

Infection: The Health Crisis in the Developing World and What We Should Do About It
(Stanford University Press, forthcoming 2017)

Chapter 1: The Diseases³

C. Protozoan Diseases

1. Malaria

Malaria infection in humans originates from the bite of a female *Anopheles* mosquito carrying the sporozoite form of a *Plasmodium* parasite in her salivary gland.⁴ Sporozoites, deposited under the skin of the host, enter the blood stream and then cross the sinusoidal cellular layer separating the blood and liver parenchyma to infect hepatocytes in the liver.⁵ Temporarily safe from the host's immune response, the sporozoites multiply rapidly to form schizonts, each containing a second form of the parasite called merozoites.⁶ The schizonts rupture, spilling thousands of merozoites into the bloodstream where they invade red blood cells and multiply until the host cells burst.⁷ This cycle continues until "the person dies of anemia, kidney failure, or brain damage, or until the disease is brought under control by the person's immune system or by drugs."⁸

Because transmission of the disease occurs only through bites from specific species of mosquitos (all within the *Anopheles* family), malaria is common only in countries where those mosquitos flourish, all of which are near the Equator. The geographic distribution of the disease is shown in Figure 4, below.

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³ Version 1.0. Updated versions of this document (and of other portions of the book of which it is a part) will be posted periodically at <http://cyber.law.harvard.edu/people/tfisher/Infection.htm>.

⁴ See Gina Kolata, *The Search for a Malaria Vaccine*, 226 *SCIENCE* 679, 680 (November 9, 1984).

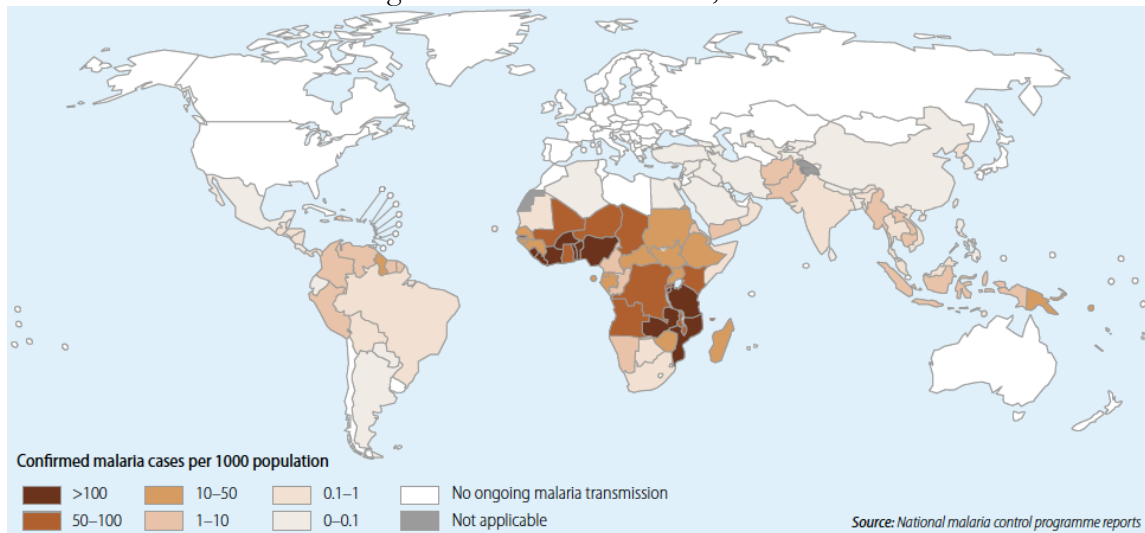
⁵ See Maria M. Mota and Ana Rodriguez, *Migration through host cells: the first steps of Plasmodium sporozoites in the mammalian host*, *CELLULAR BIOLOGY* Vol. 6, No. 12 at 1113 (2004). The exact mechanism by which sporozoites reach the blood vessel and then cross the blood/liver barrier is unknown, although it is believed that the sporozoites migrate through host cells. See *id.* at 1114.

⁶ See *supra* Kolata at 680.

