effective solution will also demand a trustworthy information management system—be it Internet, SMS, paper based, or a combination — with trained personnel using well-planned standard operating procedures to reliably monitor and quickly respond to the inevitable fluctuations in supply and demand.<sup>53, 54</sup>

*Engaging the private sector:* While the private sector's sale of antimalarial drugs has been banned in China, Thailand, and Vietnam, this distribution network still plays a major role in Myanmar, Cambodia, and Lao PDR. Where government-run health systems lack sufficient resources to provide timely access to care for all, the private sector can fill the void and provide necessary treatment, particularly for marginalized populations. It will therefore be essential to engage with the private sector to enable "T3" and optimal prevention to become the universal standard throughout the Mekong.

Control over malaria diagnosis and treatment is more challenging in the private sector. It may be difficult to ensure that patients seeking care for malaria are treated only after confirmation by an appropriate test, that the treatment is reported and tracked, and that insecticide-treated bednets are owned and used, rather than untreated ones. It is likewise difficult to control the use of monotherapy within the private sector, though government bans in Cambodia and Lao PDR have greatly reduced its availability and use.<sup>55</sup>

In some cases, financial incentives may improve the quality of care in the private sector. For example, providers could be compensated for patients with suspected malaria whose tests are negative, and for patients who are confirmed and given medication *only* when it is also reported, perhaps through SMS or other inexpensive methodologies. Subsidies or other incentives could influence bednet manufacturers and importers to change their production and marketing strategies and to encourage their current and prospective customers to switch to treated nets.<sup>56</sup>

Major issues related to the manufacture and sale of antimalarial drugs cannot be effectively addressed without engaging the pharmaceutical industry, which, although subject to government regulation, falls in the private sphere. China's pharmaceutical industry in particular is quite robust and offers great potential to shift the balance. Important objectives of such engagement include: raising production and quality-control standards; overcoming bottlenecks to

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<sup>53</sup> Another benefit of improving supply-chain management: slow supply chains can contribute to sub-therapeutic artemisinin levels of the drug (which can fuel resistance), since the same short half-life that helps make artemisinins effective also results in relatively short shelf times.

<sup>54</sup> WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion*; WHO, *Good Procurement Practices for Artemisinin-Based Antimalarial Medicine* (Geneva: WHO, 2010); WHO, *Good Practices for Selecting and Procuring Rapid Diagnostic Tests for Malaria* (Geneva: WHO 2011); Holly Young, "Preparing for the Inevitable: How Do We Tackle Drug Resistant Malaria?" *The Guardian*, July 23, 2013, <http://www.theguardian.com/global-development-professionals-network/2013/jul/23/best-bits-malaria-drug-resistance>.

<sup>55</sup> Myanmar has announced plans to begin refusing to renew monotherapy marketing licenses as they expire. This could greatly reduce the supply of monotherapy there, making it easier to encourage private providers to use ACTs.

<sup>56</sup> AusAID and BMGF, *Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Sub-Region*; WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion*.

prequalification of antimalarial drugs<sup>57</sup>; contributing to the development of new antimalarial drugs and diagnostics; and ultimately achieving an enforceable regional agreement banning the marketing and sale of oral artemisinin-based monotherapy.<sup>58</sup>

*Promoting cooperation and collaboration across sectors and borders:* By definition, national malaria-control programs are implemented within the confines of international borders. But since malaria knows no boundaries, strong coordination between provinces and between nations is indispensable. Countries must provide sufficient resources to maintain and periodically upgrade drug-efficacy data-collection sites to ensure their data is reliable. They must also be transparent in sharing that data with their neighbors, to evaluate, prioritize, plan, and implement interventions to increase access to preventive, diagnostic, and treatment services for migrants and other high-risk populations.

Combating counterfeit drug traffic and eliminating the artemisinin monotherapy trade will also require cooperation with entities well beyond the health sector, including regulatory and law-enforcement authorities and customs officials at both national and regional levels. This was demonstrated in 2006–2007, when a group of Mekong health officials, along with INTERPOL officers, presented evidence to Chinese authorities, who then conducted a criminal investigation and ultimately arrested two persons who were allegedly responsible for distributing 240,000 blister packs of counterfeit artemisinin.<sup>59</sup>

The need for public-private collaboration of effort also extends beyond health. For example, government agencies charged with protecting the labor force, along with extractive, construction, and other industries that rely on migrant populations to do their work, are among those who, according to the ERAR, collectively share an obligation to seek out and evaluate “established and innovative approaches to malaria prevention and treatment for (high-risk) populations.”<sup>60</sup>

A primary objective of the Global Fund’s Regional Artemisinin Resistance Initiative is to enhance the international and cross-sector collaboration required to tackle these tough issues. Fifteen percent of the \$100 million investment has been set aside for regional activities, rather than going to individual national malaria-control programs.

