An Introduction to Malaria in Human History

Malaria, the oldest and cumulatively the deadliest of the human infectious diseases, seeped into our very earliest human history. It was a primordial companion of our distant protohuman ancestors and an even earlier companion of the chimpanzees from which we branched off six to seven million years ago. During the last one hundred thousand years, malaria began a new chapter in the human heartland of tropical Africa. As our ancestors clustered in seasonal settlements to fish and gather, mosquitoes found a temporarily less-mobile source of nourishment. This allowed the malaria parasites carried by mosquitoes to infect a growing number of human hosts. From these humble beginnings, malaria became more deeply integral to human history. Malaria eventually traveled with some of our ancestors out of Africa into Eurasia, where new infections took root, even as it percolated more deeply throughout the African continent.

Over tens of thousands of years, as early humanity expanded in tropical Africa and across tropical Eurasia, malaria parasites continued to take advantage of our human propensity to migrate and our social need to congregate. Eventually, the parasites moved with their human hosts into the nascent river-basin communities that would ultimately develop into permanent settlements. Malaria traveled with infected hunters and adventurers across mountain ranges and deserts, and after the domestication of animals, malaria traveled more quickly, galloping across grasslands and plains. It became the principal disease burden of Eurasia as well as tropical Africa. Much later, thanks to the technological ingenuity of human beings, malaria sailed with infected passengers on shipboard across the oceans, rode the rails across the continents, and then flew aboard aircraft from one hemisphere to the other. It became a global disease.

Malaria is thus an ancient and a modern scourge. For much of its career it left little trace. It sickened us in early epochs, long before we were able

to record our experiences. Even in recent millennia, it has frequently lain silent in the diverse records of our pasts, too common a disease to claim much notice. At other times, epidemic malaria has careened violently across the landscapes of world history, leaving death and suffering in its wake.

THE PARADOXES OF MALARIA

Malaria has etched highly varied patterns into human history. In some times and places malaria has appeared as a seasonal affliction and in others as a year-round burden. It has been a debilitator of general populations and a killer that targets young children and nonimmunes. For these reasons, our cultural assessments of malaria's significance have been highly diverse, and different societies have "known" malaria in very different ways.

These different experiences with malarial infections in the past are nearly impossible to quantify. Even today, malaria remains such a common disease that only imprecise estimates of its impacts are possible. The broad and inexact contours, however, tell the big story. An estimated 2.4 billion people are at risk of infection. An estimated 300 to 500 million people suffer bouts of the disease each year. Perhaps 90 percent of these occur in tropical Africa. Malaria kills somewhere between 1.1 and 2.7 million people per year. Of these deaths, approximately one million are children in tropical Africa between the ages of eighteen months and five years.[1]

Malaria is violent and dismal, and in the past it was erratically distributed over humid and arid landscapes, along the coast and in the forest, across cityscapes and rural landscapes, in subarctic, temperate, subtropical, and tropical zones. Over the course of the twentieth century, however, malaria lost its hold on the northern temperate world, and across those liberated landscapes cultural knowledge about malaria slipped away. Today, malaria is an almost forgotten disease in much of the Western world. My uncle Gene, born in Indianola, Mississippi in 1913, is now part of the oldest generation who can recall the agony of malarial fever and still have the bitter taste of quinine flow from a reservoir of memory. What was once a global affliction – the primary public health disaster in the United States during the nineteenth century, the principal disease of British India, the core challenge of the modernizing Italian state in the twentieth century, and the elusive target of the first global eradication campaign of the World

[1] World Health Organization, *WHO Expert Committee on Malaria: Twentieth Report* (Geneva: World Health Organization, 2000), 3, 24.

Health Organization (WHO) – is now broadly regarded as a "tropical disease."

The Ecology of Malarial Infections

Malarial infections are one consequence of a complex series of ecological interactions between malaria parasites, mosquitoes, and humans. The female *Anopheles* mosquito is considered the "definitive host" for the malaria parasites because the sexual cycle of parasite reproduction takes place within the mosquito's gut. The human being who is injected with the parasites by an infected mosquito is considered the "intermediate host." In the human being, the parasites pass through a series of transformations before developing into the sexual forms known as gametocytes, which can then be drawn up when another mosquito takes her blood meal. Both humans and mosquitoes are essential for the parasite to complete its life cycle and to be able to cause malarial infections.[2]