⁷ See *id.*

⁸ *Id.* In developing countries, the majority of malaria deaths occur in infants, young children and pregnant women; most adolescents and adults have presumably developed nature immunity that limits the most severe forms of infection. See Stephen Hoffman, *Save the Children*, *NATURE* Vol. 430 at 940 (Aug. 19, 2004).

Figure 4: Malaria Prevalence, 2013⁹



Five species of the *Plasmodium* parasite are responsible for malaria in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*.¹⁰ The most lethal of the five, *P.falciparum*, is the dominant species in Africa.¹¹ *P. vivax* accounts for roughly half of the cases in Latin American and Southeast Asia,¹² but does little harm in Africa.¹³

As yet, there exists no approved effective vaccine for malaria. Investigation and testing of vaccine candidates is ongoing. Only one (RTS,S/AS01, developed by GlaxoSmithKline with support from the Malaria Vaccine Initiative) has emerged from clinical trials, and the results were only mildly encouraging: 46% reduction in clinical malaria incidence in children; 27% in infants.¹⁴ The WHO reports that two more candidates are in phase 2 trials, and 25 are somewhere in the drug-development pipeline.¹⁵ The Malaria Vaccine Initiative is less encouraging; it describes RTS,S as the only project that satisfies its requirements for a “vaccine candidate.”¹⁶

⁹ Source: Malaria Report 2014.

¹⁰ See Melanie Figtree et al., "Plasmodium Knowlesi in Human, Indonesian Borneo," *Emerging Infectious Diseases* 16, no. 4 (2010).

¹¹ See David Bell and Peter Winstanley, "Current Issues in the Treatment of Uncomplicated Malaria in Africa," *British Medical Bulletin* 71 (2004): 30.

¹² See Vincent Corbel et al., "Challenges and Prospects for Dengue and Malaria Control in Thailand, Southeast Asia," *Trends in Parasitology* 29, no. 12 (2013).

¹³ "Although *P. vivax* can occur throughout Africa, the risk of infection with this species is quite low, because of the absence in many African populations of the Duffy gene, which produces a protein necessary for *P. vivax* to invade red blood cells." WHO, "World Malaria Report," (2014): 3.

¹⁴ See P.A. Zimmerman, "Efficacy and Safety of the Rts,S/As01 Malaria Vaccine During 18 Months after Vaccination: A Phase 3 Randomized, Controlled Trial in Children and Young Infants at 11 African Sites," *PLoS Med* 11, no. 7 (2014). Early test results had been more promising. See Pedro L. Alonso et al., Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomized controlled trial, *THE LANCET* Vol. 364 at 1411 (Oct. 16, 2004).

¹⁵ See WHO, "Malaria Report 2014," 19.

¹⁶ See <http://www.malariavaccine.org/rd-vaccine-candidates.php>.

In the absence of a vaccine, inhibition of the spread of the disease is achieved through vector control: protecting people in malaria-endemic countries against mosquito bites. Two strategies are employed for this purpose: supplying residents with bednets treated with insecticide to shield them from bites while sleeping; and reducing the number of mosquitos in homes by spraying the walls with insecticide.¹⁷ The first of these initiatives has been the most extensive and successful. In the past decade, bednets treated with insecticides (ITNs) have been widely distributed (usually for free) in malaria-endemic countries. Roughly 44% of the population in those countries now sleeps under nets.¹⁸ They are inexpensive to produce, and their effect is dramatic. Studies suggest that they reduce malaria incidence by half.¹⁹ The second approach – known as “indoor residual spraying” (IRS) – is equally effective but less widely used.²⁰

Unfortunately, both of these approaches are threatened by increases in the resistance of the pertinent species of mosquitos to the most commonly used insecticides.²¹ To slow the development of this resistance, the WHO recommends that distributors of the chemicals used in IRS and the manufacturers of insecticide treated bed nets rotate the insecticides they employ. Some countries abide by this guideline, but most as yet do not.²²

Persons who, despite these efforts at vector control, acquire malaria can and should be treated with drugs. In the early twentieth century, the drug used most often was chloroquine. In the 1950s, *P.falciparum* parasites began to exhibit resistance to chloroquine, so many health-care systems in regions dominated by that species switched to sulphadoxine-pyrimethamine (SP).²³ Resistance to SP emerged soon thereafter.²⁴ Today, most health services outside of Latin America use artemisinin-based combination therapy (ACT) as the primary means of treatment.²⁵ Artemisinins are remarkably effective. For example, they have been shown to reduce infant mortality caused by malaria by 99%.²⁶

¹⁷ See supra WHO.

