

if feasible solutions are to be found. Although we cannot predict exactly what an adversary will do, we can take control of our own environments, and we must watch potential adversaries closely.

Just as public health strategies have been developed to detect and track emerging epidemics, identify population risks and vulnerabilities, and prevent or ameliorate adverse effects, analogous approaches can be used to improve cybersecurity in health care delivery organizations. First, active and real-time surveillance and communication of emerging cyberthreats could be used to profile threats and ultimately influence public policy and prevention. Second, risk-based analysis and modeling that take into account current and possible threats, the resulting risks, and the vulnerabilities and resilience

of the information system can guide policy development. Third, effective regulation may help ensure the fidelity of medical devices; finding the right balance by establishing security without creating yet another expensive and distracting set of compliance standards will require prior definition by stakeholders (patients, providers, and institutions) — perhaps in a forum hosted by the Institute of Medicine, to build on its reports on privacy and data security.<sup>5</sup>

The threats of cyberattack are clear and present in health care. It is time to organize, convene, and focus in a way that truly protects our patients, providers, and institutions. Technology has unquestionably improved health care. Let's be sure that its promised benefits continue to be delivered safely.

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1. Filkins B. SANS health care cyberthreat report: widespread compromises detected, compliance nightmare on horizon. *Norse*. February 2014.
2. Ponemon Institute. 2013 Cost of data breach study: global analysis. May 2013.
3. Krebs on Security. Wash. hospital hit by \$1.03 million cyberheist. April 2013 (<http://krebsonsecurity.com/2013/04/wash-hospital-hit-by-1-03-million-cyberheist/>).
4. Maron DF. A new cyber concern: hack attacks on medical devices. *Scientific American*. June 2013 (<http://www.scientificamerican.com/article/a-new-cyber-concern-hack/>).
5. National Research Council, Committee on Maintaining Privacy and Security in Health Care Applications of the National Information Infrastructure. For the record: protecting electronic health information. Washington, DC: National Academy Press, 1997.

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## HISTORY OF MEDICINE

# The Origins of Antimalarial-Drug Resistance

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Related article, p. 411

Drugs have been used to treat and prevent malaria for centuries. Bark from the cinchona tree, which contained an array of alkaloids with antimalarial properties, appeared in Western therapeutics in the 17th century. One of the alkaloids, quinine, was isolated in 1820 and became the drug of choice for treating malaria until World War II, when supplies of the drug for much of the world were cut off by the Japanese occupation of cinchona-growing regions in Southeast Asia. Efforts to create alternatives to quinine led to the search for synthetic antimalarial drugs. Chloroquine, first developed in the 1930s, became the most wide-

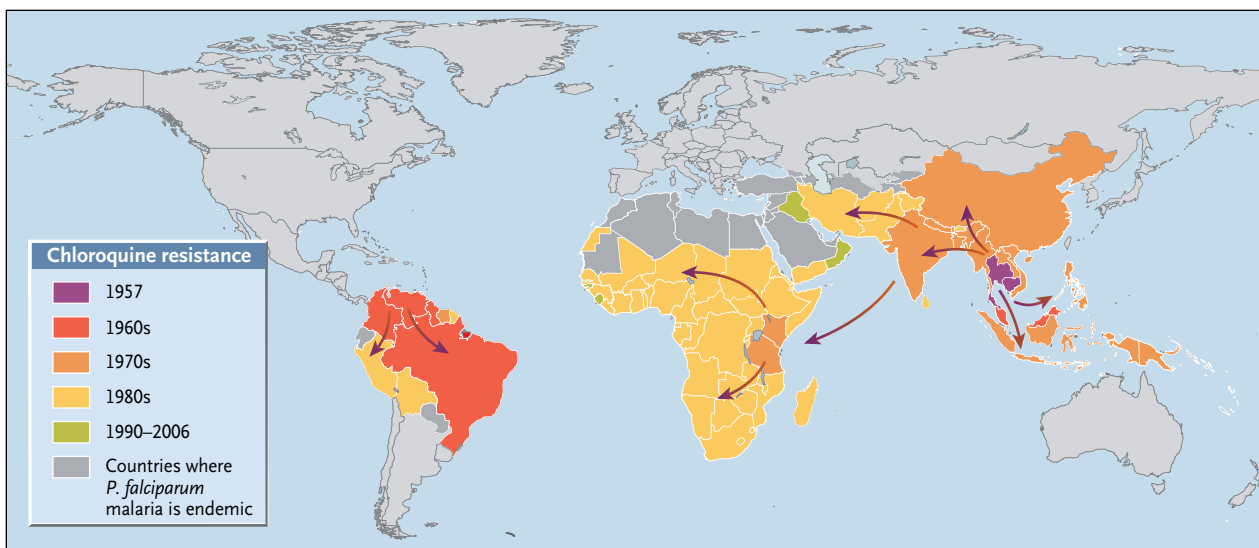
ly used synthetic antimalarial during the 1960s and 1970s.

