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## ARTEMISININ RESISTANCE THREATENS EFFORTS TO CONTROL MALARIA

### *Experts at ASTMH Session Highlight Containment Activities at Thailand-Cambodia Border*

**WASHINGTON, Nov. 19, 2009** – Evidence of resistance to the antimalarial drug artemisinin and its derivatives threatens efforts to control malaria in Southeast Asia, and experts fear artemisinin resistance may spread from the Thailand-Cambodia border to affect other malaria endemic countries. Evidence to such effect was presented today at the 58<sup>th</sup> annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH).

The prospect of spreading artemisinin resistance is particularly alarming given that malaria is one of the most devastating infectious diseases in the world, causing approximately 250 million illnesses and 850,000 deaths annually. The World Health Organization (WHO) estimates that roughly half of the world's population is at risk of malaria, and those living in lower-income countries are at particular risk. Malaria also exerts a significant economic toll, reducing economic growth rates by as much as 1.3% in countries with high disease rates.

“Artemisinin combination therapies are the most rapidly and reliably effective treatments for malaria caused by the *Plasmodium falciparum* parasite, which is responsible for the vast majority of malaria-related illnesses and deaths,” noted Dr. Pascal Ringwald of the WHO, who spoke at the ASTMH session. “The loss of artemisinin derivatives to resistance could have a devastating effect on health in tropical countries, and would threaten current global efforts to eliminate malaria, as there are very few innovative replacement therapies in the pipeline at the late stage of development.”

Artemisinin is the active component of the Chinese medicinal herb *Artemisia annua*, which has been used as an antimalarial treatment since at least the fourth century CE. Artemisinin was extracted as a drug product in the 1960s. In addition to the parent compound, a number of artemisinin derivatives are available to treat malaria; these include artesunate, artemether, artemotil, and dihydroartemisinin. Unlike other antimalarials, the artemisinins act rapidly against all stages of the *P. falciparum* parasite, including the so-called ring stage, a critical step in the parasite's life cycle. These agents provide a rapid clinical benefit and help to decrease transmission of malaria.

Drawbacks of the artemisinins are their short half-lives, and the fact that the standard 3-day treatment course is often followed by recurrent bloodstream infection and illness within days or weeks. Consequently, artemisinins are often administered in combination with a longer-acting antimalarial drug such as mefloquine, lumefantrine, amodiaquine, or piperazine. Combination therapy also reduces development of drug resistance. Increased development of drug resistance may occur when artemisinins are taken alone.

Dr. Ringwald, who directs the antimalarial drug resistance surveillance in the WHO Global Malaria Programme, discussed evidence of *P. falciparum* resistance to artemisinin in Western Cambodia, as manifest by marked prolongation of parasite clearance times. He also cited evidence of a smaller but nonetheless significant increase in clearance times on the western border of Thailand and adjacent Myanmar. "These drugs are designed to kill the parasites within 24 to 48 hours, but we're finding that it sometimes takes four or five days to kill them," he observed. "In some studies, half of the parasites are not killed within 72 hours after the beginning of the treatment, which indicates a growing resistance problem." While these data are indeed cause for serious concern, it should be noted that the vast majority of individuals are still being cured with current artemisinin-based treatments.

The WHO, with support from the Bill & Melinda Gates Foundation, and the United States Agency for International Development, and the Global Fund for AIDS, Tuberculosis, and Malaria (GFATM) has steadily intensified its artemisinin resistance containment activities since early 2007, when the resistance problem became apparent. A major objective of the containment project is to eliminate resistant parasites by detecting all malaria cases in target areas and ensuring effective treatment and parasite clearance. Another important objective is to prevent use of artemisinin monotherapy, fake drugs, and inappropriate treatment in the private sector. "Despite the proven effectiveness of combination therapy, the use of artemisinin monotherapy persists, undermining efforts to control recurrent infection and illness," Dr. Ringwald commented. "In addition, there are a number of counterfeit drugs on the market that contain few active ingredients."

Even when genuine artemisinin combination therapies are used, too often they are used to treat fever not due to malaria, further exacerbating the resistance problem. "It is critical to increase access to parasitologic diagnosis of malaria prior to treatment," commented Dr. Robert Newman, the recently appointed Director of the WHO Global Malaria Programme. "By treating all cases of fever as malaria, we not only overuse ACTs, but we also fail to provide appropriate care for the enormous number of individuals who have a non-malarial cause of their fever. In addition, it is not possible to implement an adequate malaria surveillance system without providing universal access to parasitologic diagnosis."

Dr. Ringwald expressed the hope that the ASTMH session would spur the international community to action. "We are very concerned about the possible emergence of new foci of malaria in Southeast Asia, where populations of the parasite may intersect with populations of hosts and vectors that support its existence," he said. "We hope the international community responds to our call to contain the artemisinin resistance problem in this region, and provides funding not only to support our containment activities, but also research efforts aimed at discovering and developing new antimalarial therapies."

“The growing problem of artemisinin resistance is one that we take very seriously, as malaria is one of the world’s foremost tropical diseases,” commented Thomas Wellems, MD, PhD, president of ASTMH. “Dr. Ringwald and his colleagues are to be commended for their focus on action to contain it. We hope their activities result in increased investment and research support from the world community, as well as intensified efforts to promote judicious use of artemisinin and monitoring of artemisinin resistance.”

### **About the ASTMH**

The American Society of Tropical Medicine and Hygiene (ASTMH), founded in 1903, is a worldwide organization of scientists, clinicians and program professionals whose mission is to promote global health through the prevention and control of infectious and other diseases that disproportionately afflict the global poor.

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