The term *malaria* needs to be unpacked. A borrowing from the Italian "*mala aria*" meaning "foul air," the term *malaria* rather confusingly bundles together the disease consequences of four different parasites that have broad biological similarities.[3] All are plasmodia, a particular type of single-celled life form. All have multistage life cycles that are surprisingly complex. Two of the four parasites are by far the most important – that is, two of the four have caused the lion's share of infections in the past and continue to do so today. These two principal types are called *Plasmodium falciparum* and *Plasmodium vivax*. The two parasites that cause malarial infections of minor global importance are known as *Plasmodium malariae* and *Plasmodium ovale*.[4] The "minor two" have never been the dominant forms in any configuration of historical or contemporary

[2] Meta-analyses of mosquitoes with plasmodium infections suggest that infected mosquitoes suffer increased mortality compared to uninfected mosquitoes, although the reasons for the increased mortality are not established. See Heather M. Ferguson and Andrew F. Reid, "Why Is the Effect of Malaria Parasites on Mosquito Survival Still Unresolved?" *Trends in Parasitology*, vol. 18, no. 6 (2002), 256–261.

[3] Mike W. Service and Harold Townson, "The Anopheles Vector," in ed. David A. Warrell and Herbert M. Gilles, *Essential Malariology*, 4th ed. (London: Arnold, 2002), 59–84.

[4] The malaria parasites are protozoa of the genus *Plasmodium*. Falciparum is considered to belong to the subgenus *Laverania*; vivax, malariae, and ovale to the subgenus *Plasmodium*. Falciparum, vivax, and ovale malarias occur only in human beings. Malariae is found in both humans and African apes. Robert E. Sinden and Herbert M. Gilles, "The Malaria Parasites," in Warrell and Gilles, *Essential Malariology*, 8; for a full description of the biology of the parasites see pp. 8–34.

disease, and for this reason, this book concentrates on the "big two" and traces out the historical patterns and processes through which one can glimpse the major outlines of the disease in our human past.

The four malaria parasites all produce fevers and anemia, and, if untreated, can open up a Pandora's box of complications. Some fevers erupt and then disappear; others do not. Two of the malarial infections – vivax, the most common and most broadly distributed, and ovale, the rarest form and most narrowly distributed – have relapses as one of their signature dynamics. Many months or even years may pass after a sufferer has shaken off a bout with vivax or ovale malaria, only to be felled again. This is because both vivax and ovale parasites have a dormant liver stage that releases fresh waves of parasites months or even years after an apparent "cure." By contrast, both falciparum and malariae infections are incapable of relapse. If a sufferer is cleared of a falciparum or malariae infection, she or he is free of the disease unless and until reinfected by another parasite-laden mosquito. The incubation period for the parasite (the delay from infected bite to fever) within the human being varies greatly. Falciparum incubation periods average twelve days; ovale averages seventeen days; malariae between eighteen and forty days; and vivax incubations range an average of fifteen days but can be delayed up to six to twelve months.[5]

Three of the different forms of malaria share a fever rhythm. Human beings infected with vivax, falciparum, and ovale commonly undergo a sledgehammer attack of fever every forty-eight hours. Sufferers with malariae infections are pummeled every seventy-two hours. Ovale infections were (and are) rare or nonexistent outside of tropical West Africa. The different periodicities – either of forty-eight or seventy-two hours – are signs that allowed close observers in earlier millennia to distinguish between the types of infections. In the Western world, the forty-eight-hour rhythmic assaults were called tertian fevers – because they occurred every first and third day. The seventy-two-hour fevers were quartan, because they occurred every first and fourth day. Western observers generally distinguished between the relatively low mortality of vivax and the high mortality of falciparum by calling the fevers benign tertian and malignant tertian, respectively.

Fever signals, however, sometimes get crossed up, or come in confusing patterns. A common diagnostic rubric from the seventeenth century into

[5] David A. Warrell, "Clinical Features of Malaria," in Warrell and Gilles, *Essential Malariology*, 192.

the twentieth century was to distinguish between "intermittent" fevers, in which an interval of normal temperature followed a febrile period, and "remittent" fevers, in which higher and lower temperatures fluctuated without a return to normal body temperature. The rubric promised more precision than it delivered, because the individual idiosyncrasies of malaria sufferers are highly various. Many people who are infected with malaria parasites suffer fluctuating fevers that do not have a distinctive periodicity. It is also possible to suffer two or more types of parasitical malarial infections at the same time. (Western fever theorists, recognizing this bewildering diversity, believed that fevers could mutate into different forms.) The most common forms of multiple infections are when falciparum joins forces with vivax, or less frequently, with malariae, or ovale, in subtropical or tropical areas.