Although the use of antimalarial drugs has a long history, the emergence of antimalarial-drug resistance is a relatively recent phenomenon. Chloroquine-resistant forms of *Plasmodium falciparum* malaria first appeared in Thailand in 1957 (see map). They then spread through South and Southeast Asia and by the 1970s were being seen in sub-Saharan Africa and South America. The rise in chloroquine resistance contributed to a worldwide increase in malaria-related mortality, particularly in sub-Saharan Africa. In an effort to combat resistant strains, a number of

alternative synthetic antimalarial drugs were deployed to both treat and prevent malaria. Among these were sulfadoxine-pyrimethamine and mefloquine.<sup>1</sup>

Various degrees of resistance to these replacement therapies emerged relatively quickly, though it was found that when used in combinations, these drugs could still be effective in treating malaria. The disadvantages of the new therapies were their increased cost — which made them less available to the populations that were at greatest risk — and in some cases, their adverse side effects.

It was in the context of the search for new and safer antima-



### History of Chloroquine-Resistant *P. falciparum* Malaria.

Data are from the Worldwide Antimalarial Resistance Network.

larials that would be effective in treating falciparum malaria that artemisinin-based drugs emerged from China. Artemisinin had been used by Chinese herbalists for centuries and was rediscovered by Chinese biomedical researchers in the 1970s. It did not become widely available outside China until the 1990s.

In an effort to prevent the development of resistance to artemisinin-based drugs, the World Health Organization (WHO) recommended that they be used only in combination with other antimalarials. The first widely available artemisinin combination therapy, or ACT, was Coartem, which combined an artemisinin derivative, artemether, with a long-acting antibiotic, lumefantrine. The combination drug proved to be 97% effective in curing the most deadly forms of falciparum malaria. Despite the product's effectiveness, the WHO sought to restrict its use to the treatment of complicated cases of falciparum malaria, fearing that wider use would contribute to resistance. But in the face of

mounting pressure from national health programs, the WHO reversed its policy in 2010, and ACTs have subsequently become the first-line treatment for falciparum malaria in many countries.

Unfortunately, the WHO's fear that the generalized use of ACTs would hasten the development of resistance appears to have been justified. As Ashley and colleagues report in this issue of the *Journal* (pages 411–423), resistance to artemisinin-based drugs has appeared in multiple locations in Southeast Asia.

There is a tendency to view the development of antimalarial-drug resistance as an inevitable outcome of the drugs' widespread use.<sup>2</sup> Yet antimalarial resistance has been accelerated by the way the drugs are used and by the social and economic conditions in which they are used.

A closer look at the genesis of chloroquine resistance along the Thailand–Cambodia border, which became ground zero for the emergence of chloroquine resistance in the 1950s and 1960s, reveals a great deal about the

social and biologic dynamics of antimalarial-drug resistance. The gem-mining industry in the Pailin province of Cambodia attracted a continual flow of newcomers from neighboring regions of Cambodia, Thailand, Vietnam, and Myanmar (Burma), as well as from Bangladesh. About 1000 to 1200 migrant workers arrived each month,<sup>3</sup> many of them coming from areas where the prevalence of malaria was much lower, and an estimated 80% of these workers had no immunity to the disease. The mining activity created hundreds of shafts, which collected water from seepage and rains. These shafts created breeding sites for a highly efficient malaria vector, *Anopheles dirus*, which bred in very high numbers and was hard to control with the insecticide dichlorodiphenyltrichloroethane (DDT) because the insect did not rest inside huts. The miners, who stayed for 3 to 4 months, lived in the open air and slept under very rudimentary shelters. They were thus exposed to multiple infective bites. The convergence of a

