

## Artemisinin-Resistant Malaria in Asia

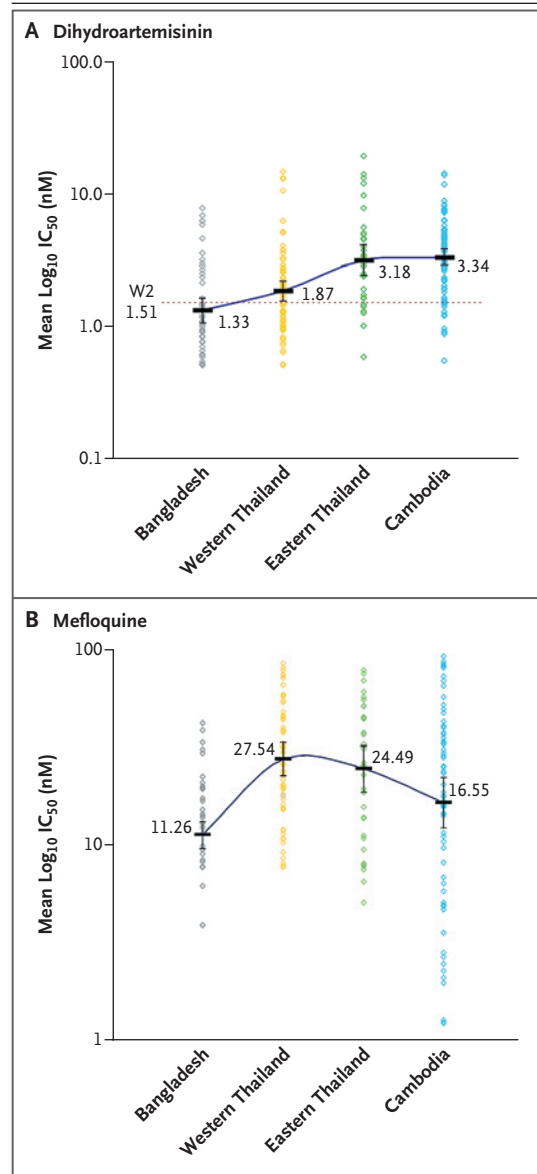
**TO THE EDITOR:** Artemisinin-based combination therapies have recently been introduced in virtually all countries in which malaria is endemic, thereby making such drugs the most essential class of antimalarial agents. The spread of artemisinin resistance could have a devastating effect on global malaria-control efforts. An important assumption in the use of such therapies is that the combination-drug partner will protect artemisinin from the development of resistance. However, recent data indicating that artemisinin resistance has already emerged along the border between Cambodia and Thailand suggest that this view may have been overly optimistic.<sup>1</sup>

On the basis of recent data, the World Health Organization is coordinating a large-scale malaria-elimination campaign in the region affected by artemisinin resistance.<sup>2</sup> The central question emerging from the ongoing discussion is how far artemisinin resistance has extended westward from its original focus. Surveillance data from the Thai Ministry of Health indicate that clinical failures of artemisinin-based therapies are largely limited to the Thai–Cambodian border, whereas efficacy with artesunate–mefloquine along the western borders of Thailand remains high.<sup>3</sup> In Cambodia, failure rates of artesunate–mefloquine are higher in the western provinces, which suggests that the current first-line therapy may be severely compromised in the region and that other options need to be evaluated. In vitro data can provide a quantitative measure of intrinsic artemisinin sensitivity, are well suited to show geographic trends, and may correlate with clinical response to treatment.

### Figure 1. In Vitro Sensitivity to Antimalarial Drugs in Bangladesh, Western Thailand, Eastern Thailand, and Cambodia.

Panel A shows the in vitro drug sensitivity, as measured by the 50% inhibitory concentration ( $IC_{50}$ ) for dihydroartemisinin, which was assessed with the use of the histidine-rich protein 2 drug-sensitivity assay performed on fresh blood samples containing *Plasmodium falciparum* malaria collected from patients in Bangladesh (gray symbols), western Thailand (yellow symbols), eastern Thailand (green symbols), and western Cambodia (blue symbols). The dotted line shows the  $IC_{50}$  for the reference parasite clone W2. Panel B shows the corresponding values for sensitivity to mefloquine in the same four regions. The I bars represent 95% confidence intervals.

We conducted in vitro studies throughout South Asia and Southeast Asia, using a standardized approach (a histidine-rich protein 2 malaria in vitro drug-susceptibility assay<sup>4</sup>) at each site. On the basis of blood samples obtained from 247 patients between the ages of 18 and 65 years who presented with uncomplicated *Plasmodium falciparum* malaria (with 100 to 100,000 parasites per cubic millimeter), we found that artemisinin susceptibility showed a continuous and significant decrease from Bangladesh throughout western and eastern Thailand (Fig. 1A).



In 49 samples collected in the Chittagong Hill Tracts in Bangladesh in 2004, the geometric mean 50% inhibitory concentration (IC<sub>50</sub>) was 1.33 nM (95% confidence interval [CI], 1.07 to 1.66). In 73 samples from patients originating in the Tak Province of western Thailand in 2004 and 2005, the IC<sub>50</sub> was 1.87 nM (95% CI, 1.57 to 2.22).<sup>4</sup> And in 37 samples collected in the Trat Province of eastern Thailand in 2005 and 2006, the IC<sub>50</sub> was 3.18 nM (95% CI, 2.45 to 4.12). Levels in western Cambodia were similar to those in eastern Thailand. In 88 samples collected in Ta Sanh in the Battambang Province of Cambodia in 2006 and 2007, the IC<sub>50</sub> was 3.34 nM (95% CI, 2.90 to 3.85).<sup>1,3,5</sup> The corresponding mean value for the artemisinin-sensitive clone W2 was 1.51 nM.

It has been suggested that increased failure rates of artesunate-mefloquine in eastern Thailand, as compared with western Thailand, may be attributed to major regional differences in the susceptibility of malaria parasites to mefloquine, the partner drug used with artemisinin in Thailand. However, even though our data indicate a steep drop in mefloquine sensitivity between that measured in samples obtained in Bangladesh (IC<sub>50</sub>, 11.26 nM; 95% CI, 9.64 to 13.16) and that in samples obtained in western Thailand (IC<sub>50</sub>, 27.54 nM; 95% CI, 22.74 to 33.36; P<0.001), levels were similar in samples obtained in eastern Thailand (IC<sub>50</sub>, 24.49 nM; 95% CI, 18.62 to 32.22) and even lower in samples obtained in Cambodia (IC<sub>50</sub>, 16.55 nM; 95% CI, 12.32 to 22.23) (Fig. 1B). Similarly high IC<sub>50</sub> levels for mefloquine were found along both the eastern and western borders of Thailand (P=0.63), whereas the difference in artemisinin sensitivity between these sites was significant (P<0.001).

These findings suggest that the increased failure rate of artemisinin-based therapies can probably be attributed to decreased artemisinin susceptibility in the east rather than to major regional differences in mefloquine sensitivity. In south-eastern Bangladesh, an area where until very recently artemisinin-based therapies have not been extensively used, artemisinin sensitivity remains high. These data indicate that it is unlikely that artemisinin resistance has spread across Thailand, and we found high susceptibility in Bangladesh.

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