The disease consequences of the "big two" are markedly different. Falciparum frequently produces severe anemia. If untreated, falciparum can also produce cerebral malaria, a condition that may lead to dangerous sequelae such as epilepsy, blindness, cognitive impairments, and behavioral disturbances, or it may lead to coma and death. Falciparum malaria can also reach the infant *in utero* if the mother is infected.[6] If the mother has acquired immunity to falciparum, however, in the postpartum period she is able to transfer antibodies passively to her infant and confer protection for the first several months of life. The sum total of the disaster falciparum causes cannot be precisely quantified, but it is thought to range between 25 to 50 percent of infected nonimmunes who go untreated. It is responsible for almost all of the deaths from malaria in the world.

By contrast, the disease consequences for those with vivax infections appear relatively minor. They include temporary debilitation during the course of and in the aftermath of the fever paroxysms. A common result of vivax malaria is anemia that may turn increasingly severe after relapses.[7] Vivax can also reach the infant *in utero*. In the postpartum period, even if the mother has acquired immunity to vivax, she is unable to pass this protection on to her baby.[8] It is possible to die from vivax infections,

[6] For an overview, see Caroline Shulman and Edgar Dorman, "Clinical Features of Malaria in Pregnancy," in Warrell and Gilles, *Essential Malariology*, 219–235.

[7] For an overview, see David A. Warrell, "Clinical Features of Malaria," in Warrell and Gilles, *Essential Malariology*, 191–205.

[8] V.A. Snewin, S. Longacre, and P.H. David, "*Plasmodium Vivax*: Older and Wiser?" *Research in Immunology*, vol. 142 (1991), 632.

particularly if the sufferer is undernourished or has a compromised immune system. The death toll of vivax – estimated at perhaps 1 to 2 percent of those with severe untreated infections during epidemics – is high compared to that of many other human infectious diseases. These differences between the parasites and the differential biological responses of their human hosts to the different forms of malarial infection suggest that we can think of human malaria as a kaleidoscope of different infections, with different overlapping patterns, most of which have left little or no evidence behind.

The parasites have different temperature requirements for reproduction within the mosquito host. Little is known, however, about the temperature requirements of *P. ovale*. It is principally confined to tropical Africa, with only occasional reports (some unconfirmed) of its presence in the west Pacific region, southern China, Burma, and Southeast Asia.[9] *P. vivax* has adapted to the widest range of temperatures and can extend its seasonal reach into the Arctic, although temperatures must exceed 15 degrees Centigrade (C) for at least a month. *P. malariae* seems to have a similar minimum temperature requirement but requires a longer time of development within the mosquito. *P. falciparum* requires more warmth than the vivax or malariae parasites. It does not reproduce when the temperature drops below 19 degrees C.[10]

Falciparum malaria, like vivax and malariae, is a global disease. However, owing to the higher temperature requirements for reproduction, the falciparum parasite has been able to extend its range only fitfully into the temperate zone. A band of potential falciparum infections straddles the tropics and extends north, for example, only into the southern reaches of China and to the south only to the lower reaches of Brazil. Some expanses of the globe, including the southern reaches of South America, from northern Argentina down to Cape Horn, and the southernmost regions of Africa including much of what is today the Republic of South Africa are altogether free from all four forms of endemic malaria.

The ecological patterns and requirements of the anopheline mosquito species that transmit malaria vary greatly. Perhaps seventy species *can* transmit malaria, and of these, forty species are thought to be of major importance. All require water in which to lay eggs and for the larvae to

[9] Sinden and Gilles, "Malaria Parasites," 25.
[10] George MacDonald, *The Epidemiology and Control of Malaria* (London: Oxford University Press, 1957), 6–16, esp. 10–11.

develop into adults. The blood meal provides essential nutrients for the cycle of producing eggs, which varies from two to three days in the tropics to longer periods (up to several weeks) in colder climates. Most female mosquitoes will produce four or five batches of eggs before they die.

The species' preferences for breeding habitats vary considerably. Some species prefer salt water; others prefer fresh water. Some breed only in marshes; others breed at the edges of streams or in springs, in ponds, or in puddles. A few species breed in leaf axils that capture rainwater. Some species live in lowlands; others live in highlands. Some strongly prefer human blood to animal blood, others the converse, and yet others do not have much preference for one over the other. Some are exquisitely suited to tropical climates; others buzz across a surprisingly wide range of terrains. There are, however, some broadly common behaviors. Most species feed between dusk and dawn. The peak periods of biting, however, vary by species. Some feed earlier in the evening; others feed after midnight. Where the mosquitoes take their blood meals also varies. Some species feed mostly indoors and are termed *endophagic;* others feed mostly outside of buildings and are thus *exophagic*. Another important variation in behavior is where the mosquitoes like to take a break from flight. The exophilic mosquitoes rest mostly outdoors; the endophilic rest indoors.