¹⁸ See WHO, "Malaria Report 2014," 10. Unfortunately, it appears that children use them less frequently than the population as a whole. See *ibid.*, 13.

¹⁹ See Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews, 2004 (2):CD000363 [*recheck]. For slightly less favorable assessments of the efficacy of ITNs, see Mark Musumba, Aklesso Egbendewe-Mondzozo, and Bruce A. McCarl, "Analysis of the Cost of Malaria in Children and Use of Insecticide-Treated Bednets in Africa," *African Development Review* 26, no. 1 (2014).

²⁰ See WHO, "Malaria Report 2014," 14.

²¹ See Stephen Hoffman. *Save the Children*, *NATURE* Vol. 430 at 940 (Aug. 19, 2004); Michelle L Gattton et al., "The Importance of Mosquito Behavioral Adaptations to Malaria Control in Africa," *Evolution* 67, no. 4 (2013).

²² See WHO, "Malaria Report 2014," 16-17.

²³ In Central America, where most malaria cases are caused by *P. vivax*, chloroquine remains the drug of choice. Recently, however, some resistance to that drug has been observed, prompting health-care services to shift increasingly toward ACT – described below.

²⁴ See Bell and Winstanley, "Treatment of Malaria in Africa," 31.

²⁵ See Robert Ridley, *Winning the Drugs War*, *NATURE* Vol. 430 at 942 (Aug. 19, 2004). Forty-two malaria endemic countries have switched to ACT. See WHO: *First Global Report on Efforts to Roll Back Malaria*, available at: www.who.int/mediacentre/news/releases/2005/pr17/en/index.html (May 3, 2005). For the WHO's current recommendations concerning their use, see WHO, "Malaria Report 2014," 24.

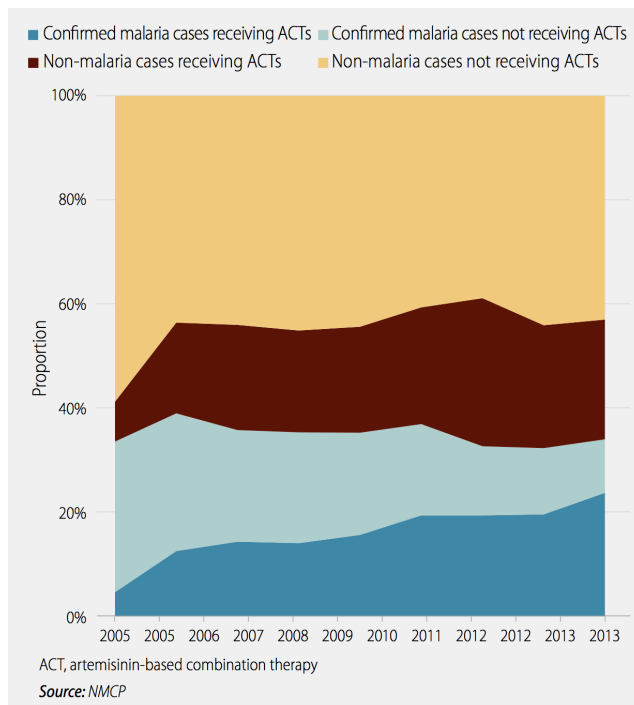
²⁶ See *ibid.*, 4. The effects on mortality and morbidity of the cycles of drugs and resistance thereto – and the large gains achieved through the switch to ACT – are well illustrated by the recent history of malaria in South

