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The Threat of Artemisinin-Resistant Malaria

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In the 1970s, Chinese government scientists working on a secret “Project 523” developed a new class of potent antimalarial drugs, the artemisinins or qinghaosu derivatives. In mostly unpublished work that has just been recognized by a 2011 Lasker Award to Tu Youyou, researchers in China isolated the active compounds from the plant *Artemisia annua*, tested them in mice, analyzed the chemical structure of the artemisinins, and demonstrated their high potency and rapid efficacy in human trials. Although they were widely used in China during the 1980s, only in the 1990s did the artemisinins come to wider global attention in the form of artemisinin-based combination therapies. Over the past decade, these highly efficacious treatments, along with other malaria-control measures, have contributed to significant reductions of the malaria burden in many areas of the world, including parts of Africa.

Together, these successes and increased funding have revived the bold aspiration to eradicate malaria. About one quarter of malaria-afflicted countries are already shifting their focus from malaria control to elimination. Past successful malaria-elimination schemes have all depended on reliable curative drugs, used in conjunction with vector-control methods. Similarly, current elimination plans rely on the long-term availability of effective antimalarial drugs — a requirement that is pivotally dependent on the efficacy of artemisinins. The artemisinin derivative artesunate has also proven to be the best drug against severe falciparum malaria. Losing the artemisinins to resistance would be a disaster for the control and treatment of malaria and would bring eradication efforts to a standstill.

Reduced susceptibility of *Plasmodium falciparum* to artemisinin derivatives has been documented in the Cambodia–Thailand border region.[1,2] Although most *P. falciparum* infections still eventually clear after treatment with artemisinin-based combination therapies, resistant parasites take 3 or 4 days to do so, as compared with less than 2 days for artemisinin-sensitive parasites. This delayed clearance could be a step toward high-level

resistance and frank treatment failure. Since the artemisinins have very short half-lives, this loss of potency also renders the more slowly eliminated drugs that are part of combination therapies vulnerable to development of resistance. The gravity of this threat has been recognized, and an ambitious program to contain artemisinin resistance has been launched under the guidance of the World Health Organization (WHO).[3] Still, several critically important questions about artemisinin resistance and containment merit urgent attention.

Antimalarial drug resistance is traditionally defined as persistence or recurrence of malaria parasites after appropriate drug treatment. However, an effective partner drug can obscure decreased efficacy of the artemisinin component of combination therapies. Since rapid initial parasite clearance is the hallmark of the artemisinins, the clearance rate (the slope of the log-linear parasite-clearance curve) is a more sensitive method for detecting reduced susceptibility to artemisinins (see figure). An important question for elimination and containment efforts is how delayed parasite clearance affects recrudescence, gametocyte-carriage rates, and infectivity to mosquito vectors — factors that influence the burden of disease and the potential for transmission.

Understanding the biology of artemisinin-resistant *P. falciparum* is crucial for the development of new treatments and reliable in vitro tests to detect resistance, which are currently unavailable. Modeling of parasite-clearance curves suggests that artemisinin resistance affects ring-stage parasites more than the more mature trophozoite and schizont stages (see figure).[4] In vitro tests focusing on the inhibition of ring-stage parasites could become valuable surveillance tools.

The molecular mechanism or mechanisms of artemisinin resistance are unknown. Molecular markers would greatly facilitate containment efforts in Southeast Asia, which are starting with no knowledge of the extent or directions of spread of artemisinin resistance from its focus of origin. Molecular surveillance can be more readily standardized and widely and rapidly deployed than surveillance based on clinical protocols or in vitro assays. Recent evidence demonstrates that resistance is a genetically heritable trait of the parasites, but research to identify artemisinin-resistance markers has thus far focused on specific candidate genes, none of which have been associated with delayed parasite clearance. A comprehensive genomewide search for the molecular basis of delayed parasite clearance, using genomewide association studies and assessing signatures of recent strong selection, is warranted.

The WHO in collaboration with numerous stakeholders has recently launched the Global Plan for Artemisinin Resistance Containment.[3] Reliable intelligence on whether artemisinin resistance has already disseminated or independently emerged beyond the Cambodia–Thailand border region is critical for containment. If resistance is confined to a limited area, elimination of all *P. falciparum* parasites from the region will be the only way to prevent artemisinin resistance from spreading.[5]

Additional interventions beyond conventional malaria-control measures are needed. In Southeast Asia, factors such as mobile migrant populations and forest-dwelling mosquitoes may render vector-control methods such as bed nets and spraying less effective, necessitating greater reliance on drugs. Possibilities include regional mass drug-administration campaigns and screening and treatment of parasitemic persons, both of which have theoretical and operational advantages and disadvantages. Mathematical modeling can be an important tool for guiding these strategies. Primaquine is currently the only available drug that can prevent transmission of mature gametocytes, the sexual stage of the parasite that is responsible for transmission. Although low doses are gametocytocidal, concern remains that even low doses can cause intravascular hemolysis in patients with glucose-6-

phosphate dehydrogenase deficiency, and further evaluation is urgently needed before any large-scale use of primaquine can be recommended.

Operational and behavioral research to ensure optimal deployment, coverage, and midcourse adjustment of containment strategies is important, including actions to remove from the market oral artemisinin-based monotherapies — major drivers of the spread of resistance.[3] Since it is essential that containment efforts reach migrating populations, studies must be undertaken of their migration patterns and health care–seeking behavior.

Another major problem is the widespread marketing and use of counterfeit or falsified antimalarial drugs, often containing traces of artemisinins, which not only leave cases of life-threatening malaria inadequately treated but exert additional selective drug pressure that could lead to resistance. Monitoring drug quality, regulating drug supplies, adopting and enforcing relevant legislation, raising awareness, and conducting research on improved detection methods are all necessary activities. Interpol, national authorities, drug companies, academic groups, the United States Pharmacopeia, and the WHO are collaborating on these actions.