These behavioral variations are critically important because in conjunction with a wide range of human cultural practices that influence the availability of blood meals (such as sleeping indoors or outdoors and near a smoking fire or not, and penning livestock near human habitations or at a distance) they can have a significant influence on the local epidemiology of malarial infections. These mosquito behaviors, some of which have changed over time to exploit new opportunities, have made the lessons learned in localized malaria control difficult to extend even within a subregion. Anopheline mosquitoes, thus, are key actors in the drama of human malaria, although their roles have begun to be understood only since the late nineteenth century.

The female anopheline mosquitoes find some people to be more attractive sources of blood meals than others. The attractions are stimulated by the exhalation of carbon dioxide and other human odors, as well as by warmth and moisture. Some researchers suggest that there are other determinants. Some studies indicate that the malaria parasites may trigger chemical reactions in humans that render them more attractive to mosquitoes. It seems possible that we will come to better understand these

more subtle attractants, stimulated by biochemical interactions, as a result of this research.[11]

The parasites' life cycles involve incubation in both human and mosquito hosts, and thus the relationships between mosquito, parasite, and human host are best conceived of as a triad. These triadic relationships are very complex and incompletely understood by researchers, but it is clear that, in the temperate regions, the malaria plasmodia respond to biological and seasonal clues in the human host. In the tropics, where there are mosquitoes year round, it is thought that the plasmodia respond to other clues. There, bites from uninfected mosquitoes may stimulate the formation of gametocytes within the human host and thereby increase the human reservoir of infection at the beginning of the transmission season.[12]

Another set of complex and incompletely understood relationships exists between the human hosts, the plants that we eat, and the malaria parasites. These relationships are sometimes referred to as the Human-Plant-Parasite (H-P-P) complex. Some of the core tuberous foodstuffs in the tropics, such as yams and cassava, release chemicals into the human bloodstream that partially inhibit the reproduction of the parasites. In the Mediterranean region, the fava bean, a staple foodstuff, has the same effect. Some common tropical spices act as oxidants and similarly may depress the parasite load of an infected individual.[13]

Other complex relationships exist between malaria and other diseases. For example, throughout much of tropical Africa, the broad distribution of the fly vector for trypanosomiasis (sleeping sickness) prevented the introduction from southern Eurasia and northern Africa of large

[11] Children infected by falciparum malaria in the gametocyte stage of plasmodial development (postmalarial attack) attract about twice as many mosquitoes as children who were either uninfected or infected with the earlier (premalarial attack) stages of plasmodia. When the infection was cleared, the children who had been twice as attractive to mosquitoes returned to a neutral status, with the same level of attractiveness to mosquitoes as the other children. Renaud Lacroix et al., "Malaria Infection Increases Attractiveness of Humans to Mosquitoes," *PLoS Biology*, vol. 3, no. 9 (2005): 1590–1593.

[12] Richard E.L. Paul, Mawlouth Diallo, and Paul T. Brey, "Mosquitoes and Transmission of Malaria Parasites – Not Just Vectors," *Malaria Journal*, vol. 3, no. 1 (2004), 2–3. This can be found online at http://www.malariajournal.com/content/3/1/39.

[13] Fatimah Jackson, "Ecological Modeling of Human-Plant-Parasite Coevolutionary Triads: Theoretical Perspectives on the Interrelationships of Human HbβS, G6PD, *Manihot esculenta*, *Vicia faba*, and *Plasmodium falciparum*," in ed. L.S. Greene and M.E. Danubio, *Adaptation to Malaria: The Interaction of Biology and Culture* (Amsterdam: Gordon and Breach, 1997), 139–207; Nina L. Etkin, "Plants as Antimalarial Drugs: Relation to G6PD Deficiency and Evolutionary Implications," in Greene and Danubio, *Adaptation to Malaria*, 139–176; Stuart J. Edelstein, *The Sickled Cell: From Myths to Molecules* (Cambridge, MA: Harvard University Press, 1986), 60–63.

domesticated animals that were susceptible to the disease. Because of the general absence of an alternate blood source from domesticated livestock, the tropical African mosquito vectors developed a uniquely strong preference for human blood meals. This preference, in turn, greatly intensified the transmission of malaria. Other complex relationships exist between the malarial infections. One study in the Ivory Coast, for example, indicates that infection with malariae affords some protection against falciparum; another in Papua New Guinea indicates that vivax has a similar effect.[14] Other studies suggest that a balance between falciparum and vivax exists in parts of the world where both infections coexist.[15]

