Magic Bullets To Conquer Malaria
Magic Bullets To Conquer Malaria
From Quinine to Qinghaosu

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Cover photo: Malaria is transmitted to humans and animals by the bite of a female Anopheles mosquito. Plasmodium sporozoites develop inside oocysts in the midgut of the mosquito and are released in large numbers into its body cavity, the hemocoel. The false-colored electron micrograph shows a sporozoite migrating through the cytoplasm of midgut epithelia. Image by Ute Frevert; colorization by Margaret Shear, PLoS Biology.
For Vilia

Memories of our life together will never fade
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Preface

This book chronicles the search for and use of medicines to conquer malaria, one of the world’s most devastating and debilitating infectious diseases. Currently there are about half a billion cases of malaria worldwide. The deadly malaria parasite, *Plasmodium falciparum*, on its own kills a million people per year, mostly children under the age of 5 years. Malaria imposes a significant economic toll. It is estimated that African nations alone lose $12 billion in gross domestic product each year due to malaria, which slows their annual economic growth by more than 1%. In some countries, malaria is responsible for up to 40% of the public health expenditures and malaria treatments can consume a third or more of the income of poor households. Faced with such enormous public health and economic problems, in 2008 the Roll Back Malaria (RBM) partnership launched the Global Action Plan aimed at reducing malaria mortality and morbidity by half from the rates in 2000, reducing the number of deaths to zero by 2015, and moving the goal of the program from control to eradication. If the plan is successful, 4.2 million lives could be saved by 2015.

The RBM partnership, started in 1998 as an alliance of four United Nations agencies, has now grown to become a coalition of more than 500 partners. The coalition’s ambitious assault, coordinated by RBM and referred to in the press as “the billion-dollar malaria moment” because of the substantial increases in resources from the Bill and Melinda Gates Foundation; the Global Fund to Fight AIDS, Tuberculosis and Malaria; the World Bank; and the President’s Malaria Initiative, echoes in some measure a past campaign at eradication.
Indeed, as far back as 1955 the World Health Assembly endorsed a policy of global eradication of malaria. This international campaign was fueled by the effectiveness of the residual insecticide DDT (dichlorodiphenyltrichloroethane) to destroy malaria-transmitting mosquitoes as well as the availability of a powerful and inexpensive medicine (chloroquine). In addition, there was the optimistic prospect of interrupting malaria transmission based on the mathematical modeling of malaria epidemiology carried out by Sir Ronald Ross and George MacDonald. With such an armory and strategy, the World Health Organization (WHO) expected that there would be a quick fix.

This was the landscape of malaria research in 1957, the year of my entry into the field, a time that could not have been less encouraging to a newly minted Ph.D. in biochemical parasitology, since if eradication succeeded, it surely would make any need for my efforts superfluous. However, less than a decade after the WHO announcement, all hopes for eradication were dashed and the Global Malaria Eradication Program was in tatters. By 1962, there were already increasing numbers of reports that chloroquine was not the infallible drug the “eradicators” had believed it to be, mosquitoes were no longer susceptible to the killing power of DDT, and there was a new and devastating war in Southeast Asia, with more and more civilians and soldiers succumbing to malaria. It became apparent that malaria would once again rank as a top medical priority for the U.S. Department of Defense. Thus, in 1963, the Malaria Research and Development Program of the U.S. Army was established, with an initial major objective of treating chloroquine-resistant malaria. In late August 1963, an international workshop entitled “Cultivation of Plasmodia and the Immunology of Malaria,” organized by Elvio Sadun of the Walter Reed Army Institute of Research (WRAIR), was convened in Washington, D.C. Its goals were to summarize the available information, to delineate some of the most urgent problems, to explore new approaches to current problems, and to devise methods to grow malaria parasites in the laboratory. On the basis of the discussions at the conference, it was clear that although a vaccine against malaria was a justifiable goal, its development would be long-term. The immediate problem, however, was to find new drugs to protect and treat people exposed to the increasing numbers of malaria parasite strains that no longer responded to chloroquine. Sadun organized a program at WRAIR to conduct investigations in malaria, to attract highly capable scientists from various disciplines to carry out malaria research, and to produce a continuing flow of highly trained people able to contribute to the management and control of this disease. In addition, a
new Commission on Malaria was established by the Armed Forces Epidemiological Board in October 1964, and the director of WRAIR, Colonel William Tigertt, began the largest antimalarial drug screening program ever undertaken—one that continues to this day.