The threat posed by emerging artemisinin resistance on the Cambodia–Thailand border is widely acknowledged, but an effective response requires that critical operational and basic research questions be answered quickly. Researchers, funders, and policy leaders must recognize the urgency of the problem, take action to address simultaneously several important knowledge gaps, and focus immediately on eliminating the threat of artemisinin resistance. It will be essential to coordinate research and containment efforts globally and to share data, research tools, and experiences. Important existing global forums for action include the WHO, the WorldWide Antimalarial Resistance Network, and the Malaria Research and Reference Reagent Resource Center. The artemisinins have been crucial to recent successes in reducing the malaria burden, and artemisinin-based combination therapies are essential to all plans for malaria elimination. Losing artemisinins to resistance will not only jeopardize the goal of malaria eradication, but will also result in large increases in African childhood mortality like those that occurred during the last century when chloroquine failed against newly evolved drug-resistant parasites.

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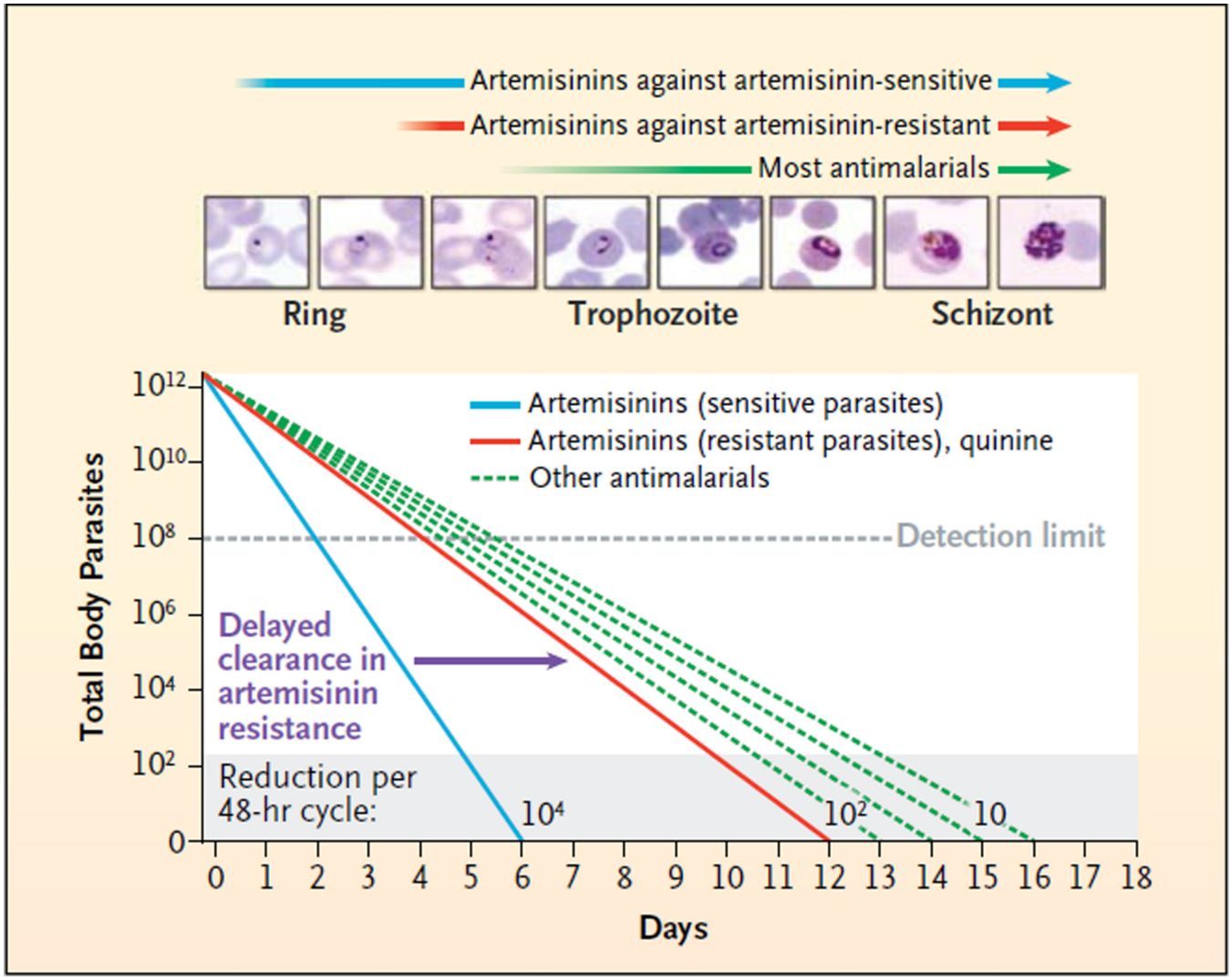

Figure 1. Dynamics of Parasite-Killing Activity of Artemisinins and Other Antimalarial Drugs

Against sensitive *P. falciparum* infection, the fast-acting and rapidly cleared artemisinins are the most potent antimalarial drugs known, reducing the parasite load by a factor of 10,000 per 48-hour asexual-stage parasite cycle. In the partially resistant strains of *P. falciparum* that are commonly found on the Cambodia–Thailand border, the parasite load is now reduced only by a factor of 100 per cycle — an effect similar to that of slower-acting drugs such as quinine (bottom of figure). Another unique and advantageous feature of the artemisinins is their broad stage-specificity, but this seems to be compromised in the resistant Southeast Asian parasites (top). Parasites that are at the ring stage during the brief period of exposure to rapidly eliminated artemisinins have reduced susceptibility, which results in delayed parasite clearance following treatment.