THE HISTORICAL EPIDEMIOLOGY OF MALARIA

Beginning in the early nineteenth century, European and North American medical writers began to describe the geographical distribution of malarial infections and to assess the impacts of malaria on their regions.[16] The authors of these studies wrote about malarial environments where the principal breeding grounds for the local anopheline vectors were swampy and where the principal infections were vivax. These two features were broadly characteristic of both the eastern North American malarial zone and the western European malarial zone. These authors drew on culturally specific regional knowledge to explain the relationship between swamps and fevers. By the middle of the nineteenth century, a wealth of empirical observation seemed to establish the link between the effluvia of the swamps – the miasmas – and malarial fever.[17]

[14] Robert Sallares, "Pathocoenoses Ancient and Modern," *History and Philosophy of the Life Sciences*, vol. 27 (2005), 210–212.

[15] Snewin et al., "*Plasmodium Vivax*: Older and Wiser?," 634.

[16] John MacCulloch, *An Essay on the Remittent and Intermittent Diseases* (Philadelphia: Carey and Lea, 1830); Oliver Wendell Holmes, "Dissertation on Intermittent Fevers in New England," *Boylston Prize Dissertations for the Years 1836 and 1837* (Boston: C.C. Little and J. Brown, 1838); Daniel Drake, *A Systematic Treatise, Historical, Etiological, and Practical, of the Principal Diseases of the Interior Valley of North America* (Cincinnati: W.B. Smith and Co., 1850).

[17] Consider, e.g., the summary in 1864 by William H. Van Buren, one of the founders of the U.S. Sanitary Commission, of contemporary understandings of malaria:

a. Individuals undoubtedly differ in degree of susceptibility, or in their liability to be attacked by miasmatic disease, but there is no amount of natural vigor of constitution, or positive high health, which will confer immunity against the effects of the poison.
b. The young are usually more liable to the disease than those of mature age.
c. Poisoning from malaria is more liable to take place between the hours of sunset and sunrise, and in those who are fasting, fatigued, or deprived of sleep.

The miasmatic theory of malarial fever could explain a great deal across large stretches of North America and Western Europe. It was inapt in many other world regions, however, where the vector mosquitoes bred in mountain streams, tidal floodplains, or hoof-print-size puddles. Fever theorists, confronted with this confounding complexity, advanced a more complex geographically based approach, describing the different landscape configurations that were dangerous to human health. These European writers played a major role in the early conceptualization of medical topography, and they also noticed that Europeans during their first years in the tropics generally came down with devastating fevers, and that they also "acclimated" to the tropics during an extended stay. The breadth of malarial infections in tropical South Asia led to racial notions that some peoples were more susceptible to fever than others, and that malaria had broad, enervating effects throughout entire cultural zones.[18]

This book is concerned, in part, with the changing distribution of malarial infections – what is known in modern parlance as spatial epidemiology – and in this sense, it follows in the footsteps of some of these early medical writers. Unlike the early authors, this book is also concerned with the changing nature, significance, and distribution of these infections over time. In modern parlance, the field of study that integrates both spatial and temporal dimensions of the changing patterns of disease is known as historical epidemiology. On a global canvas, this book traces the movements of malarial infections – in deep time from tropical Africa into Eurasia; later from Afro-Eurasia to the Americas; and relatively

d. After exposure to malaria, the attack of disease is not necessarily immediate; a period of incubation, varying from six to twenty days, usually intervenes, and during this the individual may enjoy perfect health. The attack, when it occurs, may assume the form of intermittent or remittent fever, or any of the other forms of miasmatic disease, varying in nature and degree of severity according to the impressibility of the individual and the virulence of the poison; or, the amount of poison imbibed may not have been sufficient to cause an explosion of purely miasmatic disease, but only enough to impress the miasmatic or paroxysmal type upon some intercurrent malady occasioned by another exposure.
e. After long exposure to malaria, even though no actual attack of sickness may have occurred, a debilitated condition of health is liable to arise, characterized by a sallow complexion, diminished strength, and impoverished blood; this is known as malarial cachexia.

William H. Van Buren, "Quinine as a Prophylactic against Malarious Diseases," in ed. William A. Hammond, MD, *Military, Medical and Surgical Essays Prepared for the United States Sanitary Commission* (Philadelphia: J.B. Lippincott and Co., 1864), 95–96.

[18] Mark Harrison, *Climates and Constitutions: Health, Race, Environment, and British Imperialism in India, 1600–1850* (New Delhi: Oxford University Press, 1999).