A Second International Panel Workshop was held at WRAIR in 1966 to discuss the biology of malaria. At this workshop, to which I was invited, attention was given to the biochemistry of the parasite, the possible use of antibacterials for the prevention or treatment of chloroquine-resistant malaria, and in particular the potential value of combining sulfonamides with pyrimethamine (Daraprim) for therapy. Two workers at the National Institutes of Health had observed that pyrimethamine killed the malaria parasite by preventing its reproduction; however, they left unanswered the question of precisely why the killing took place. That is where I, as a budding biochemist, entered the picture. In 1968, my laboratory (then consisting of a graduate student, Charles Walsh, and myself!), supported by a grant from the U.S. Army, was looking into the simple building blocks needed to manufacture the parasite’s DNA. Much to our surprise, we found that the malarial parasites contained all the enzymes necessary to synthesize pyrimidines from scratch but the enzymes for purine synthesis were absent. This discovery led to an understanding of how pyrimethamine worked: it acted on a specific enzyme in the pyrimidine pathway, and when this enzyme was “knocked out” by the drug, the parasites were unable to make DNA and could not reproduce. As a result of this unintended foray into malaria therapy, I joined an increasing number of researchers who found themselves interested in how and why antimalarial medicines worked. Indeed, for the next three decades, a considerable portion of my research effort was dedicated to discovering the biochemical Achilles’ heels of the parasite.

By 1972, when the Global Malaria Eradication Program was formally declared dead, new approaches toward control of malaria were being considered by public health agencies. In 1975, a group of donor nations provided money to establish the United Nations Development Programme/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) to forge weapons for use in the fight against the six major tropical diseases, namely, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, leprosy, and malaria. This ambitious program was designed to encourage research into the development of new drugs and vaccines, to establish research centers in countries where the diseases were endemic, to carry out field research and field trials, and to study the socioeconomic problems hindering progress. When the first TDR Task Force
on the Chemotherapy of Malaria (CHEMAL) met in Geneva in 1976, the participants felt that there was a need to investigate the modes of action of existing drugs, including the biochemistry of the parasites and the ways in which drug resistance develops; to find experimental models; to uncover better ways to deploy existing drugs; to seek ways of preventing the development of drug resistance; and to explore new ways to develop effective and potent antimalarials. The work of CHEMAL would take place through a Steering Committee. I was invited to become a member of the CHEMAL Steering Committee and served on that committee from 1978 to 1986. Close links were established between WRAIR, CHEMAL, and the pharmaceutical industry, and the first product of the cooperative venture was mefloquine. Later, CHEMAL would be involved in development of the novel Chinese antimalarial qinghaosu.

In 1999 the Medicines for Malaria Venture (MMV), based in Geneva, was founded. It is a nonprofit organization focused on the discovery, development, and delivery of new medicines for the treatment and prevention of malaria. It receives support from public and philanthropic funds and partners with academia, the pharmaceutical industry, and countries where malaria is endemic to realize its goals of finding and deploying “magic bullets” to cure malaria.

Recently four interventions, sleeping under insecticide-treated bed nets, spraying houses with insecticide, preventive drug treatments for pregnant women, and curing the sick with effective medicines, have promoted renewed interest and commitment to eliminating malaria. Although these are keystones in the RBM program, effective medicines offer the only practical solution to significantly reduce the spread of the disease and case management remains a cornerstone of malaria control strategies. At this time, as we contemplate a renewed attack to rid ourselves of the burden malaria places on half of the world’s population, it seems appropriate to examine how the drugs in the armory came into being, how they have been used and abused, the mechanisms of drug action, and the ways in which the parasite is able to fight back either by multiplying or surviving in the presence of a concentration of a drug that normally is able to destroy or prevent the parasite from reproducing. I hope that through an examination of drug treatments past and present, the problem of drug resistance, the greatest impediment to eradication, will be better understood so that its effects can be thwarted, and we will come to better appreciate the medicines (and other tactics) needed to head off the impending catastrophe that now looms large in the world.
A Note to the Reader

Interspersed in the text, chemical formulas and structures appear. These should not be a deterrent should your knowledge of chemistry be limited. Rather, the formulas and structures are provided so that those with the appropriate background as well as some without it may better appreciate the relationship between chemical structure and function. Even without reference to these chemical formulas and structures, the text itself should be entirely comprehensible to all.

Portions of chapters 1, 2, and 10 have been published previously in my books *The Power of Plagues* (ASM Press, 2006) and *The Elusive Malaria Vaccine. Miracle or Mirage?* (ASM Press, 2009).

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