The use of artemisinins has been increasing fast, especially in Africa. The percentage of persons who seek treatment at African public health facilities for malaria-like symptoms who are given ACT has risen sharply since 2005. Unfortunately, administration of these drugs to people who are not infected by the malaria parasite but instead suffer from other ailments has also grown rapidly.²⁷ This has had two bad effects. First, the drugs do those people no good, which causes some of them to lose faith in western medicine and makes them less likely to rely on the health-care system in the future. Second, it accelerates the emergence of strains of the malaria parasites that are resistant to the drugs. Fortunately, artemisinins are less likely than their predecessors to provoke resistance, apparently because they kill off the parasites more rapidly and thus shorten the window for mutation.²⁸ But, despite this advantage, resistance to them is now showing up increasingly often. (The problem is exacerbated by continued sales of oral artemisinin monotherapies [which lead to resistance more quickly than the combination therapies] by some Indian generic companies, despite opposition to the practice by the WHO.²⁹)

Pregnant women and infants can be shielded against the active form of malaria through prophylactic administration of the same drugs. A regimen known as “intermittent preventive treatment in pregnancy” (IPTp), which entails periodic administration of SP during the second and third trimesters, has been shown to reduce maternal anaemia, low

Africa. See R Maharaj et al., "Epidemiology of Malaria in South Africa: From Control to Elimination," *South African Medical Journal* 103 (2013).

²⁷ The following chart tracks estimated ACT treatment received among malaria and non-malaria cases at public-health facilities in the WHO Africa region. The growth of the dark blue zone is encouraging; the equally dramatic growth of the maroon zone is not.



See WHO, "Malaria Report 2014," 27.

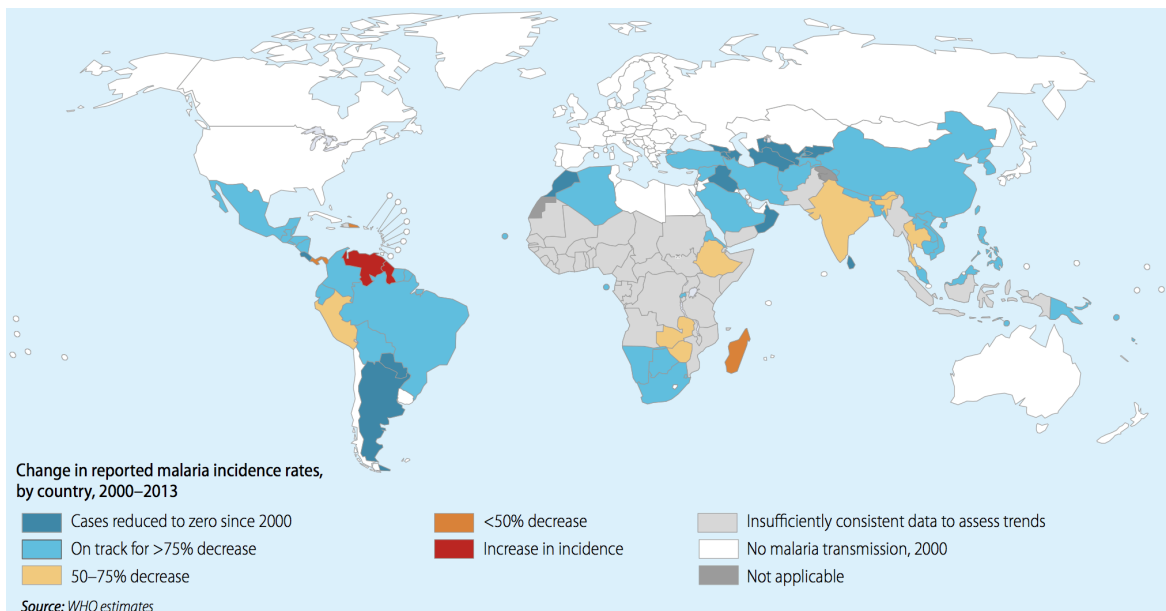
²⁸ See Bell and Winstanley, "Treatment of Malaria in Africa," 32.