*Myanmar:* Seven of 10 citizens of Myanmar live in malaria-endemic areas; over three-quarters of all malaria cases and deaths in the Mekong occur there. It is clear that this country with its chronically under-resourced health system needs urgent additional attention. Myanmar’s recent reforms and rapprochement with the United States provide an opening that could benefit millions in Myanmar while simultaneously reducing its role in amplifying and spreading artemisinin resistance.

*Demonstrating political will:* Successfully tackling these critical challenges will require that the nations of the Mekong and the broader world community keep artemisinin resistance high on political agendas, both domestic and international.

It is encouraging that antimalarial drug resistance has received considerable political attention this past year. In a major declaration at the November 2012 East Asia Summit, heads of state of all member nations reaffirmed their commitment to the Global Plan for Artemisinin Resistance Containment; in September, alongside the 68th United Nations General Assembly, world leaders commemorated the launch of the “Multisectoral Action Framework for Malaria” (a joint effort of

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<sup>57</sup> This would enable more regional producers of ACT to enter the global market while providing additional incentive to shift away from production of artemisinin monotherapy.

<sup>58</sup> AusAID and BMGF, *Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Sub-Region*.

<sup>59</sup> WHO, *Malaria in the Greater Mekong Subregion: Regional and Country Profiles*.

<sup>60</sup> WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion*.

Roll Back Malaria and the United Nations Development Programme)<sup>61</sup>; and the formation of the Asia-Pacific Leaders Malaria Alliance was announced at the October 2013 East Asia Summit.

However, maintaining the spotlight on this problem will not be easy, given a host of other pressing health and development needs, local political sensitivities, and the challenging global financial situation.<sup>62, 63</sup>

## Conclusion

Malaria has been called “one of the world’s great unnecessary killers.”<sup>64</sup> A concerted effort is underway to change that. As a result, over a million deaths have been averted over the past decade, and 34 nations are on a path to eliminating malaria within their borders, joining over 100 that have already done so over the last century.

Meanwhile, even as the world strives to reduce and even dares to imagine the possibility of eliminating malaria’s terrible burden, an equally grave threat looms—of a day, perhaps very soon, when the drugs we use to combat malaria are rendered impotent.

The essential elements of combating antimalarial resistance are straightforward: “T3: Test, Treat, Track,” and prevention. However, there are considerable challenges in ensuring that monotherapy and drug-quality issues are resolved so that rational treatment becomes universal, and that vulnerable populations in remote areas receive good access to reliable health care. More resources are required, and collaboration—both public/private and across sectors and borders—is essential.

The United States is well poised to play a lead role in keeping this issue front and center on the world’s agenda. USAID, CDC, and the Department of Defense have long had a strong health presence in the Mekong. Since its inception in 2009, the State Department’s Lower Mekong Initiative has worked within and across sectors to build greater cohesion among the Mekong countries and assist them in enhancing their capabilities. The United States has struggled to make the Asia-Pacific rebalance less threatening and more tangible to China and others in the region. Smart collaboration to combat artemisinin resistance would advance U.S. national-security interests while also advancing shared humanitarian interests.

With no drugs on the horizon to replace artemisinin when it can no longer kill malaria parasites, the window of opportunity is narrow. Still, there is an opportunity to overcome this threat, and to enable the long and winding path toward malaria elimination to continue.

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<sup>61</sup> Atif Khurshid and Trey Watkins, “Multisectoral Action Framework for Malaria Launched Alongside 68th United Nations General Assembly,” UN Development Programme, September 24, 2013, <http://www.undp.org/content/undp/en/home/presscenter/pressreleases/2013/09/24/multisectoral-action-framework-for-malaria-launched-alongside-68th-united-nations-general-assembly/>.

<sup>62</sup> For example, even as countries strive for regional consensus to deal with counterfeit and substandard medications, this issue is also highly sensitive since in any given country, the source of many of these “bad drugs” is a neighboring country.

<sup>63</sup> AusAID and BMGF, *Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Sub-Region*; WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion*.

<sup>64</sup> Bryan Walsh, “Drug-Resistant Malaria is Spreading, and It Could Be a Public Health Disaster,” *Time*, April 6, 2012, <http://healthland.time.com/2012/04/06/drug-resistant-malaria-is-spreading-and-it-could-be-a-public-health-disaster/>.

As Dr. Robert Newman, director of WHO's Global Malaria Program, has stated, the "consequences of widespread resistance to artemisinin would be catastrophic. We must act now to protect south-east Asia today and sub-Saharan Africa tomorrow."<sup>65</sup>

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<sup>65</sup> Thomas, "WHO Launches Emergency Response to Antimalarial Drug Resistance."

# Glossary

**Anopheles:** a species of mosquito that transmits the malaria parasite.

**Artemisinin:** an extract of *qing hao*, a traditional Chinese herbal medicine, used as an antimalarial due to its action against the malaria parasite, *Plasmodium falciparum*.

**Artemisinin combination therapy (ACT):** therapy for malaria that combines artemisinin with a longer-acting drug. Artemisinin quickly reduces the number of parasites and the partner drug kills any remaining parasites.