highly efficient vector, a nonimmune population, and mining conditions that encouraged both vector breeding and malaria transmission fueled recurrent epidemics of malaria, which apparently started in the 1940s or early 1950s; 80% of the cases were *P. falciparum*.

In 1955, public health authorities in Pailin began distributing chloroquine to workers daily; later, the frequency was reduced to twice a week. In 1960, they began administering chloroquine indirectly through medicated salt. This method increased coverage but made it difficult to ensure that each worker consumed an adequate dose of the drug. The repeated application of subcurative concentrations of chloroquine to a highly infected population set the stage for the emergence of chloroquine-resistant strains of *P. falciparum*. The subsequent transmission of resistant strains of falciparum to new waves of nonimmune workers, month after month, and their treatment



An audio interview with Dr. Packard is available at NEJM.org

with high but often noncurative doses of chloroquine amplified resistance. By 1973, 90% of falciparum malaria cases were resistant to chloroquine, and 70% exhibited high levels of resistance.

From the Thai–Cambodian border, resistant falciparum malaria spread to surrounding areas along with the returning migrant workers. Secondary patterns of dispersal from these surrounding

areas contributed to the wider dissemination of chloroquine resistance throughout South and Southeast Asia.

Mass drug-administration (MDA) programs elsewhere in the world during the 1950s and 1960s may also have contributed to the rise of chloroquine resistance. There is a strong correlation between the geographic areas where MDA programs were initiated and the places where chloroquine resistance first emerged. Also contributing to the development of resistance was the widespread availability of chloroquine in shops and private pharmacies, lax regulation of use of the drug, and the absence of effective primary care systems.

It is not surprising that Pailin was an early site for the emergence of artemisinin resistance. Some observers have suggested that malaria parasites in that region may be particularly prone to mutation. Yet it is clear that although the drugs have changed, the social and economic conditions under which they are used have not. Pailin remains the center of an extensive migrant labor system, with limited health resources. In addition, the widespread availability in the region of cheap counterfeit drugs containing subclinical quantities of artemisinin and the marketing and use of noncombination forms of the drug have created an ideal mix of conditions for both the development and spread of artemisinin resistance.<sup>4</sup>

An intensive campaign is currently under way to eliminate artemisinin resistance in the greater Mekong Delta region and prevent its further spread. These efforts focus on identifying and treating to cure all cases of malaria in the region. Whether these efforts will be successful is unclear. But efforts to address the social and economic conditions that contribute to the spread of malaria and foster antimalarial resistance, including the marketing of monotherapies and counterfeit drugs, are essential steps for preventing artemisinin-based drugs from following the path of chloroquine. Given the cyclical history of drug development followed by the emergence of resistance, it is also critical that investments continue to be made in the development and production of new generations of antimalarial therapies.

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1. Packard RM. The making of a tropical disease: a short history of malaria. Baltimore: Johns Hopkins University Press, 2007.
2. White NJ. Antimalarial drug resistance. *J Clin Invest* 2004;113:1084-92.
3. Verdrager J. Localized permanent epidemics: the genesis of chloroquine resistance in *Plasmodium falciparum*. *Southeast Asian J Trop Med Public Health* 1995;26:23-8.
4. Dondorp AM, Yeung S, White L, et al. Artemisinin resistance: current status and scenarios for containment. *Nat Rev Microbiol* 2010;8:272-80.

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## Big Marijuana — Lessons from Big Tobacco

Kimber P. Richter, Ph.D., M.P.H., and Sharon Levy, M.D., M.P.H.

The United States is divided over the legalization of marijuana. Arguments in favor in-

clude protection of individual rights, elimination of criminal sentencing for minor offenses,

collection of tax revenue, and elimination of the black market. Counterarguments include the