²⁹ See WHO, "Malaria Report 2014," 28.

birth rate, and perinatal mortality.³⁰ A similar regimen given to infants (IPTi) substantially reduces anaemia and other manifestations of the disease during the first year of life.³¹ A slightly different combination, when given to healthy children between 3 and 59 months old living in areas of highly seasonal malaria transmission, has also proven highly effective.³²

In combination, the vector-control programs and the increasingly widespread distribution of ACT drugs have substantially reduced both the prevalence and mortality of malaria. A few key indicators: Between 2000 and 2013, the total number of people throughout the globe who had the disease in a given year declined from roughly 227 million to roughly 198 million; infection prevalence among children in sub-Saharan Africa (the most endangered group) declined from 26% to 14%; and the number of people who died from the disease worldwide declined 47%.³³ Figure 5, below, shows where progress in the fight against the disease has been most rapid.

Figure 5: Changes in Malaria Incidence Rates, 2000-2013³⁴



But much remains to be done. The progress made to date has not benefitted all communities. In some parts of Africa, malaria prevalence has remained steady or even increased.³⁵ And despite the advances that have been made, the disease remains distressingly

³⁰ See *ibid.*, 4.

³¹ See *ibid.*

³² See *ibid.*, 18-19.

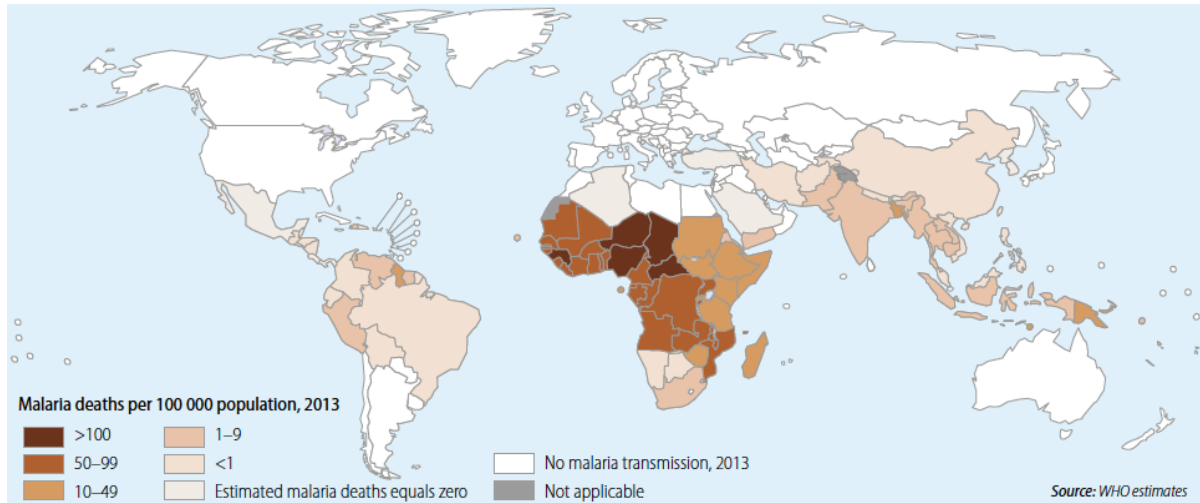
³³ See *ibid.*, xii, 2, 38.

³⁴ See *ibid.*

³⁵ See Sungano Mharakurwaa et al., "Malaria Epidemiology and Control in Southern Africa," *Acta Tropica* 121 (2012); Abdisalan M Noor et al., "The Changing Risk of Plasmodium Falciparum Malaria Infection in Africa: 2000–10: A Spatial and Temporal Analysis of Transmission Intensity," *The Lancet* 383 (2014).; Huguette Gaelle Ngassa Mbenda, Gauri Awasthi, and Poonam Singh, "Does Malaria Epidemiology Project Cameroon as 'Africa in Miniature'?", *Journal of Bioscience* 39, no. 4 (2014).

common. 584,000 deaths per year – 78% of which are of children under 5 years old³⁶ – is a high number. Figure 6, below, shows where those deaths are concentrated.