**Artemisinin resistance:** unresponsiveness (or significantly reduced responsiveness) of the malaria parasite to artemisinin due to one or more genetic mutations within the parasite.

**Asia Pacific Malaria Elimination Network:** a 14-nation group, including Cambodia, China, Thailand, and Vietnam, developed in 2009 to increase capacity, research, and surveillance in the wider region.

**Chloroquine:** one of the first mass-administered antimalarial drugs developed to prevent and treat malaria. In most areas of the world, *Plasmodium falciparum* is now resistant to chloroquine treatment. Resistance is not yet a problem in treating malaria caused by other malaria parasites, except for malaria caused by *Plasmodium vivax* in Indonesia and Papua New Guinea.

**Drug-resistant genotypes:** a genetic makeup that results in resistance to antimalarial drugs.

**Emergency Response to Artemisinin Resistance (ERAR):** World Health Organization (WHO) initiative launched in April 2013 that reinforces the goals of the Global Plan for Artemisinin Resistance Containment and highlights key action areas required to eliminate malaria in the Mekong.

**Endemic country:** a country in which a disease is widespread.

**Global Plan for Artemisinin-Resistance Containment:** a plan designed in 2011 to protect ACT as an effective treatment for *P. falciparum* malarial infections. The goals are to eliminate resistance where it already exists and prevent it in areas where resistance has not yet occurred.

**Greater Mekong Subregion (GMS):** a portion of the Asia-Pacific region that includes Cambodia, Myanmar, parts of Southern China, Thailand, Laos PDR, and Vietnam. The Greater Mekong Subregion is referred to as “the Mekong” in this report.

**Indoor residual spraying (IRS):** a preventive measure that includes spraying diluted insecticides within a dwelling in order to kill mosquitoes that spread malaria.

**Insecticide-treated nets (ITNs):** one of the primary preventive measures taken against malaria whereby nets treated with insecticide are used to shield individuals from mosquitoes in areas such as beds.

**INTERPOL:** an intergovernmental organization that works to facilitate international police cooperation. Originally established in 1923 as the International Criminal Police Commission, it adopted its current name in 1956.

**Malaria:** a deadly parasitic disease that is transferred by mosquitoes.

**Malaria Control in War Areas:** an initiative developed during World War II to control malaria around military training bases in the southern United States where malaria was still rampant. By suppressing malaria around the bases, the group could also control the spread of the disease to civilian populations.

**Malaria monotherapy:** any therapy in which one malaria-specific drug, such as artemisinin, is taken alone and not in combination with another medication.

**Malaria No More:** a nongovernmental organization formed in 2006 that seeks to end malaria-related deaths in Africa.

**Mass drug administration:** a tool in malaria elimination campaigns in which everyone in a designated geographical area receives treatment, regardless of whether or not they exhibit symptoms or have been diagnosed.

**National Malaria Control Programs:** national programs that conduct therapeutic efficacy studies and have a large role in shaping national malaria treatment policies.

***Plasmodium falciparum*:** a parasite that causes malaria (also referred to as *P. falciparum*). Of the five species that cause malaria, it is the largest source of malaria cases and malaria-related deaths.

**President's Malaria Initiative:** an initiative launched by President George W. Bush in 2005 that dedicated \$1.2 billion to combating malaria in largely affected regions such as Africa and Southeast Asia.

**Rapid diagnostic test (RDT):** an alternative to using a microscope to diagnose malaria. Like microscopy, it uses a blood sample, but does not require extensive training and allows for rapid detection of parasites.

**Roll Back Malaria:** WHO program established in 1988 that catalyzed the global effort to eradicate malaria.

**Sulfadoxine-pyrimethamine:** a combination of two drugs, sulfadoxine and pyrimethamine, used to kill malaria parasites. As with chloroquine, the parasites have become widely resistant to this treatment.

**Therapeutic efficacy studies:** studies routinely conducted by national malaria control programs to monitor drug effectiveness for malaria.

**T3: Test, treat, track:** A WHO campaign launched in 2012 that seeks to ensure that all suspected malaria cases are properly tested, that confirmed cases are treated with high-quality ACTs, and that the disease is tracked through timely and accurate surveillance systems.

**US Pharmacopeia (USP):** a nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements. Its drug standards are enforceable in the United States by the Food and Drug Administration, and are relied upon in more than 140 countries. It is a collaborator in a drug quality-monitoring network that aims to prevent the distribution of counterfeit drugs in the Mekong.

**World Wide Artemisinin Resistance Network:** a global surveillance network that provides training and technical assistance to laboratories in Mekong countries, and brings together study groups to analyze dosing, parasite clearance, molecular markers, and other research issues.









1616 Rhode Island Avenue NW | Washington DC 20036  
t. (202) 887-0200 | f. (202) 775-3199 | [www.csis.org](http://www.csis.org)

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