Figure 6: Malaria Mortality, 2013³⁷



If we obliged to rely exclusively on our current disease-control strategies, the chances that we will soon eradicate the disease are not good. Especially worrisome is the recent emergence near the Mekong River of variants of *P. falciparum* that are at least partially resistant to all currently available drugs, including the ACTs.³⁸ If the offspring of those parasites reach Africa, millions of people will die. That prospect has prompted some observers to plead for redoubled suppression efforts in Southeast Asia, in hopes of eliminating the deadly variant before it can spread. But purging the disease from the highly mobile populations along the national borders in the region and from the residents of the remote forest villages is a daunting task.³⁹

Once again, therefore, we confront the importance of developing new, more efficacious drugs and, better yet, a vaccine. Unfortunately, the obstacles to the discovery, testing, and deployment of a malaria vaccine are formidable. At least in theory, three strategies are possible. The first approach would attack the sporozoites as they enter the body and invade and reproduce in the liver.⁴⁰ Ideally, this kind of vaccine would induce both an antibody and T-cell response, similar to that observed in the development of natural protective immunity.⁴¹ If successful, this type of vaccine would result in complete protective immunity. The second approach would limit the invasion of erythrocytes and the subsequent multiplication and pathological effects.⁴² This approach would still permit

³⁶ See WHO, "Malaria Report 2014."

³⁷ Source: *ibid.*, 33.

³⁸ See *ibid.*, 29.

³⁹ See Corbel et al., "Challenges and Prospects for Dengue and Malaria Control in Thailand, Southeast Asia," 631.

⁴⁰ See *id.*

⁴¹ See *id.*

⁴² See *id.*

infection, but would prevent at least the more severe outbreaks of the disease. The third approach aims to prevent the spread of viable parasites to other people, thus limiting the potential for an outbreak within a given population. Such vaccines have been labeled “transmission blocking vaccines.”⁴³ (GSK’s drug, RTS,S, discussed above, pursues the first of these paths,⁴⁴ but has had limited success.) All three approaches are hampered by a common technical problem: Human parasites have much larger genomes than viruses. They also undergo multi-stage life cycles and produce enormous variability in proteins, making the development of an effective single vaccine nearly impossible.⁴⁵ The recent completion of the *P.falciparum* genome sequence as well as the genome sequences of model rodent parasites may help scientists to surmount this hurdle,⁴⁶ but have not done so yet.

The impediments created by this technical barrier are compounded by some more prosaic difficulties. Clinical trials of vaccine candidates must be performed on infants in communities where malaria is endemic. Persuading mothers, many of whom are illiterate, that they should allow their children to be treated with drugs that have not yet been shown to be safe and effective is no easy task.⁴⁷ But unless we can meet these challenges, we are unlikely to eradicate the disease.

⁴³ See id.

⁴⁴ See Pedro L. Alonso et al., Efficacy of the RTS,S/AS02A vaccine against Plasmodium falciparum infection and disease in young African children: randomized controlled trial, *THE LANCET* Vol. 364 at 1411 (Oct. 16, 2004).

⁴⁵ See Stephen Hoffman, *Save the Children*, *NATURE* Vol. 430 at 940 (Aug. 19, 2004). See Patrick E. Duffy et al., Malaria vaccines: using models of immunity and functional genomics tools to accelerate the development of vaccines against Plasmodium falciparum, *VACCINE* Vol. 23 at 2237 (2005).

⁴⁶ See Patrick E. Duffy et al., Malaria vaccines: using models of immunity and functional genomics tools to accelerate the development of vaccines against Plasmodium falciparum, *VACCINE* Vol. 23 at 2235 (2005); Daniel Carucci, *Know thine enemy*, *NATURE* Vol. 430 at 945 (Aug. 19, 2004). The ability to develop vaccines through newly refined techniques for infecting healthy volunteers may also accelerate research, see Michael F. Good, “The Ability to Inoculate Purified Malaria Sporozoites Will Accelerate Vaccine and Drug Discovery,” *American Journal of Tropical Medical Hygiene* 91, no. 3 (2014). – although it is difficult to imagine large numbers of people volunteering for such projects.

⁴⁷ See Muhammed O. Afolabi et al., “Early Phase Clinical Trials with Human Immunodeficiency Virus-1 and Malaria Vectored Vaccines in the Gambia: Frontline Challenges in Study Design and Implementation,” *ibid.* 90, no. 5; David I Ojaka et al., “Acceptance of a Malaria Vaccine by Caregivers of Sick Children in Kenya,” *Malaria Journal* 13 (2014).

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